Immunobiology and Lung Inflammation:

(Faculty: Arndt, Binstadt,* Hertz, Jenkins, Hogquist, Mansky, Mueller, Panoskaltsis-Mortari, Rao, Shimizu, Van Ness, Williams*)

Immunology is a long standing institutional strength of Minnesota. With the Center for Immunology we offer pre-doctoral and postdoctoral trainees broad opportunities to study fundamental mechanisms of B cell and T cell function and determinants of immune function. P. Sirimaramao, PhD, Professor of Veterinary Biology and Medicine adds specific expertise as a lung immunologist interested in asthma and inflammation.

Patrick Arndt, MD, Associate Professor of Medicine

Lung Neutrophil Recruitment & Signaling in Inflammation: My research focuses on the mechanisms regulating neutrophil recruitment to the lung after exposure to Toll-like receptor (TLR) agonists or to live bacteria. We examine the role of adaptor proteins, such as pro-myelocytic leukemia retinoic acid receptor α (PRAM) and adhesion- and degranulation-promoting adaptor protein (ADAP) whose roles in acute lung inflammation are not known. In collaborative studies I am examining the roles of the receptor interacting protein RIP140 and the sheddase ADAM17 that cleaves TNFα and IL-6 in their regulation of acute lung inflammation. These proteins may have unique effects on the regulation of pulmonary neutrophil recruitment and acute inflammation in the lung after exposure to bacteria or TLR agonists.

Bryce Binstadt, MD, PhD* ** Assistant Professor of Pediatrics, Division of Pediatric Rheumatology.

Mechanisms of Systemic Auto-Immunity. My laboratory in the Center for Immunology uses mouse models to study the pathogenesis of autoimmune diseases, with particular focus on defining mechanisms mediating cardiovascular inflammation in the context of systemic autoantibody-mediated disorders.

Marc Jenkins, Ph.D., Distinguished McKnight Professor, Microbiology, Director, Center for Immunology

Molecular Regulation of T Cell Activation In Vivo: We investigate CD4+ helper T and B cell activation in vivo with direct tracking of antigen-specific cells. Using gene-targeted recipients or antibody blocking approaches, we identify molecules that are critical for in vivo T and B cell signal transduction, proliferation, lymphokine production, survival, and differentiation. The goal is to achieve a basic understanding of these processes so that they can be manipulated to improve vaccines and prevent autoimmunity.

Marshall Hertz, M.D., Professor of Medicine, Director, Center for Lung Science & Health

Molecular Basis of Obliterative Bronchiolitis and Acute Rejection after Lung Transplant: We use genomic analysis of human samples from lung transplant patients to identify patterns of gene activation and/or repression involved in the development of obliterative bronchiolitis and other complications.

Kristin Hogquist, PhD,* Professor of Laboratory Medicine and Pathology

T Cell Functions. My lab is interested in CD8 T cell development and function. We study how thymic selection processes shape the T cell repertoire to achieve a highly effective and self-tolerant adaptive immune system. Current research is focused on positive and negative selection, and the human immune response to Epstein Barr Virus (EBV).

Louis Mansky, PhD, Professor, Dentistry & Microbiology; Director, Molecular Virology Institute

Cell and Molecular Biology of HIV and HTLV; My lab uses cell and molecular biology approaches to study HIV and HTLV replication. We are interested in how reverse transcriptase and cellular proteins (eg, APOBEC3 proteins) influence HIV genetic variation, evolution, and drug resistance. We are particularly interested in HIV replication in non-dividing cells, including alveolar macrophages. We also study the mechanisms of HTLV Gag trafficking and virus particle assembly, using biophysical approaches.
Daniel Mueller, M.D., Professor of Medicine, Director, Rheumatology Division

**Molecular Basis of Immune Tolerance:** My laboratory investigates the regulation of growth and effector functions in T cells. We study the control of these events by the self-tolerance mechanism known as clonal anergy, a key issue in allograft survival after transplantation. We are working to establish both the normal regulation of the IL-2 gene during antigen stimulation, and the nature of the IL-2 expression-defect that develops in anergic T cells.

Angela Panoskaltsis-Mortari, Ph.D, Associate Professor of Pediatrics & Medicine

**Lung Regeneration & Bioengineering:** My lab is bioengineering human lungs for transplant using decellularized cadaver or pig lung as matrix and seeding it with patient derived stem cells and endothelial cells. Within this project is the study of the role of matrix in directing stem cell behavior. One of my T32 trainees is using decellularized lung matrix from normal and fibrotic lungs as well as lungs of different ages to evaluate differentiation of alveolar cells and iPS cells to lung cells. I also study the biology of bone marrow transplant-related lung injury and therapeutic interventions and cell therapies for the early and late forms of injury, idiopathic pneumonia syndrome and obliterative bronchiolitis, respectively.

P. Sriramarao, PhD. Professor of Animal Science & Medicine; Associate Dean for Research

**Mechanisms of Leukocyte & Eosinophil Trafficking in Asthma and Allergic Airway Inflammation:** We study eosinophil generation, trafficking and recruitment to sites of inflammation using intravital imaging techniques we have developed. We examine the modulation of Th1/Th2 cytokines, role of adhesion molecules, carbohydrate binding proteins and carbohydrate processing enzymes, cytokines and chemokines mediating leukocyte-endothelial trafficking in the lung and pulmonary microcirculation, immune modulation and associated signal transduction events in models of airway allergic disease.

Yoji Shimizu, Ph.D. , Professor of Lab Medicine & Pathology, Director, MSTP Program

**Integrin Signaling in Lymphocytes:** Our research focuses on the critical roles that cell adhesion and migration play in human T cell activation and differentiation. We work towards elucidating intracellular signaling events that regulate adhesive interactions that allow the immune system to respond to pathogens, using this information to develop novel therapies for the treatment of cancer and other diseases.

Brian Van Ness, Ph.D. Professor of Genetics, Cell Biology & Development

**Regulation of Immunoglobulin Gene Expression:** My research is directed at defining genetic deregulation that contributes to lymphoid malignancies, particularly multiple myeloma. The difficulty in treating myeloma comes in part from the variability in genetic and signaling pathways that are deregulated in the plasma cells and the cells in the bone marrow microenvironment. Using both cell lines and mouse models we explore how different genes can influence disease progression and therapeutic response, particularly mechanisms leading to emerging drug resistance. We also use ovel informatic and computational approaches with large genotype data sets to define disease risk in lymphoid cancer as well as lung cancers. Targeted genotyping is also being developed for a wide array of pharmacogenomic associations with response, resistance and toxicities of drugs, with the ultimate goal of genetic characterization of patients that will direct individualized therapy.

Bryan Williams, MD, PhD,* ** Assistant Professor of Medicine and Microbiology

**Host-pathogen interactions in the CF lung.** My research seeks to better understand the host response to bacterial metabolism found in the infectious milieu of the CF lung. I discovered a bacterial metabolite in *P. aeruginosa* (agmatine) that may be involved in directly stimulating the immune system of the lung. Some of these same metabolites are also made by lung immune cells, and may in turn affect the bacteria. This interdisciplinary project involves basic microbiology and biochemistry, as well as lung immunology and physiology. This research should identify potential therapeutic modalities targeted at both anti-microbial and immunomodulatory effects.