Programmatic Area:
Integrative Physiology of Diabetes and Obesity
Examples of Preclinical Topic Areas shared by more than one group

- Nutrient signaling - obesity/diabetes
- Ingestive Behavior and Taste
- Gastric bypass surgery – mechanisms
- Protein turnover / mTOR / eIF-2 kinases
- Insulin and IGF signaling
- Inflammation
- Exercise – Inactivity research
- Diabetes complications
- Atypical antipsychotics- metabolic side effects
Example Preclinical Obesity Research Resources

- Seahorse System
- 2 H1 NMR minispects for rat and mice body composition
- Animal DEXA scan
- High def H1 MRI animal imaging at both campuses
- 2 CLAMS systems (TSE and Columbus Instr) mice
- CLAMS for rats (CI)
- Automated feeding cages (rats)
- Minimitter system
- Telemetric monitoring of body function and SNS

- Bariatric surgeries in rats
- Levin rat & NONcNZO10/LtJ (RCS10) obesity models
- Mouse CAT scan
- Xenogen mouse imaging system
- Electrophysiological monitoring of SNS, ingestive behavior and taste
- Multiple Bead array and other systems for hormone multiplexing
Selected Preclinical Obesity Researchers*

*Exercise/inactivity and diabetes complications underrepresented in this listing
Alaa S. Awad, M.D., FASN
College of Medicine – Dept of Medicine
E-mail: aawad@hmc.psu.edu

Areas of research:
• Inflammation in diabetic nephropathy.
• Podocyte microenvironment.
• Podocyte/macrophage interaction.
• Arginase 2 in Diabetic Nephropathy.

Areas/models/techniques/unique resources:
• Diabetic nephropathy rat and mouse model.
• Immunology of DN (CD11b Cre, CD11b Cre/DTA, CD11c Cre, TNF-α flox, CD11b Cre/TNF-α flox, CCR2 KO).
• Macrophage differentiation in vitro (M0, M1 and M2 macrophages) & migration.
• Endothelial function in DN (Arginase 2 KO mice, glomerular endothelial cells).
• Podocytes (cell line, in vitro permeability assay).

Areas where collaboration would help:
• Pre-clinical drug development in diabetic nephropathy.
Kirsteen N Browning, PhD
College of Medicine
Department of Neural and Behavioral Science
Phone: 717 531 8267
Email: knb13@psu.edu

Current Research Focus
Our laboratory focuses on vago-vagal reflex control of subdiaphragmatic viscera, particularly the gastrointestinal tract and pancreas. Our research is focused particularly on vagal afferent (sensory) neural plasticity and receptor trafficking mechanisms.

Experimental Approaches
In vitro electrophysiology (brainstem slices and acutely dissociated culture)
In vivo recordings of gastric motility and tone
Immunohistochemistry

Areas of Collaboration needed
Molecular approaches to measure changes in neuronal protein, receptor or gene expression levels
Re-organization of neuronal inputs
Douglas R. Cavener
Professor and Head of Biology
Penn State – University Park
email: drc9@psu.edu

• **Interests / Models**
  – Regulation of proinsulin synthesis and trafficking in beta cells
  – Monogenic neonatal diabetes
  – Regulation of glucose and fat metabolism mediated by translational control of gene expression (e.g., EIF2 kinases: PERK GCN2 etc…)
  – Mouse genetic models of diabetes and obesity

• **Currents needs to improve of our research capabilities**
  – Rodent and human islet biology core lab
  – Experts in islet biology
  – Mouse metabolic phenotype core support for Hershey/UP campuses
  – High throughput and inexpensive insulin assays.
  – Metabolomics and genomics related to diabetes and obesity
  – Collaborators investigating human variation underlying monogenic, type 1 and type 2 diabetes and obesity
Rebecca Corwin
Department of Nutritional Sciences
Penn State – University Park
e-mail: rxc13@psu.edu

Known for:
• rat model of binge-type eating

What we are doing:
• Studying the neurobiology of binge-type eating using our model

Areas/models/techniques available for collaboration:
• Brains from rat model
• Behavior: operant, home cage
• Neuronal techniques: stereotaxic surgery, tissue site infusions

Areas where collaboration would be helpful:
• IHC, neuronal tracing, in situ hybridization (we could send you brains!)
• Microdialysis expertise?
Andras Hajnal, M.D. Ph.D.
Neural & Behavioral Sciences and Surgery
PSU College of Medicine
e-mail: ahajnal@psu.edu

Areas of research:
- Interaction between metabolic states, hormones, orosensory factors and central dopamine functions
- Neural regulation of meal size and food preferences during the development of obesity/diabetes
- Central taste and motivational processes in obesity
- Effects of gastric bypass surgery on taste and food reward functions in animal models of obesity

Areas/models/techniques available for collaboration:
- Chronic Microdialysis for Sampling Transmitters and Recording Neuronal Activity During Feeding, Oral and Postoral Stimulations in Obese and Weight-Reduced Rats
- Gastric bypass surgeries, OLEFT rats, Levin model

Areas where collaboration would be helpful:
- Genomics, microarray-based approaches for neural specific genes;
- PET imaging in human and rodents;
- Molecular imaging and chemical sensors for chronic transmitter monitoring in the brain.
From Dr Hajnal: Chronic Microdialysis for Sampling Transmitters and Recording Neuronal Activity During Feeding, Oral and Postoral Stimulation in Obese and Weight-Reduced Rats
Leonard S. (Jim) Jefferson
Evan Pugh Professor and Chair
Cellular and Molecular Physiology
Penn State – Hershey
email: Jjefferson@psu.edu

Scot R. Kimball
Professor
Cellular and Molecular Physiology
Penn State – Hershey
email: skimball@psu.edu

Areas of research:

- Signaling pathways and molecular mechanism of skeletal muscle hypertrophy and atrophy
- Nutritional and hormonal control of mRNA translation in skeletal muscle, liver, and retina
- Dysregulated troponin T mRNA splicing in skeletal muscle of obese animals
- Regulation, turnover, and assembly of components of mTORC1
LSJ & SRK continued

**Experimental approaches:**
- Animal models of type 1 and type 2 diabetes and obesity
- Perfused preparations of rat/mouse skeletal muscle and liver/cell culture
- Ectopic expression of cDNA constructs in rat skeletal muscle in vivo
- Analysis of mRNA splice variants
- Confocal microscopy/cellular localization of labeled proteins
- Immunoprecipitation analysis of protein complex assembly

**Areas where collaboration would be helpful:**
- Metabolomics and genomics related to diabetes and obesity
- Collaborations investigating skeletal muscle hypertrophy/atrophy
- Tissue specific knockout/transgenic animal models and MEFs
- Collaborators using mass spec to identify posttranslational modifications of proteins
- Collaborators who are experts in confocal microscopy
Kathryn F. LaNoue
College of Medicine
Dept of Cellular & Molecular Physiology
E-mail: kfl1@psu.edu

Major Focuses:
Role of Adenosine Receptors in Muscle Insulin Resistance
Amino acid metabolism in diabetic retinopathy

Major Technical Expertise:
Especially skilled in metabolic research

Areas of Collaboration needed:
need collaborations that enable me to use molecular biology tools such as siRNA
Areas of research:

- Gastric bypass surgery – Proteomics – animal models and human tissue bank
- Drug side effects related to body weight and metabolism – atypical antipsychotics, topiramate, rimonabant
- Energy balance and metabolic flexibility in animal models
- BCAAs and BCAA metabolism in obesity and nutrient signaling to adipose tissue

Areas/models/techniques available for collaboration:

- mTOR floxed and het, adiponectin Cre, CB1R KO-ob/ob, SUR1 KO, Sur1 KO-ob/ob, DIO, BCAA metabolism KOs, NONcNZO10/LtJ
- Brucker Instr. Rat & Mouse H1-NMR minispec, TSE and Columbus Instr CLAMS
- Longitudinal gastric bypass tissue bank (muscle, subcutaneous and visceral adipose) and plasma bank from meal challenge studies
- Tissues or collaborations on rodent models of gastric bypass surgeries (Roux-en Y, Ileal interposition etc…)

Areas where collaboration would be helpful:

- Metabolomics, Bioinformatics, Hypothalamus function studies (cFOS etc…)
- Functional genomics on our longitudinal samples
- Mass Spec Phosphorylation Site identification
Chris Norbury
College of Medicine – MICROBIOLOGY & IMMUNOLOGY
E-mail: ccn1@psu.edu
Phone: 717 531 7204

Major Focuses:
*Immunity and Disease*

Current Projects:
• Antiviral immunity, particularly the role of the innate immune system, such as dendritic cells, macrophages and pattern recognition receptors and their role in immunity.
• Cross talk with the diabetes field is that we have worked on the role of tissue resident macrophages in diabetic retinopathy.

Major Technical Expertise:
Looking at the roles of tissue resident or inflammatory dendritic cell or macrophage subpopulations in inflammation, and in recovery from inflammation. Looking at myeloid derived suppressor cells which dampen inflammation and promote the resolution of inflammation in a viral infection setting. Work exclusively in mouse, and that is where we have all of our expertise and reagent base. We perform flow cytometry at a pretty sophisticated level to identify the function of individual cell types, rather than operating at a tissue-level. We generally do not measure bulk cytokine levels by ELISA, as these assays can be very misleading.

Areas of Collaboration needed:
We really don’t know a lot about the pathology of these diseases, and a collaboration would need to involve other labs measuring those factors in addition to us measuring immune correlates.
Brian Reeves, M.D., Dept of Medicine- Nephrology, Penn State College of Medicine
E-mail: wreeves@hmc.psu.edu

Areas of research:

**Inflammatory mechanisms of kidney disease.**
Best known for work defining the roles of inflammatory cytokines and TLR receptors in acute kidney injury. Beginning studies of cytokines and TLR4 in diabetic nephropathy

**Areas/models/techniques/unique resources:**

- murine models induced by ischemia or nephrotoxic drugs (cisplatin).
- STZ-induced diabetes and db/db mice, KOs: TNF KO, TNFR1, TNFR2 KO, TLR4 KO.
- Bone marrow chimeras to examine the role of bone marrow derived cells.
- Kidney-specific deletions of TNF and TLR signaling using cre-lox technology.
- Cytokines profiling with Luminex technology
- Inflammatory cell infiltrates in the kidney using flow cytometry

**Areas where collaboration would help:**

- quantitative histology of glomerular and tubular injury
- measurements of renal blood flow
- better models of diabetic nephropathy
Ann M. Rogers, MD
Director, Penn State Surgical Weight Loss Program
Penn State Milton S. Hershey Medical Center
Email: arogers@hmc.psu.edu

Areas of research:
- Multidisciplinary outcomes in weight loss surgery
- Animal models of metabolic surgery
- Minimally invasive surgery and surgical education
- Natural orifice transluminal endoscopic surgery

Areas/models/techniques available for collaboration:
- Large-scale longitudinal database of bariatric patients
- Animal research facilities and protocols
- Skills and simulation laboratories

Areas where collaboration would be helpful:
- Clinical collaborators for the study of the effects of weight loss surgery on breast cancer, heart disease, hypertension, etc.
- Functional MRI/collaboration on taste and olfaction
Connie J. Rogers, Ph.D., M.P.H.
Department of Nutritional Sciences
Penn State – University Park
email: cjr102@psu.edu

Areas of research:
• Biological impact of obesity on innate and adaptive immune responses (with an interest in anti-tumor immune mechanisms)
• Metabolic signaling in immune cells, and the role of obesity in altering these pathways
• Understanding the role of physical activity (and the underlying biological mechanisms) in reducing the pro-inflammatory environment of obesity and reversing the obesity-induced deficits in adaptive immune function

Areas/models/techniques available for collaboration:
• Murine DIO models/ have Mini-mitter murine voluntary running wheel system (n=60)
• Cellular & molecular immunological assays (e.g. tissue isolation: both systemic & mucosal immune compartments, cellular purification, effector function assays, vaccinations etc.)
• Murine DEXA

Areas where collaboration would be helpful:
• Clinical collaborators – access to human immune cells
• Expertise evaluating signal transduction pathways
Yuguang (Roger) Shi  
College of Medicine – Dept of Cellular & Molecular Physiology  
Penn State – Hershey  
E-mail: yus11@psu.edu  
Phone: 717-531-0003 ext 283789  

Major Focuses:  
*Molecular Mechanisms Underlying the Causes of Diabetes and Obesity*  

Previous Contributions:  
• Identified and Characterized PERK, an eIF-2α kinase that regulates ER-stress  
• Identified and characterized several first in class lipid metabolic enzymes involved in synthesis and remodeling of Triglycerides (MGAT2, SCD2), Phospholipids (LPGAT1), Cardiolipin (ALCAT1, CLS1)  

Current Projects:  
• Defective cardiolipin remodeling in mitochondrial dysfunction - diabetes and obesity  
• Regulation of incretin/glucose-sensing of pancreatic β-cells by an islet specific kinase.  

Major Technical Expertise:  
Seahorse system for cellular metabolism, Molecular biology, Knockout mice, lipid enzyme assay, mitochondrial assay, islet isolation, insulin secretion assay, signal transduction, kinase assay.  

Areas of Collaboration needed:  
Animal behavior test, lipidomics, kinomics
Ian Simpson, Ph.D.
Dept of Neural & Behavioral Sciences
Penn State- Hershey
Phone: 717 531 4156  email: ixs10@psu.edu

• **Areas of research: ***Diabetes and Stroke*
  
  – Determine underlying cause(s) that result in impaired stroke recovery in diabetics.
  – Type II animal models include ob/ob, db/db and NONcNZO10/LtJ
  – Inflammation, BBB breakdown, microglial and astrocytic activation.
Current Research Focus
• Our laboratory focuses on the role of the CNS in obesity-induced hypertension.
• We are specifically interested how circulating factors such as leptin and insulin activate brain circuits to elevate sympathetic outflow and arterial blood pressure.

Experimental Approaches / Collaborations
• In vivo and in vitro electrophysiology
• Brain microinjection
• Telemetry system to chronically record sympathetic nerve activity and blood pressure
• Sympathetic nerve recordings in humans

Areas of Collaboration
• Cellular approaches to understand signal transduction and gene expression in the central nervous system
• Gene expression and/or proteomics
• Gene delivery or siRNA in vivo
R. Alberto Travaglì, PhD

College of Medicine
Department of Neural and Behavioral Science
Phone: 717 531 8267
Email: rat13@psu.edu

Current Research Focus
My laboratory focuses on vago-vagal reflex control of subdiaphragmatic viscera, particularly the gastrointestinal tract and pancreas. Our research is focused on autonomic homeostatic mechanisms particularly neuronal remodeling following functional gastrointestinal or pancreatic disorders.

Experimental Approaches
In vitro electrophysiology (brainstem slices)
In vivo recordings of gastric motility and tone; pancreatic secretion
Immunohistochemistry
Single cell RT-PCR

Areas of Collaboration needed
Molecular approaches to measure neuronal plasticity (protein, receptor, gene expression levels)
Neuronal re-organization and re-patterning
John (Jack) P. Vanden Heuvel  
Veterinarian and Biomedical Sciences, College of Agriculture,  
Molecular Toxicology, Center of Excellence in Nutrigenomics  
Penn State – University Park,  
E-mail: jpv2@psu.edu  
Phone: (814) 863-8532

Major Focuses:  *Nutrient signaling, nuclear receptors and PPARs*

Current Projects:
- focused on NRs that respond to dietary fatty acids, e.g., PPAR, RXR and LXR  
- Role of PPARs; PPARα, β/δ and γ in toxicology, carcinogenesis and nutrition

Major Technical Expertise:
- High through-put screening assays for over 40 nuclear receptors: human, rat and mouse.  
- Gene expression microarray and analysis.  
- Expertise on dietary fatty acids, in particular omega-3 polyunsaturated fatty acids (*fish oil EPA, DHA and plant-derived ALA. Current studies are examining the beneficial effects of these fatty acids on inflammation and chemoprevention, e.g., breast and pancreas*)  
- Approaches to examine communication between adipocytes and cancer cells in cell culture systems.  
- Clinical Nutrigenomics: effects of diet on inflammatory markers in lymphocytes isolated from individuals or in ex vivo experiments.  
- Genotyping for SNPs in various nuclear receptors.

Areas of Collaboration needed:
- Approaches to understanding genetic variability and phenotype (statistical analysis, identification of novel SNPs and splice variants).  
- Drug discovery collaborators. We have the techniques to screen, but have limited access to large scale chemical libraries
Hanspeter Waldner, PhD
Microbiology and Immunology
PSU College of Medicine
Email: hpwaldner@psu.edu

Areas of research:
• Mechanisms that maintain or break tolerance to T cell-mediated autoimmune diseases such as Multiple Sclerosis (MS) and Type 1 diabetes (T1D)
• Mechanisms by which defined genetic loci confer tolerance to Type 1 diabetes induction
• Small molecules as tools to perturb the genome to identify mechanisms of biology and autoimmune disease

Areas for collaboration:
• Genetically engineered mouse models of MS and T1D

Areas where collaboration would be helpful:
• Expertise in intestinal microbiota
Jacob Werner, VMD

- Attending Veterinarian for Agricultural Animals and Wildlife, University Park
- Assisted in animal model development (e.g. large or small collaborated in research through Dr. Nadine Barrie Smith’s Lab in the College of Engineering
- Research has been in animal model development and research in transdermal ultrasound mediated insulin delivery and glucose monitoring
- Available to collaborate and assist in animal model development as well as interested in collaborating in conducting research
-Research Interests: Function and development of innate lymphocytes of the immune system, such as gamma/delta T cells, NK cells and NK T cells, in health and disease.

-Main Expertise:
- Use of genetically modified mouse models to study roles of various innate lymphocyte subsets and immune activating molecules in immune activation under physiological and pathological conditions.
- How various innate lymphocytes are involved in the promotion of metabolic dysfunction and vascular complications, particularly atherosclerosis.

-Needed Collaboration Areas: physiological and pathological analysis of metabolic dysfunctions and complications