Immunology at UAB
Immunology at UAB: a long tradition of excellence

• Claude Bennett
  – Dreyer and Bennett, Two genes one polypeptide hypothesis to explain antibody diversity
  – Former Microbiology Chair
  – Former UAB President
  – Current CEO at local Biotech firm

• Max Cooper
  – B and T cells as two separate antigen recognition systems
  – Immune recognition by jawless fish: lamprey and hagfish
Partners for Training Opportunities

The UAB Immunology Training Program
Immunologists from A-Z!

William W. Andrews, MD - Clinical/Translational
T Prescott Atkinson, MD, PhD - Allergy, Clinical/Translational, Immunology
Scott Barnum, PhD - Autoimmunity, Inflammation, Neuroimmunology
Khurram Bashir, MD - Clinical/Translational
Etty (Tika) Benveniste, PhD - Neuroimmunology
J. Edwin Blalock, PhD - Allergy, Developmental Immunology, Immunogenetics
Suresh Boppana, MD - Clinical/Translational, Neuroimmunology
Louis Bridges, MD, PhD - Clinical/Translational, Immunogenetics
David E. Briles, PhD - Host Defense
Elizabeth Brown, PhD, MPH - Autoimmunity, Immunogenetics
Donald J. Buchsbaum, PhD - Cancer Immunology, Clinical/Translational
P. Pat Bucy, MD, PhD - Clinical/Translational, Developmental Immunology
Daniel C. Bullard, PhD - Inflammation
Peter D. Burrows, PhD - Developmental Immunology, Immunogenetics
David D. Chaplin, MD, PhD - Developmental Immunology, Inflammation
Noel K. Childers, DDS, PhD - Clinical/Translational, Microbial Immunology
James Collawn, PhD - Microbial Immunology
Yingzi Cong, PhD - Autoimmunity, Clinical/Translational, Immunogenetics
David T. Curiel, MD, PhD - Clinical/Translational
Randall S. Davis, MD - Developmental Immunology, Immunogenetics
Jeffrey Edberg, MD - Clinical/Translational
Craig A. Elmets, MD - Clinical/Translational
Charles O. Elson III, MD - Clinical/Translational, Immunology, Microbial Immunology
David O. Freedman, MD - Clinical/Translational
Kohtarou Fujishashi, DDS, PhD - Microbial Immunology
James F. George, PhD - Transplantation Immunology
Vithal K. Ghanta, PhD - Cancer Immunology
Paul Goepfert, MD Goepfert, MD - Cancer Immunology
Beatrice Hahn, MD - Clinical/Translational, Host Defense, Immunogenetics
Laurie E. Harrington, PhD - Zdenek Hel, PhD - Susan Hollingshead, PhD - Host Defense, Immunogenetics
Hui-Chen Hsu, PhD - Host Defense
Louis Justement, PhD - Developmental Immunology
Judith A. Kapp, PhD - Transplantation Immunology
Richard A. Kaslow, MD - Clinical/Translational, Immunogenetics
John F. Kearney, PhD - Developmental Immunology
Robert Kimberly MD - Clinical/Translational, Inflammation
Christopher Klug, PhD - Cancer Immunology
Hiromi Kubagawa, MD - Developmental Immunology, Host Defense
Richard D. Lopez, MD - Host Defense
Robin G. Lorenz, MD, PhD - Cancer Immunology, Inflammation, Microbial Immunology
Sadis Matalon, PhD - Host Defense
Jiri Mestecky, MD, PhD - Clinical/Translational
Suzanne M. Michalek, PhD - Host Defense, Inflammation, Microbial Immunology
John Mountz, MD, PhD - Autoimmunity, Clinical/Translational
Moon Hahn, MD - Host Defense
Jan Novak, PhD - Autoimmunity
Hongwei Qin, PhD - Paghan Rui, PhD - Chander Raman, PhD - Autoimmunity
David A. Randolph, MD, PhD - Clinical/Translational, Developmental Immunology
Russell W. Read, MD - Harry Schroeder, MD, PhD - Clinical/Translational, Developmental Immunology, Immunogenetics
Lisa Schwiebert, PhD - Allergy, Inflammation
Chad Steele, PhD - Host Defense, Immunogenetics
Alexander Szalai, PhD - Host Defense, Immunogenetics
Jannning (James) Tang, PhD - Immunogenetics
Laura Timares, PhD - Developmental Immunology
Hubert Tse, PhD - Autoimmunity
Mark R. Walter, PhD - Developmental Immunology, Neuroimmunology
Casey Weaver, MD - Developmental Immunology
Douglas A. Weigent, PhD - Neuroimmunology
Jannning (James) Wu, DVM, PhD - Autoimmunity
Hui Xu, PhD - Janet Yother, PhD - Host Defense
Habiha Yusuf, PhD - Allan Zajic, PhD - Host Defense
Huang-Ge Zhang, DVM, MD, PhD - Clinical/Translational
Tong Zhou, MD - Clinical/Translational
About the Program in Immunology

The multi-disciplinary Program in Immunology consists of over 100 UAB Faculty who identify themselves as basic or clinical immunologists and are members of multiple units at UAB. A desire for excellence on the part of the UAB faculty, coupled with the relative youth of the institution, has promoted a collective attitude of interdepartmental cooperation and collegiality.

With over $45M in FY 2008 from the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Arthritis, Musculoskeletal, and Skin Diseases (NIAMS), the two NIH funding agencies most focused on host defense, immunology, and inflammation research, this represented about 25% of the entire NIH research portfolio at UAB.

UAB is the home of several internationally prominent research programs, e.g., Developmental Immunology, Mucosal Immunology, Clinical Immunology and Rheumatology Division, Arthritis and Musculoskeletal Center, Host Defense, Virology and Vaccine Biology. Newer programs in Cancer Immunology, Allergy, Immunogenetics, Inflammation and Tissue Injury, Transplantation Immunology, Neuroimmunology, and Basic Immunology of the T cell and innate systems are poised to become highly competitive.

For a brief history of the Program in Immunology at UAB, written by Dr. Claude Bennett, please click here.

Mission and Goals

The Program in Immunology was created to enhance the wide distribution of immunology-related research at UAB. This trans-departmental program seeks to enhance communication among faculty in order to identify and stimulate additional synergies across campus. The main goals of the program are to:

- Facilitate research through coordination and collaboration
- Establish a committed Program Administration that broadly represents participating Departments and Centers to implement cross-cutting activities
- Enhance state-of-the-art technologies, including model systems, imaging, and cell therapeutics
- Advance the translational research capacity, including pre- and post-doctoral training improvements
- Establish a graduate training program in Immunology.
The UAB Program in Immunology

A Multi-Departmental Initiative Involving Students, Fellows and Faculty Campus-Wide

Sponsors a seminar series hosting speakers pursuing cutting edge immunology

http://immunology.dom.uab.edu/
UAB Core Facilities

Specialized Research Facilities

- Animal Resources Program
- Biomedical Informatics
- Biostatistics and Informatics Shared Facility
- Brain Tumor Tissue Core Facility
- Brain Tumor Animal Models Core Facility
- High Resolution Imaging Shared Facility
- Cell Senescence Culture Facility
- Cell Therapy Laboratory
- Center for AIDS Research DNA Sequencing and Analysis Core
- Center for AIDS Research Flow Cytometry Core
- Center for AIDS Research Virology & Molecular Biology Core
- Comparative Pathology Laboratory
- Epitope Recognition Immunoreagent Core
- Fermentation Facility
- Arthritis & Musculoskeletal Center Analytic Preparation Cytometry Facility
- Gammacell 40 Irradiation Facility
- Genomics Core
- Laboratory for Multi-Modality Imaging Assessment and Small Animal Imaging Core
- Laser Capture Microdissection Laboratory
- Leukocyte/Endothelial Cell Adhesion Molecule) Mutant Mouse Resource
- Mass Spectrometry and Proteomics Shared Facility
- Molecular and Genetic Bioinformatics Facility
- Nuclear Magnetic Resonance (NMR) Shared Facility
- Peptide Synthesis Core Facility
- In Vivo Physiology & Phenotyping
- Transgenic Mouse Facility (TMF)
- X-Ray Crystallography Shared Facility
Peter Burrows, Ph.D.
Dept. of Microbiology

B-cells
Fc Receptors
**Expression and Function of FcRLA, an Fc receptor related intracellular protein**

**Teresa C. Santiago, Linda M. Hendershot and Peter D. Burrows**

- **Partial Ig domain**
- **Ig domain**
- **Mucin-like domain**

**FcRLA**

- **D1**
- **D2**
- **D3**
- **D4**

**FcRLA** is expressed by normal peripheral blood B cells.

- **FcRLA (Alexa 488)**
- **PNA (Alexa 555)**
- **IgD (Alexa 647)**

**FcRLA** is enriched in tonsil germinal centers.

**FcRLA** binds intracellular IgM in Ramos B cells.

**FcRLA** associates with IgG in the IM9 cell line.

**Expression of IgM and FcRLA in HEK 293 transfected cells**

**Analysis of FcRLA (MGC4595) expression by Lymphochip microarray**

- **CD5+/CD19+**
- **CD5+/CD19-**

**N = 40**

**P = 0.02 unpaired T test**

- **Anti-Human FcRLA**
- **Anti-Human cIgM**

**PNA (Alexa 555)**

**IgD (Alexa 647)**

**Antibodies against FcRLA**

- **+mIgM +sIgM +FcRLA**
- **+mIgM +FcRLA +sIgM +FcRLA**
- **+mIgM +sIgM +FcRLA**

**Expression of IgM and FcRLA in HEK 293 transfected cells**

- **HEK 293 transfected cells**

**B-CLL**
Randy Cron, M.D., Ph.D.
Dept. of Pediatrics

Autoimmunity – Pediatric Rheumatology
Transcription Factors
HIV
CD154 Dysregulation in Systemic Lupus

- NFAT2
- STAT5

CD4 T Cell Host Transcription Factors Exploited by HIV-1

- FoxP3
- NFAT2
- c-Maf
Tara DaSilva, Ph.D.
Dept of Physical Medicine and Rehabilitation
Neuroimmunology
Multiple Sclerosis
DaSilva - Neuroimmunology of Multiple Sclerosis

I. How does inflammation lead to myelin destruction?

- **Cytokine secretion**
  - Th1: IFN-\(\gamma\)
  - Th17: IL-17A, IL-17F

- **Microglia activation**
  - IFN-\(\gamma\)

- **Myelin destruction**

- **Treatment**
  - IFN\(\beta\)
  - unknown

II. What factors promote remyelination?

- **Proliferation**
  - Oligodendrocyte Progenitor Cell

- **Failure to remyelinate**
  - Oligodendrocyte Precursors
  - Immature Oligodendrocyte
  - Mature Oligodendrocyte
Charles Elson, M.D., Ph.D.
Dept. of Medicine

Autoimmunity – Crohn’s Disease
Th cell populations
Elson Lab Recent Projects

• The homeostatic CD4 T cell response to microbiota antigens in the intestine using T cell receptor transgenic and cytokine reporter mouse lines

• Identification of microbiota antigens that stimulate pathogenic T cell responses in IBD in mice and humans

• Development of assays for microbiota antigen-specific T cell responses in human IBD

• Application of a microbiota antigen microarray to probe the adaptive immune response in human populations with immune-mediated diseases
A dominant, coordinated T regulatory cell-IgA response to the intestinal microbiota

[Cong, et.al., Proc Natl Acad Sci USA, 2009]
Lou Justement, Ph.D.

Dept. of Microbiology

B-Cells

Lymphocyte Signaling
Analysis of Molecular and Biochemical Processes that Regulate Immune Cell Biology

CURRENT PROJECTS

1. Analysis of the Functional Role that the Adaptor Protein HSH2 Plays in Regulating B Cell Class Switching and Terminal Differentiation
2. Analysis of the Role that HSH2 Plays in Regulating T Cell Differentiation into Effector Populations
3. Examination of the Role that the Transmembrane Receptor TLT2 Plays in Modulating the Response of Innate and Adaptive Immune Cells to Agonists that Signal via G Protein-Coupled Receptors
4. Analysis of the Cell:Cell Interactions that are Critical for Development and Maintenance of the Marginal Zone
5. Analysis of Cell:Cell Interactions that are Critical for Initiation and Progression of the Germinal Center Response

EXPERIMENTAL APPROACHES:
• Gene targeted mouse models, including knockout, knockin and transgenic mice
• High throughput systems, including gene array, bioplex, mass spectrometry and kinomic assays
• Disease models, including infectious, autoimmune, acute and chronic inflammatory, and asthma
• Organisms studied include human and mouse
• Cell types examined include all B cell subpopulations, T cell effector populations, neutrophils, and monocyte/macrophages
• Experimental assays include, biochemical (e.g. kinase and phosphatase analysis, Ca2+ mobilization, ROS production, protein:protein interactions), and functional (e.g. chemotaxis, Ab production, cytokine/chemokine production)

Contact: Lou Justement
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RECENT PUBLICATIONS:
Modulation of Allergic Asthma and Type One diabetes by B cells and Antibodies

John F Kearney

University of Alabama at Birmingham
Dept of Microbiology
Asthma and Type I diabetes are increasing in the Western world. Lack of immune stimulation during development leads to inappropriate responses to harmless organisms later in life. Many bacteria and allergen-bearing microorganisms share common epitopes.

Our hypothesis is that germ-line encoded innate-like antibodies against bacterial components compete with innate receptors and inhibit sensitization to the allergenic cargo in the case of Asthma and prevent autosensitization to pancreatic β cell autoantigens in Type 1 diabetes.

The models for these diseases use an array of anti-idiotype reagents, transgenic and heavy chain knockin mice established in our laboratory with specificity for antigens expressed by *A. fumigatum* such as chitin, α1-3 glucans and sialylacto-N-tetraose, and also by Group A and B Streptococci and Enterobacter. In addition we have an Af3.16 αβ T cell receptor transgenic mouse reactive with *A.fumigatus*. 
Robert Kimberly, MD
Dept. of Medicine

Autoimmunity – SLE
Fc Receptors – Genetics to Biology
Neutrophils
Molecular and cellular biology of Fc receptor function

1. The premise of this work is that each of the human Fc receptors for antibody is “specialized” despite binding shared ligands and that understanding the nature and mechanism of this specialization will provide the basis for selective targeting. Some ‘specialization’ comes from the ligand binding ectodomain (which class and subclass of antibody does the receptor bind), but more importantly, the unique cytoplasmic domains (apart from the association gamma chain) provide the scaffold for machinery to enhance antigen presentation, or degranulation, or inhibition of tyrosine signaling, or PKC regulation etc. (see Model Figure v4jpg).

The genetic architecture of human autoimmune disease, with an emphasis on SLE and systemic vasculitis

1. Many autoimmune diseases express themselves in family clusters, supporting the notion that there are genetic contributions to disease susceptibility. The sibling risk (lambda s, or risk that a sib will get the disease given a sib with the disease) for SLE is 30, -- meaning that the sib of an affected individual is 30x that of the normal population risk. We are major participants in both national and international consortia to define genetic variants contributing to disease risk, and the major opportunity is now to define the biology of the different variants, -- ie, the functional immunology of each of the contributing variants. (see P01 Figure 2.jpg for schema)

The biology of ANCA-associated vasculitides

1. Anti-neutrophil cytoplasmic antibodies target granule contents typically found in myeloid series cells. Granules are translocated to the cell surface and displayed like cell surface molecules. The granule contents can also be displayed on neutrophil NETs. On the cell surface, the target antigens bind antibody which in turn can activate cells, stimulate pro-inflammatory programs and lead to vessel and tissue injury. Innovations in these mechanisms, including novel genetic variants, are an important focus of research (see attached).
John Mountz, Ph.D.
Dept of Medicine

Autoimmunity – SLE
B-Cells
Death Pathways
Immunology of Ageing
Project 1 - IL-17 regulated spontaneous germinal centers (GC) in autoimmune BXD2 mice that develop both lupus and arthritis.

**GC**: germinal center
**DZ**: dark zone
**LZ**: light zone

- **IL-17**
- **IL-17-RA**
- **CXCL12/CXCL13**
- **CXCR4**
- **CXCR5**
- **NF-κB Pathway**
- **TRAF6**
- **ACT1**
- **CD4**
- **B220**
- **IL17**
- **RGS13**
- **RGS16**
- **Mountz Lab at UAB**
Project 2 – Determination of the therapeutic safety and efficacy of TRA-8, an anti-hDR5 antibody, for rheumatoid arthritis

Generation of hu/mo chimeric DR5 Tg mice
Induction of arthritis
Non-invasive molecular live imaging of joint damages

Treatment with TRA-8
Control
TRA-8 treated

Death

Human DR5 Mouse DR5 Chimeric DR5

Mountz Lab at UAB
Project 3 - Studies of T cell senescence in centenarians (Aged)

Mountz Lab at UAB

- Leptin
- Metabolic syndrome
  - obesity
- Fat, other
- Thymic output
- Leptin
  - Metabolic syndrome
    - obesity
- Increased inflammatory cytokines, TLR
- Thymic output
- Naive T
- Non-specific development/activation
- Specific appropriate activation

Thymus
- Stress
- Infection
- Chronic inflammation
- Naive Recent Emigrant
- Mainly Central or Effector Memory
- Stress
- Infection
- Chronic inflammation
- Terminally Differentiated

CD95
- Induce
- Inhibit

Macrophage, DCs, pDCs
- Increased inflammatory cytokines, TLR

Mountz Lab at UAB
Pathogenesis of IgA nephropathy: role of glycans

Jan Novak, Department of Microbiology

IgA nephropathy, most common primary glomerulonephritis in the world, is an autoimmune disease:

- Circulating **immune complexes** deposit in mesangium and **stimulate mesangial cells** to proliferate and secrete extracellular matrix proteins and cytokines/chemokines, leading to glomerular injury;
- IgA1 with galactose-deficient O-linked glycans in the hinge region is **autoantigen**;
- IgG or IgA1 antibodies recognize this neoantigen, resulting in the formation of **immune complexes** in the circulation.

**Current and future studies:**
- Genetics and biochemistry of aberrant IgA1 glycosylation
- Molecular mechanisms of pathogenesis of IgA1-containing immune complexes
- Structure and function of anti-glycan antibodies
- Analysis of O-glycans by high-resolution mass spectrometry
- Proteomic biomarkers of IgA nephropathy
- Development of new animal model of IgA nephropathy
- IgA1-mediated signaling in mesangial cells

**Selected publications:**
- *J. Biol. Chem.* 280, 19136-19145, 2005

IgA1 glomerular deposits in IgA nephropathy
Differential glycosylation of HIV-1 gp120 affects antibody recognition

Jan Novak, Department of Microbiology

- HIV-1 entry is mediated by the interaction between a variably glycosylated envelope glycoprotein (Env, composed of gp120 and gp41) and host-cell receptors.
- HIV-1 gp120 DNA was cloned in a vector driving its oligomerization in the absence of gp41 subunit and was expressed in various cell lines.
- gp120 glycosylation was dependent on cell line used for its production, and also was affected by metabolic manipulations. Changes included different proportion of high-mannose vs. complex glycans and their specific structures.
- This differential glycosylation affected binding of antibodies, including serum antibodies from HIV-1-infected individuals and glycan-specific and V3 loop-specific monoclonal antibodies.

Current and future studies:
- Cell-specific glycosylation of gp120
- Glycan-dependent antibody recognition
- Analysis of gp120 glycans by high-resolution mass spectrometry
- Glycosylation-dependent cell entry

Selected publications:
- J. Biol. Chem. 285, 20860-20869, 2010
Chander Raman, Ph.D.
Dept. of Medicine

Autoimmunity
- Multiple Sclerosis and SLE
Th populations
B-cells
Dendritic Cells

Raman LAB – Overall Research Focus

Innate (dendritic cells) and adaptive immune effector (T-cell and B-cells) populations in the immunopathogenesis of autoimmunity: Mechanisms of activation, differentiation and tolerance

Recent Publications:


Raman Lab – Research Projects

- Immunopathogenesis and therapy of Multiple Sclerosis
  - Regulation of T-lymphocyte activation, differentiation and persistence (Th1, Th17, natural and induced Treg cells) by co-receptors (CD5), adaptor molecules (SH3bp5L) and interferons (IFN-β and IFN-γ). *(Partly funded by a grant from the National Multiple Sclerosis Society)*
  - Role of B-cell in pathogenesis and regulation of multiple sclerosis (B-1a B-cells and B10 B-cells)
  - Role of glycogen synthase kinase 3 (GSK3) in regulating inflammation in multiple sclerosis *(funded by a NIH RO1 grant)*.
  - Cooperative activities if type 1 interferon (IFN-β) and type 2 interferon (IFN-γ) in therapy and immunopathogenesis of multiple sclerosis.
  - CD5 regulation of B-1a B-cell development and activation in systemic lupus erythematosus *(funded by a NIH ROI grant)*.
  - CD5 regulation of dendritic cells in immune tolerance and contact hypersensitivity *(funded by a new NIH-R21 grant)*.
Harry Schroeder, M.D., Ph.D.
Dept. of Medicine

B-cells
Autoimmunity
HIV Immunonolgy
The amino acid content of CDR-H3 is the product of both germline selection of $D_H$ sequence and somatic selection.

CDR-H3, the most diverse component of the antigen binding site, lies at its center.

**Distribution of amino acids in CDR-H3’s from bone marrow mature B cells**

[Graph showing amino acid distribution]
We are determining the extent to which B cell development and humoral immune responses depend on proper control of CDR-H3

The spectrum of CDR-H3 diversity is altered by changing the sequence of D<sub>H</sub>

- This allows:
  - Progression through normal checkpoints of B cell development
  - Access to all V<sub>H</sub>, J<sub>H</sub>, as well as κ & λ LC
  - Class switching to all isotypes
  - Somatic hypermutation
- We create mice expressing a polyclonal antibody repertoire with a skewed gradient of D<sub>H</sub> dependent CDR-H3 diversity
- These mice allows testing of the role of CDR-H3 control on adaptive immunity
  - B cell development
  - Susceptibility to autoimmune disease (SLE)
  - Protection against infection (HIV, influenza)

Laboratory of Harry W Schroeder Jr MD PhD

James Tang, Ph.D.
Dept. of Medicine

T-Cell Immunity
HIV Pathogenesis/Immunity
Program in Epidemiology of Infection and Immunity (PEII)

Program Director
• Richard A. Kaslow, MD, MPH
  • rkaslow@uab.edu

Laboratory Director
• Jianming “James” Tang, PhD
  • jtang@uab.edu

Objective
• Immunogenetics & pharmacogenetics

Track record
• >40 publications since 1996, when PEII was established
Ongoing Projects: Tang

- K02 project (NIAID)
  - 2007-2012: Cytokines and HIV/AIDS.
- R03 project (NCI)
  - 2007-2010: HLA and brain cancer
- Others (collaborative projects with Kaslow)
  - 2008-2013: Genetics and heterosexual HIV-1 transmission
  - 2005-2015: HIV-1 immune escape mutations
  - 2005-2015: biodefense (immune responses to anthrax vaccine)
  - 2005-2010: HIV-related malignancies
Tang - Close Interactions with Other ID Faculty

- Paul A. Goepfert & Sonya Heath
  - T-cell activation
  - HIV-1 CTL mapping and escape
- William Geisler
  - Immunity to genital chlamydia infection
- Scott Parker
  - Biodefense (antibody response to vaccination)
Laura Timares, Ph.D.

Langerhan Cells
Dendritic ells
Laura Timares – Modulation of Cutaneous Dendritic Cells for Vaccines

CUTANEOUS DENDRITIC CELLS of THE SKIN

- Stratum corneum
- Epidermis
- basement membrane
- Dermis

Langerhans Cell (immature DC)
Lymphatic
Dermal DC
Interdigitating DCs (mature DC)
Apoptotic LC
Dressing

Stress / Injury
Wound
Infection
Tumor
Contact
Sensitization

Activated Migratory Langerhans Cell
Veiled cell (migratory DC)

T cells
Draining lymph node
Hubert Tse, Ph.D.
Dept of Microbiology
Autoimmunity – Type I Diabetes
Characterize the synergistic effect of reactive oxygen species and innate immune-derived pro-inflammatory cytokines as it pertains to T cell autoreactivity in the Non-Obese Diabetic (NOD) mouse model of Type 1 Diabetes.

Determine how the absence of superoxide synthesis in the NOD.\textit{Ncf1}^{m1J}\ mouse correlates to Type 1 Diabetes resistance.
- Resistance at the level of inefficient T cell adaptive immune maturation or absence of innate immune effector molecules that directly destroy pancreatic $\beta$ cells?

Synergism of Innate Immune-derived signals for Efficient Adaptive Immune Maturation.
- Analyze TLR Signaling Pathways (TLR2, 3, 4, and 9) in NOD and NOD.\textit{Ncf1}^{m1J}\ macrophages and dendritic cells after TLR-agonist (HKLM, poly I:C, LPS, CpG) stimulation, are there defects in ROS-dependent innate immune signals that prevent autoreactive T cell maturation and subsequently, result in T1D protection in NOD.\textit{Ncf1}^{m1J}\ mice?

Examine the role of reactive oxygen species synthesis in Th17 T cell plasticity and differentiation.
Immuneopathophysiology of Type 1 Diabetes

**Autoantigen**

- Dendritic cell/APC
  - DR3, DR4, DQ8/autoantigen
  - CD8\(^+\) CTL
  - CD4\(^+\) Cell (TH2)
  - CD40L
  - B Cell

**Activated TH1 CD4\(^+\) T Cell**

- IL-12
  - CD4\(^+\) Cell (TH0)
  - IFN-\(\gamma\)
  - FasL perforin

**Activated Macrophage/dendritic cell**

- IL-1, TNF, LT, NO, \(O_2^-\), PGE\(_2\)

**β cell death**

- Chess 2002

**β islet cells**

- Antibody mediated injury
Mark Walter, Ph.D.
Dept of Microbiology

Protein Crystallography
Cytokines/Cytokine Receptors
CRYSTAL STRUCTURE ANALYSIS OF CELL SIGNALING COMPLEXES
Mark R Walter, Ph.D.

Yoon et al. STRUCTURE 18, 638-648
CRYSTAL STRUCTURE ANALYSIS OF VIRAL CYTOKINE ANTAGONISTS

Mark R. Walter, Ph.D.

Nuara et al. PNAS 105, 1861-1866
Casey Weaver, M.D., Ph.D.
Dept. Pathology
T-Cells
Autoimmunity – Crohn’s Disease
Major Research Themes/Opportunities

• Define mechanisms that control CD4 T cell developmental decisions and fates through engineering of novel transgenic and targeted mutant mice.
• Define mechanisms that contribute to developmental plasticity in the Th17 lineage, and how divergent Th17 subtypes contribute to autoimmune disease.
• Dissect molecular mechanisms by which important immune genes are regulated; development of novel transgenic models for mapping function of cis-elements.
Recent Publications - Weaver Lab


• Lee et al. Late Developmental Plasticity in the T helper (Th) 17 Lineage. *Immunity* 30:92-107, 2009.

