Diabetes and Autoimmunity

Abul Abbas\[1\]

Our research focuses on the regulation of T-cell responses, and the signals that determine the choice between effector and regulatory cells and between lymphocyte activation and tolerance.

Other Research in Dr. Abbas's Lab:

Immune Regulation \[2\] \[1\]

Mark Anderson\[3\]

The Anderson lab has direct interest in genetic models and mechanisms of autoimmune disease. Current projects include detailed analyses of autoimmune phenotypes in our existing animal models and the generation of new models.

Other Research in Dr. Anderson's Lab:

Immune Regulation \[2\]

Jeffrey Bluestone \[4\]

The research in my laboratory concerns the fundamental events that regulate T-cell activation during immune responses to autoantigens in diabetes and other autoimmune diseases. Our efforts to modulate T cell activation have centered on understanding and altering the positive signals delivered by the antigen-specific T cell receptor and secondary, so-called co-stimulatory signals, or engaging the negative regulatory events such as CTLA-4, PD-1 and Notch that control T cell signal transduction. The studies focus on the yin/yang of the CD28/CTLA-4 pathways which are essential for a homeostatic T cell response. We have used soluble receptor antagonists, monoclonal antibodies and animals deficient in individual members of the CD28/CTLA-4/B7 pathways to define their individual roles in autoimmunity. In addition, we are interested in the negative regulation of immunity focused on the role of PD-1/PD-L1 pathways in the control of tissue specific tolerance. Lastly, we have a major interest in regulatory T cells (Treg) that control immune homeostasis. Using a variety of approaches including two-photon microscopy, genetic manipulation and antagonist therapies, we hope to develop new insights into Treg function and therapeutic application. Together, the insights gained from these studies will help in the development of a new generation of tolerogenic drugs that will "turn off" selected parts of the immune system, leaving the disease-fighting capabilities intact.
Other Research in Dr. Bluestone's Lab:


Harold Chapman[6]

My lab is currently interested in mechanisms of antigen presentation as they relate to allergy and autoimmunity. We are currently pursuing two questions in this area: How is endosomal acidification, and hence endosomal protease activity, regulated in dendritic cells? This question addresses the signaling determinants of assembly of vacuolar ATPase and MHC class II peptide in single endosomes. And secondly how are carbohydrate coats of allergens processed in dendritic cells, and is this a point of dysregulation in allergy? Recent studies point to the carbohydrate coat of certain allergens/pathogens as both potential CD1 antigens for NKT cells and as modulators of antigen processing relevant to MHC class II peptide loading. We are addressing both of these questions with ex vivo models of endosomal peptide loading and T cell activation.

Recent relevant publications:


Other Research in Dr. Chapman's Lab:

Allergy and Asthma [9]

Jason Cyster[10]

Autoreactive B cells that escape the bone marrow or that are generated in germinal centers need to be kept in check. The Cyster lab studies the basis for the competitive elimination of autoantigen binding B cells and the role of FoxP3+ regulatory T cells in preventing autoantibody responses.

Other Research in Dr. Cyster's Lab:


Max Krummel[13]

The lab is currently using advanced imaging to visualize T cell activation in autoimmune draining lymph nodes and effector sites. A mouse model of diabetes serves as a setting in
which dendritic cells bearing autoantigen can be visualized during their interactions with T lymphocytes. T lymphocytes and their reactivity are revealed using fluorescent dyes, including GFP fusions.

**Other Research in Dr. Krummel's Lab:**


**Lewis Lanier** [15]

Recent studies have implicated NK cells and T cells expressing ?NK receptors? as either protective or pathogenic in several autoimmune diseases. For example, we have shown that mice lacking the DAP12 adapter protein, which provides signaling for several myeloid and NK cell receptors, are more resistant to experimental autoimmune encephalomyelitis, a disease similar to multiple sclerosis (Bakker et al., Immunity. 2000 [16]). Another NK receptor, NKG2D, which is expressed on NK cells and CD8+ T cells, is involved in the destruction of the pancreas in the NOD mice, a strain of mice that spontaneously develops type I diabetes. Blocking NKG2D with a neutralizing monoclonal antibody prevents autoimmune diabetes in these animals (Ogasawara et al., Immunity. 2004 [17]). Studies of the signaling and function of these NK receptors may provide new insights into autoimmunity and provide new targets for therapy.

**Other Research in Dr. Lanier’s Lab:**


**Clifford Lowell** [19]

The lab is working with the Lyn Kinase knockout mice that are a well established model of lupus-like autoimmunity. In particular, we are focused on how myeloid leukocytes contribute to the breakdown of tolerance in this model. Our hypothesis is that overproduction of a number of cytokines may contribute in this knockout strain.

**Other Research in Dr. Lowell’s Lab:**


**Averil Ma** [21]

The proper regulation of innate immunity is critical for preventing autoimmunity. Our laboratory's interest in this area has focused on the intracellular mechanisms by which innate immune signaling, including TNF and TLR induced signal transduction events are regulated. In particular, by targeting the A20 gene in mice, we have found that a novel molecule called A20 is essential for restricting both TNF and TLR induced activation signals in macrophages and dendritic cells (Lee et al, Science. 2000 [22]; Boone et al, Nature Immunology. 2004 [23]). We have further found that A20 is a unique ubiquitin modifying enzyme that regulates both the activity and stability of signaling proteins such as RIP and TRAF6 (Wertz et al, Nature. 2004 [24].
Boone et al, Nature Immunology, 2004. A20 is a biochemically unique molecule that both deactivates and degrades target proteins. In addition, recent genetic studies suggest that A20 is important for regulating autoimmunity in human patients. Ongoing studies focus on the physiological targets of A20's enzymatic activity, and the roles of A20 in regulating dendritic cell activation, immune responses, and autoimmunity.

Other Research in Dr. Ma's Lab:


Ari Molofsky [25]

Obesity rates are rising throughout the world, driving an epidemic of type 2 diabetes mellitus. Inflammation in adipose tissue contributes to this disease progression. In contrast, immune cells associated with type 2 immune responses are abundant in lean adipose tissue and can protect against diabetes. The Molofsky lab is interested in the regulation and metabolic function of adipose tissue type 2 immunity, with a particular focus on innate lymphoid cells and regulatory T cells.

Other Research in Dr. Molofsky's Lab:


Melanie Ott [26]

We are interested in the chronic immune activation induced by persistent viral infections such as HIV and the link to chronic immune activation observed in autoimmune disease, specifically in type I diabetes. We focus on the protein deacetylase SIRT1 as an important regulator of T cell function and study its role in CD4+ effector T cells as well as regulatory T cells.

Other Research in Dr. Ott's Lab:

HIV and Viral Immunity [18]

Marion Peters [27]

The role of the immune system in biliary based inflammation and the importance of antigen location in immune responses in the liver. The laboratory has developed transgenic mice which express a foreign antigen on hepatocytes or biliary epithelium. These mice develop chronic active hepatitis or cholestatic liver disease after adoptive transfer of antigen specific CD4 and CD8 T cells (OT-I and OT-II). While antigen specific responses initiate disease, innate immune cells of the liver regulate the response. Our lab studies the role of antigen location, organ specific and innate immune cells as well as cytokines in the control of this inflammation.
Other Research in Dr. Peters's Lab:

HIV and Viral Immunity[18]

Jennifer Puck[28]

Jennifer Puck, MD, came to UCSF in 2006 as Professor of Pediatrics in the Division of Immunology and Rheumatology and Associate Program Director for Pediatrics in the CTSI Clinical Research Center. Dr. Puck's research is in human primary immunodeficiencies. Her scientific contributions include mapping and identification of the genes for X-linked severe combined immunodeficiency (XSCID) and autoimmune lymphoproliferative syndrome (ALPS); a clinical trial of retroviral gene therapy for patients with XSCID who failed bone marrow transplantation; and definition of the disease and gene defects in STAT3 in hyper-IgE syndrome, or Job's syndrome, a multisystem disorder. On the translational side, she has developed a test to screen all newborns for severe lymphocyte disorders and is planning a large pilot trial. Dr. Puck also uses mouse models to probe lymphocyte development and is investigating a new gene identified by her lab that when knocked out results in arrest of T cell development from common lymphoid precursors.

Other Research in Dr. Puck's Lab:


Will Seaman[29]

We have a long history of studying the mechanisms of autoimmunity and have recently returned to it with our studies of TIM-2, a receptor which we have shown to bind and endocytose H-ferritin, and whose expression we have demonstrated on activated B cells.

Other Research in Dr. Seaman's Lab:


Matthias Wabl[30]

We study three mouse models of autoimmune disease. The B/W mouse closely recapitulates human lupus. The Trex1-deficient mouse manifests autoimmune disease predominantly by heart failure, but most Trex1-deficient human patients suffer from Aicardi-Goutières syndrome (an inflammation of the brain) and lupus. The AID-deficient mouse suffers from autoimmune gastritis. In the first two types of mice, we have some evidence that endogenous retroelements are a cause for the autoimmune disease. For example, drugs that increase the cDNA concentration of retroelements exacerbate disease in B/W mice. On the other hand, the disease in mice deficient for the enzyme Trex1 (which degrades endogenous retroelements) can be ameliorated by transgenic human APOBEC3 enzymes, which also inhibit retroelements. Potentially important for therapy, drugs that inhibit reverse transcriptase
prevent the disease in the majority of mice.

In the third mouse model, we study an as yet mysterious function of the enzyme Activation-induced cytidine deaminase (AID) in innate immunity. AID is a DNA mutator that mediates switch recombination and hypermutation at the immunoglobulin loci. Curiously, AID-deficient patients and mice develop autoimmune or inflammatory disorders including lupus disease, diabetes mellitus, polyarthritis, autoimmune hepatitis, hemolytic anemia, immune thrombo--cyto-penia, Crohn's disease, chronic uveitis and autoimmune gastritis. Because we determined that AID also inhibits retrotransposon activity, these autoimmune diseases may be triggered in a manner analogous to the etiology of the autoimmune disease in Trex1 deficiency.

Other Research in Dr. Wabl's Lab:


Arthur Weiss [32]

We are studying the mechanism by which mutations that alter the expression or function of kinases and phosphatases can lead to autoimmunity, specifically in a mouse model of lupus. We are attempting to understand the pathogenesis of lupus using well defined genetic lesions and identifying genetic modifiers that influence the organ-specific involvement of the disease.

Other Research in Dr. Weiss's Lab:


David Wofsy [33]

Dr. Wofsy conducts clinical trials of biologic agents that have shown promise as novel therapies for autoimmune diseases, particularly systemic lupus erythematosus. At present, these trials involve the following agents: CTLA4Ig, anti-CD20, TACI-Ig, TNFR-Ig, and mycophenolate mofetil.

Find out more about Dr. Wofsy's research [33]

Julie Zikherman [34]

Systemic lupus erythematosus (SLE) is characterized by anti-nuclear autoantibodies (ANAs) produced by auto-reactive B cells that contribute to morbidity and mortality. Yet, how ANAs arise in disease and how they are normally controlled is not known. Even in healthy humans, 75% of newly generated B cells exhibit ANA reactivity. This autoreactivity is partially censored at a developmental checkpoint that is perturbed in patients with SLE. Our laboratory is taking advantage of a novel fluorescent reporter mouse line, Nur77-GFP, that identifies autoreactive
B cells with ANA specificity in a diverse, normal repertoire. By combining this reporter with genetic models of autoimmune disease, we hope to uncover how autoreactive B cells are selected and become aberrantly activated in these settings.

Other Research in Dr. Zikherman’s Lab: