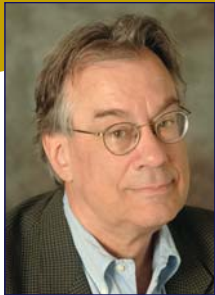


Division of Immunology



Cox Terhorst, PhD, Chief

● Overview

The Immunology Division at Beth Israel Deaconess Medical Center conducts basic research into innate and adaptive immune responses using knockout and knock-in approaches. The goals of the Division are: 1) to carry out cutting-edge basic research of innate and adaptive immune responses; 2) to teach graduate students and research fellows; and 3) to provide a nurturing environment for the career development of research fellows and faculty. The Division employs 2 research faculty, 12 research fellows and 3 graduate students.

Active collaborations exist with investigators in the Divisions of Gastroenterology, Allergy and Inflammation and Rheumatology at BIDMC. Drs. Cox Terhorst and George Tsokos, Chief of the Division of Rheumatology, co-direct a T32 Training Program on Systemic Autoimmunity.

Cox Terhorst serves as Associate Director of the Harvard Center for the Study of Inflammatory Bowel Diseases and of the Harvard Center for Primary Immuno Deficiencies. He is also Course Director of Immunology 219 "The Primary Immunodeficiencies."

● Research Activities

Pathogenesis of experimental Inflammatory Bowel Disease – Studies with genetically well-defined mouse models of Inflammatory Bowel Diseases, i.e. experimental colitis, led to an understanding that perturbations of the finely tuned balance between the immune system and the vast antigenic load of the colon can result in disease. Aggressor CD4+ T helper 1 (Th1) cells accumulate in the lamina propria followed by inflammation of the intestinal mucosa. Bacterial antigens are presented to these T cells by professional

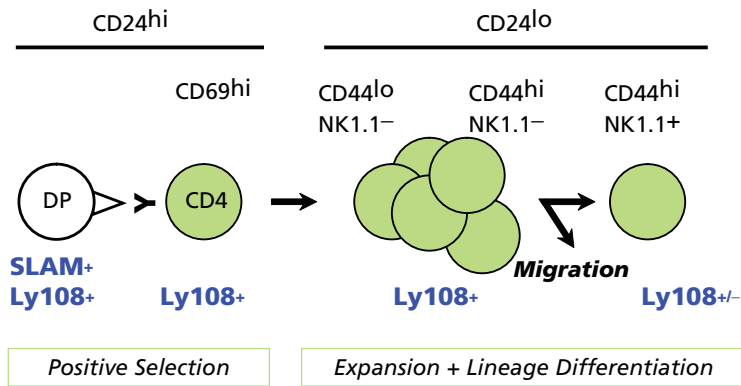
Antigen Presenting Cells (APC). In healthy mice the aggressor Th1 cells are prevented from expanding and thus initiating colitis by regulatory T cells (Treg). However, we do not understand the interactions of these cell types in the regulation of normal and abnormal immune responses to colonic bacteria.

Research Funding • AY'07

Federal Direct	3,925,210
Federal Indirect	1,588,813
Other Direct	1,318,467
Other Indirect	164,707

Our current studies are designed to examine the homeostatic balance between colitis inducing Th1 cells and Treg cells. The fundamental strategy is to examine the contribution of key dendritic cells, macrophages and T cell surface receptor / ligand pairs in the education of the pathogenic T cells and Treg cells in IBD. The results of these studies have already suggested therapeutic strategies that can be applied to IBD patients, for we have successfully used a series of antibody reagents to ameliorate experimental colitis in the mouse.

Glucocorticoid-induced TNFR family-related gene, GITR, is known to be a constitutively expressed marker for Treg cells. GITR generates a negative signal in the Treg cell upon encountering GITR-ligand. Our studies with GITR- and GITR-ligand-deficient mice are designed to test the central hypothesis that GITR-ligand, which is up-regulated on the surface of non-T cells in the inflamed colon, regulates T regulatory cell functions. The results have suggested therapeutic strategies that enhance the number and the persistence of an active state of Treg cells in IBD patients.



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- SLAM and Ly108 expression on double positive thymocytes is required for NKT cell maturation. Immature thymic CD24^{hi} double-positive cells express high levels of both Ly108 and SLAM. During selection, these thymocytes further mature into CD24^{hi} CD69^{hi} single positive cells that downregulate SLAM expression, while maintaining Ly108 expression. These single positive cells further mature into CD24^{lo} CD44^{lo} NK1.1⁻ which expand and subsequently mature into CD24^{lo} CD44^{hi} NK1.1⁻ cells, both of which preserve Ly108 expression. At this point, the mature NKT cells either remain in the thymus or migrate to the periphery, where in each case they terminally differentiate into CD24^{lo} CD44^{hi} NK1.1⁺ cells. Fully mature cells in the thymus are Ly108^{lo}, while those that mature in the spleen are Ly108^{hi}.

X-linked lymphoproliferative disease –

Childhood primary immunodeficiency disorders can be viewed as “experiments of nature” in which a discrete genetic defect affects the expression and/or the structure/function of essential lymphocyte proteins and results in immune dysfunctions. X-linked lymphoproliferative (XLP) disease is a primary immunodeficiency caused by a defect in the SH2D1A gene with three major disease manifestations: fatal infectious mononucleosis, B cell lymphomas and dysgammaglobulinemia. SH2D1A encodes SAP (SLAM Associated Protein), which is a single free SH2-domain protein that controls signal transduction in T lymphocytes, NKT cells, NK cells, and a B cell subset. SAP interacts with the cytoplasmic tails of six of the SLAM-family of receptors and, through a second set of unique interactions, recruits tyrosine kinases to the SLAM receptors. We thus have the systems in place to clarify how the absence of SAP causes XLP.

The SLAM gene family controls innate and adaptive immunity – SLAM (Signaling Lymphocyte Activation Molecule or SLAMF1) is a self-ligand receptor at the interface between

T cells and professional antigen presenting cells with a role in innate and acquired immunity. We find that SLAM f1-, f2-, f4-, f6- and f8- deficient mice have abnormal responses to both bacteria and parasites. This is the result of a defect in the final stage of CD4⁺ T cell differentiation and/or of defective killing of bacteria by SLAM-deficient macrophages, tissue dendritic cells and neutrophils. Thus, SLAM family members serve as regulators of the innate and adaptive immune response to bacterial and viral infections. Surprisingly, polymorphisms in the SLAM gene family are implicated in a propensity for mouse lupus. Together with the Tsokos lab we have just begun to evaluate whether distinct polymorphisms in the human SLAM genes can be correlated with the disease manifestations of SLE patients.

● *Selected Publications*

Calpe S, Wang N, Romero X, Berger SB, Lanyi A, Engel P, Terhorst C. The SLAM and SAP gene families control innate and adaptive immune responses. *Adv Immunol* 2008; 97:177-250.

Sintes J, Romero X, Marin P, Terhorst C, Engel P. Differential expression of CD150 (SLAM) family receptors by human hematopoietic stem and progenitor cells. *Exp Hematol* 2008; 36:1199-204.

Maganto-Garcia E, Punzon C, Terhorst C, Fresno M. Rab5 activation by Toll-like receptor 2 is required for Trypanosoma cruzi internalization and replication in macrophages. *Traffic* 2008; 9:1299-315.

Graham DS, Vyse TJ, Fortin PR, Montpetit A, Cai YC, Lim S, McKenzie T, Farwell L, Rhodes B, Chad L, Hudson TJ, Sharpe A, Terhorst C, Greenwood CM, Wither J, Rioux JD. Association of LY9 in UK and Canadian SLE families. *Genes Immun* 2008; 9:93-102.

Li W, Sofi MH, Rietdijk S, Wang N, Terhorst C, Chang CH. The SLAM-associated protein signaling pathway is required for development of CD4⁺ T cells selected by homotypic thymocyte interaction. *Immunity* 2007; 27:763-74.

Griewank K, Borowski C, Rietdijk S, Wang N, Julien A, Wei DG, Mamchak AA, Terhorst C, Bendelac A. Homotypic interactions mediated by SLAMf1 and SLAMf6 receptors control NKT cell lineage development. *Immunity* 2007; 27:751-62.

Cao O, Dobrzynski E, Wang L, Nayak S, Mingle B, Terhorst C, Herzog RW. Induction and role of regulatory CD4⁺CD25⁺ T cells in tolerance to the transgene product following hepatic *in vivo* gene transfer. *Blood* 2007; 110:1132-40.

● Faculty

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