Immunology

Cox Terhorst, PhD, Chief

Boaz van Driel, PhD, Pre-Doctoral Fellow

The non-clinical Division of Immunology conducts research with a focus on molecular mechanisms of innate and adaptive immune responses to bacteria, viruses and self-antigens. The major goal of the Division is to elucidate signaling networks that control activation, cell growth and migration of T cells, natural killer cells, dendritic cells

Cox Terhorst, PhD

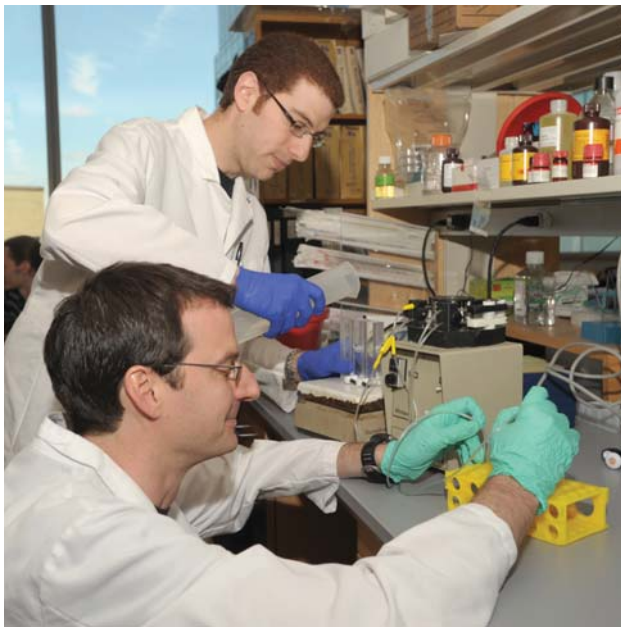
and macrophages and to identify aberrant steps in these networks that lead to human primary immune deficiencies, inflammatory bowel diseases and systemic lupus erythematosus. The human studies are done in active collaboration with scientists and physicians at BIDMC and in the Harvard Centers for the Study of Inflammatory Bowel Diseases and for Primary Immunodeficiencies. Using both mutant mice and monoclonal antibodies against key cell surface receptors, novel targets for pharmacological intervention in inflammatory bowel diseases have been identified.

2009–2010 HIGHLIGHTS

How the SLAM family of nine cell surface receptors control both adaptive and innate immunity is actively being addressed by investigators in the Division using mice and human cells. We find that three of the nine SLAM family receptors, i.e. SLAMF1, 2 and 6, are microbial sensors that control the killing of *E. coli* by macrophages. SLAMF1 regulates activity of the NADPH oxidase NOX2 complex and phagolysosomal maturation after entering the phagosome, following interaction with the bacterial outer membrane proteins.

SLAMF1 recruits a complex containing the intracellular class III phosphatidylinositol kinase Vps34, its regulatory protein kinase Vps15 and the autophagy-associated molecule beclin-1 to the phagosome, which is responsible for inducing the accumulation of phosphatidylinositol-3-phosphate, a regulator of both NOX2 function and phagosomal or endosomal fusion. Thus, SLAMF1 connects the Gram-negative bacterial phagosome to ubiquitous cellular machinery responsible for the control of bacterial killing. Antibodies directed against mouse SLAMF1 ameliorate experimental chronic enterocolitis.

The Division of Immunology also focuses on determining how polymorphisms and isoforms of several SLAMF genes are implicated in a pre-disposition to develop lupus. Per example, using our genetically altered mice we found that SLAMF6 is involved in lupus-related autoimmunity in mice. Introduction of a SLAMF6 isoform, SLAMF6-H1, into a lupus-prone strain, which does not express the isoform, markedly diminishes T cell dependent autoimmunity. Thus, an immune response suppressing isoform of SLAMF6 regulates the pathogenesis of lupus. Together with the Tsokos lab (Rheumatology) we are evaluating which human SLAMF genes can be causal to disease manifestations of SLE patients.



Scott Berger, PhD, and **Xavi Romero-Ros, PhD**, Research Fellows

SELECTED PUBLICATIONS

Manocha M, Rietdijk S, Laouar A, Liao G, Bhan A, Borst J, Terhorst C, Manjunath N. Blocking CD27-CD70 costimulatory pathway suppresses experimental colitis. *J Immunol* 2009; 183:270-6.

Freitag TL, Rietdijk S, Junker Y, Popov Y, Bhan AK, Kelly CP, Terhorst C, Schuppan D. Gliadin-primed CD4+CD45RBlowCD25- T cells drive gluten-dependent small intestinal damage after adoptive transfer into lymphopenic mice. *Gut* 2009; 58:1597-605.

Martino AT, Nayak S, Hoffman BE, Cooper M, Liao G, Markusic DM, Byrne BJ, Terhorst C, Herzog RW. Tolerance induction to cytoplasmic beta-galactosidase by hepatic AAV gene transfer: implications for antigen presentation and immunotoxicity. *PLoS One* 2009; 4:e6376.

Wang N, Calpe S, Westcott J, Castro W, Ma C, Engel P, Schatzle JD, Terhorst C. The adapters EAT-2A and -2B are positive regulators of CD244- and CD84-dependent NK cell functions in the C57BL/6 mouse. *J Immunol* 2010; 185:5683-7.

Berger SB, Romero X, Ma C, Wang G, Faubion WA, Liao G, Compeer E, Keszei M, Rameh L, Wang N, Boes M, Regueiro JR, Reinecker HC, Terhorst C. SLAM is a microbial sensor that regulates bacterial phagosome functions in macrophages. *Nat Immunol* 2010; 11:920-7.

Walter JE, Rucci F, Patrizi L, Recher M, Regenass S, Paganini T, Keszei M, Pessach I, Lang PA, Poliani PL, Giliani S, Al-Herz W, Cowan MJ, Puck JM, Bleesing J, Niehues T, Schuetz C, Malech H, DeRavin SS, Facchetti F, Gennery AR, Andersson E, Kamani NR, Sekiguchi J, Alenezi HM, Chinen J, Dbaibo G, ElGhazali G, Fontana A, Pasic S, Detre C, Terhorst C, Alt FW, Notarangelo LD. Expansion of immunoglobulin-secreting cells and defects in B cell tolerance in Rag-dependent immunodeficiency. *J Exp Med* 2010; 207:1541-54.

Liao G, Nayak S, Regueiro JR, Berger SB, Detre C, Romero X, de Waal Malefyt R, Chatila TA, Herzog RW, Terhorst C. GITR engagement preferentially enhances proliferation of functionally competent CD4+CD25+FoxP3+ regulatory T cells. *Int Immunol* 2010; 22:259-70.

Rucci F, Notarangelo LD, Fazeli A, Patrizi L, Hickernell T, Paganini T, Coakley KM, Detre C, Keszei M, Walter JE, Feldman L, Cheng HL, Poliani PL, Wang JH, Balter BB, Recher M, Andersson EM, Zha S, Giliani S, Terhorst C, Alt FW, Yan CT. Homozygous DNA ligase IV R278H mutation in mice leads to leaky SCID and represents a model for human LIG4 syndrome. *Proc Natl Acad Sci USA* 2010; 107:3024-9.

FACULTY

Cox Terhorst, PhD

Ninghai Wang, MD, PhD

HONORS AND AWARDS

Cox Terhorst, PhD, received the 2009 Saspitis Award from the Hungarian Society of Immunology, and was the 2009 Leonardo Lecturer at the Istituto Scientifico San Raffaele in Milan, Italy.

RESEARCH FUNDING

	Direct	Indirect
Federal	**3,452,424**	**1,221,177**
Non Federal	**331,103**	**130,438**