

Division of Immunology



Cox Terhorst, PhD, Chief

● Overview

The Immunology Division at Beth Israel Deaconess Medical Center conducts basic research of 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 3 research faculty, 10 research fellows and 2 graduate students.

Active collaborations exist with investigators in the Divisions of Gastroenterology, Allergy and Inflammation and Rheumatology at BIDMC and with members of the Harvard Center for the Study of Inflammatory Bowel Diseases and of the newly formed Harvard Center for Primary Immuno Deficiencies. Cox Terhorst serves as Associate-Director of each center. He is also Course Director of Immunology 219 “The Primary Immunodeficiencies”, which is attended by Graduate Students of the Harvard Immunology Program and by undergraduates from Harvard College.

● 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 Th1 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.....	2,685,579
Federal Indirect.....	1,256,913
Other Direct.....	189,058
Other Indirect.....	20,522

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 APC 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 experiment colitis in the mouse.

Glucocorticoid-induced TNFR family-related gene, GITR, is known to be a constitutively expressed marker for Treg cells. We have cloned mouse GITR-ligand, which triggers signal transduction initiated by GITR and blocks suppression by Treg cells. Thus, GITR generates a negative signal in the Treg cell upon encountering GITR-ligand. Our studies with 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, blocks T regulatory cell functions by activating a GITR dependent negative signal. The results of these studies should suggest therapeutic strategies that enhance the number and the persistence of an active state of Treg cells in IBD patients.

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 dys-gammaglobulinemia. SH2D1A encodes SAP (SLAM Associated Protein), which is a single free SH2-domain protein that controls signal transduction in T lymphocytes, NK cells, a B cell subset and platelets. Physicochemical and biochemical studies emphasize the unique interactions of SAP with the cytoplasmic tails of six of the SLAM-family of receptors. Through a second set of unique interactions, SAP recruits tyrosine phosphokinases 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 – The SLAM family of nine cell surface receptors is emerging as a crucial set of regulatory genes for both adaptive and innate immunity. SLAM (Signaling Lymphocyte Activation Molecule or SLAMF1) is a self-ligand receptor at the interface between T cells and professional antigen presenting cells. But, SLAMF1 is also the primary receptor for measles virus, which causes severe immune suppression. We find that SLAMF1-, 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.

Preliminary genetic studies in humans and mice indicate that variations in one or several of the genes in the SLAM locus may influence a propensity to develop SLE.

The gene for EAT-2 (SH2D1B) maps in close proximity to the SLAM genes on human and mouse chromosome 1. Three dimen-



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• The Immunology team

sional structure analyses demonstrate that the adapter EAT-2 is very similar to SAP, and it too interacts with the cytoplasmic tails of members of the SLAM family. We are currently investigating the role of EAT-2A and -B in macrophages, neutrophils, dendritic cells and platelets using our recently developed EAT-2A, EAT2-B and EAT2-(A+B) knockout mice.

• *Selected Publications*

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.

Chen G, Tai AK, Lin M, Chang F, Terhorst C, Huber BT. Increased proliferation of CD8+ T cells in SAP-deficient mice is associated with impaired activation-induced cell death. *Eur J Immunol* 2007; 37:663-74.

Fernandez-Malave E, Wang N, Pulgar M, Schamel WW, Alarcon B, Terhorst C. Overlapping functions of human CD3delta and mouse CD3gamma in alphabeta T-cell development revealed in a humanized CD3gamma-mouse. *Blood* 2006; 108:3420-7.

Griewank K, Borowski C, Rietdijk S, Wang N, Julien A, Wei DG, Mamchak AA, Terhorst C and Bendelac A. Homotypic interactions mediated by Ly108 and SLAM control NKT lineage development. *Immunity* 2007; 27(5):751-62.

Li W, Sofi MH, Rietdijk S, Wang N, Terhorst C, and Chang C-H. The SLAM-associated protein (SAP) and PKC θ are required for Thymocyte-mediated CD4 T cell development. *Immunity* 2007; 27(5):763-74.

• *Faculty*

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