

Division of Transplant Immunology



Terry B. Strom, MD, Chief

● *Overview*

The Division of Transplant Immunology is both an independent entity and a major component of Beth Israel Deaconess Medical Center's Transplant Center. The division employs 6 Research Faculty, 12 Research Fellows and 3 Research Technicians. The Division serves a research, not clinical, function.

● *Educational Programs*

The Division of Transplant Immunology sponsors a highly successful fellowship training program. Many former trainees of the faculty are now prominent academicians or hold senior positions in industry. The Division holds weekly laboratory meetings, participates with other labs in a weekly journal club and holds a monthly science seminar. Dr. Terry Strom is a faculty member of Harvard's graduate program in Immunology. The Harvard Medical School Program in Immunology holds weekly seminars. Drs. Strom and Diane Mathis (Joslin, HMS) direct interlocking Juvenile Diabetes Research Foundation Centers. These Centers hold monthly seminars and a yearly retreat.

● *Research Activities*

The focus of the highly interactive Strom, Zheng, Li, Koulmanda and Gao laboratories is immune tolerance. The goal is to create immune tolerance in the clinic. To work toward this goal, we attempt to define the precise nature of immune tolerance and of immunoregulatory T cells at the molecular and cellular levels. Transplant tolerance is obtained when the functional supremacy of donor reactive immunoregulatory T cells is obtained and remains dominant following the cessation

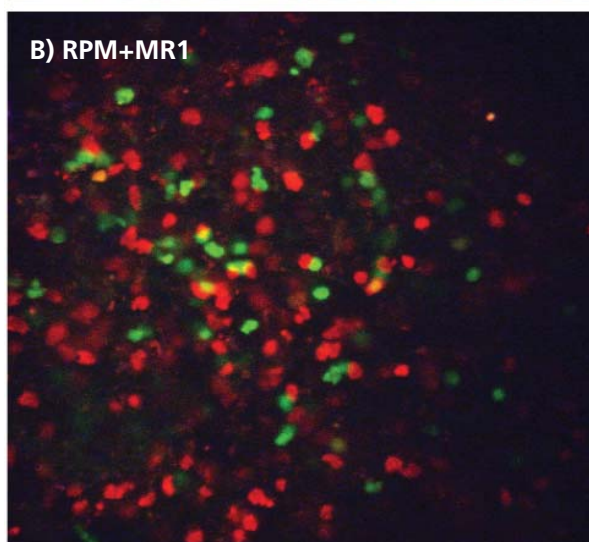
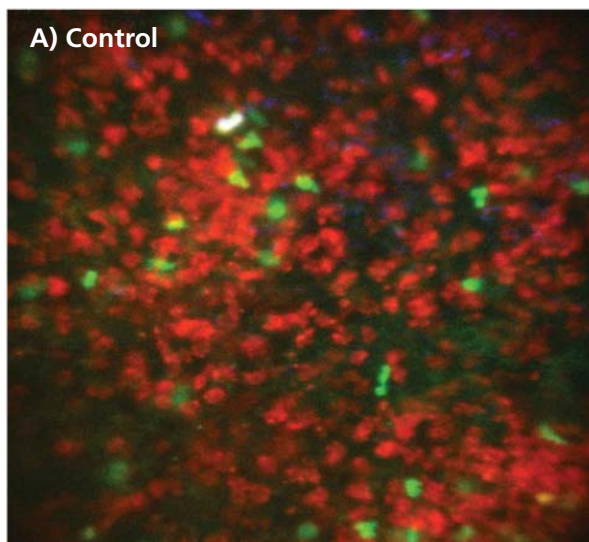
of immunosuppression. A distinctive cell surface phenotype for immunoregulatory T cells has been discerned. This molecular signature consists of two ectoenzymes that catalyze the formation of adenosine, an immunoregulatory substance, which contributes importantly to immunoregulatory T cell function.

This laboratory places strong emphasis in the development of innovative biotherapeutics. The first effort to use mAbs and cytokine related fusion proteins directed against activated, but not resting, T cells directly led to the development of anti-CD25 mAbs for use in transplantation and autoimmunity.

Research Funding • AY'07

Federal Direct.....	2,108,527
Federal Indirect.....	1,016,274
Other Direct.....	1,009,118
Other Indirect.....	67,214

More recently, novel biotherapeutic proteins developed and tested within our lab have shown great promise in the murine model of type 1 diabetes and difficult mouse and non-human primate models of islet and cardiac transplantation. As a direct result of these efforts, we have obtained valuable information concerning the role of certain T cell growth factors, T cell immunoglobulin mucin domain proteins (Tim) and acute phase reactants on T cell apoptosis, and on the differing vulnerabilities of regulatory, transplant protective and cytopathic-transplant destructive, T cells. Other work has given insight as to the effect of certain therapies on inhibition or promotion of activation-induced T cell death, an event that is crucial for tolerance induction.



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• *In vivo* time-lapse imaging showing the dynamic change of nTreg (green), Teff (red) and iTreg (green+red) in the islet allografts. Representative confocal images of islet grafts at 2-week time point when the allograft in the control group (A) is rejected while the allograft is tolerized in Rapamycin (PRM) and Anti-CD154 mAb (MR1) treated host (B).

The basic biology governing the commitment of naïve or activated T cells to distinctive T cell subset phenotypes has been explored in detail, with new insights provided concerning the reciprocal commitment to tissue protective Foxp3⁺ regulatory cells or to virulent tissue injuring Th17 T cells. The critical role of certain pro- and anti-inflammatory cytokines upon T cell lineage commitments, pancreatic islet cell viability/expansion and insulin signaling has also fostered a healthy respect for the resilience

of tissues under immune attack and means to overcome the confounding role of adverse inflammation upon tolerance induction. Two new novel therapeutic regimens, power mix and the use of apha1 anti-trypsin, an acute phase reactant protein, are slated for clinical trial in humans with new onset diabetes and islet transplantation, as a result of preliminary funding support from the NIH and JDRF funded Immune Tolerance Network. Finally, the Strom lab probes mouse, non-human primate and human tissue samples for biomarkers associated with adverse or tolerance-inducing immunity. Through identification of molecular signatures (biomarkers), we hope the potential for precise guidance of therapy in the clinic can be enhanced.

The Li lab is interested in how tolerance to organ transplants can be induced and maintained with specific emphasis on T cell costimulatory molecules and cytokines. His lab recently discovered important crosstalk between the growth factor signaling pathways and the T cell costimulatory pathways in controlling the fate of activated T cells that respond to alloantigens. His group also discovered OX40 as a new costimulatory molecule that can support the rejection response when the canonical CD28 and CD154 costimulatory pathways are absent or intentionally blocked. Moreover, studies in Xian's lab suggest that OX40 likely controls a critical checkpoint where antigen-specific memory T cells and regulatory T cells are regulated. More recently, Xian's lab identified a previously unknown pathway by which cells in the innate immune system regulate the adaptive T cell response in transplant models, and this pathway appears to control the susceptibility of tolerance induction by the costimulatory blockade strategy. Xian's research may eventually lead to a better understanding of how T cell tolerance is induced and maintained.

The Gao lab is interested in the generation/function of Foxp3⁺ regulatory T cells (Tregs). By using Foxp3GFP knock-in mice, they characterized Tregs as CD4⁺ T cells expressing CD39 and CD73, two ectoenzymes that catalyze the generation of adenosine, which contributes to Treg suppressive function. In addition, the Gao lab found that rapamycin

induces, whereas cyclosporine blocks, *de novo* induction of alloantigen-specific Tregs mediating donor-specific skin graft protection. More important, they reported that pro-inflammatory cytokines IL-6 and IL-21 not only inhibit Treg generation but also induce pathogenic Th17 cells in the presence of TGF- β . Along this line, conventional B2 B cells excel in converting naïve T cells into Tregs upon TGF- β stimulation, whereas peritoneal B1 B cells drive a tissue destructive Th1/Th17 response. Therefore, the commitment of T cell lineage is strongly influenced by the cytokine milieu and APC type. Nonetheless, unlike natural Tregs, such *ex vivo* induced Tregs are not stable *in vivo*, as they can, under inflammatory conditions, lose Foxp3 (GFP) expression and became effector T cells. Elucidation of the molecular and cellular processes that govern the development and stable function of regulatory vs. pathogenic cells will be the research focus of the Gao lab in the next few years.

● *Awards and Honors*

Xian C. Li received the AST/Roche Achievement Award, 2008, from the American Society of Transplantation. Alexander Kroemer was granted an AST/Astellas Fellowship Grant Award, 2008, the American Society of Transplantation, and Gulcin Demirci and Xiang Xiao Zheng received 2008 AST/Young Investigator Awards from the American Society of Transplantation.

● *Selected Publications*

Porrett PM, Yuan X, LaRosa DF, Walsh PT, Yang J, Gao W, Li P, Zhang J, Hancock WW, Sayegh MH, Koulmanda M, Strom TB, Turka LA. Mechanisms underlying blockade of allograft acceptance by TLR ligands. *J Immunol* 2008; 181:1692-9.

Zhong X*, Gao W*, Degauque N*, Bai C, Lu Y, Kenny J, Oukka M, Strom TB, Rothstein TL. Reciprocal generation of Th1/Th17 and Treg cells by B1 and B2 B cells. *Eur J Immunol* 2007; 37:2400-4. *Co-first authors.

● *Faculty*

Gulcin Demirci, MD	Xian C. Li, MD, PhD
Wenda Gao, PhD	Terry B. Strom, MD
Maria Koulmanda, MSc, PhD	Xin Xiao Zheng, MD

Degauque N, Mariat C, Kenny J, Zhang D, Gao W, Vu MD, Alexopoulos S, Oukka M, Umetsu DT, DeKruyff RH, Kuchroo V, Zheng XX, Strom TB. Immunostimulatory Tim-1-specific antibody deprograms Tregs and prevents transplant tolerance in mice. *J Clin Invest* 2008; 118:735-41.

Kroemer A, Xiao X, Vu MD, Gao W, Minamimura K, Chen M, Maki T, Li XC. OX40 controls functionally different T cell subsets and their resistance to depletion therapy. *J Immunol* 2007; 179:5584-5591.

Ding H, He Y, Li K, Yang J, Li X, Lu R, Gao W. Neutrophil gelatinase-associated lipocalin (NGAL) as an early urinary marker for renal tubular injury of IgA nephropathy. *Clin Immunol* 2007; 123:307-14.

Dwyer KM, Deaglio S, Gao W, Friedman D, Strom TB, Robson RC. CD39 and control of cellular immune response. *Purinergic Signal* 2007; 3:171-80.

Demirci G, Li XC. Novel roles of OX40 in the allograft response. *Current Opin Organ Transplant* 2008; 13:26-30.

Kroemer A, Edtinger K, Li XC. The innate NK cells in transplant rejection and tolerance induction. *Current Opin Organ Transplant* 2008; 13:339-43.

Kroemer A, Xiao X, Degauque N, Edtinger K, Wei HM, Demirci G, Li XC. The innate NK cells, allograft rejection, and a key role for IL-15. *J Immunol* 2008; 180:7818-2b.