Rozalyn Anderson PhD
Associate Professor of Medicine
Metabolism of Aging

Dr. Anderson studies the Biology of Aging. Aging is the biggest risk factor for a range of highly prevalent diseases including diabetes, cancer, and neurodegenerative disease. The primary goal of Dr. Anderson's group is to understand at the cellular and molecular level what happens with age to create vulnerability for all these chronic conditions. The central theme of her work is the regulation of metabolism and the role that metabolism plays in aging and disease. One of the ways to learn about aging is through the study of caloric restriction (CR), a dietary intervention that delays aging and the onset of age-associated disease. Her studies in cells, in mice, and in monkeys, point to a key role for mitochondrial energy metabolism in the mechanisms of CR, and have identified the transcriptional co-activator PGC-1a as a potential target to counter the negative effects of age. Dr. Anderson's research team uses pharmacological and genetic approaches to define the mechanisms of delayed aging and how cells and tissues (skeletal muscle, liver, adipose tissue, brain) coordinate to produce this amazing longevity program.

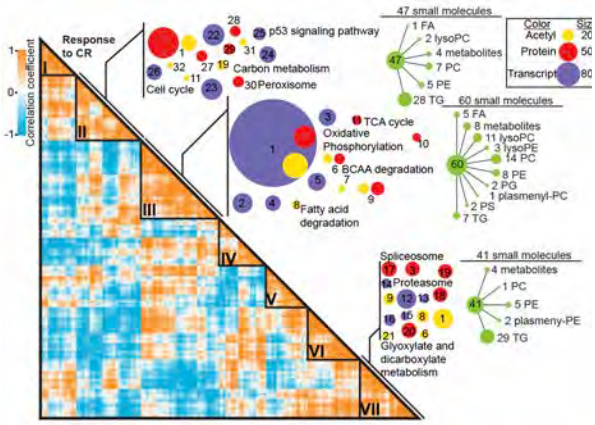


Figure: Metabolic Networks involved in Delayed Aging.
Molecular profiles of rhesus monkey hepatic tissues were generated. Metabolites, genes, proteins, and acetylation status responsive to caloric restriction were identified. Correlation analysis revealed **Mega-Clusters** of factors whose patterns of change in response to CR were linked.
Rhoads et al. 2018

Alan Attie PhD
Professor of Biochemistry
Genetics of Obesity, Diabetes, and Dyslipidemia

The Attie Laboratory uses mouse genetics to discover genes and pathways leading to metabolic disease, especially obesity and diabetes. Many of the gene under study affect the growth of pancreatic β-cells or their ability to sense nutrients and secrete insulin. The genes include transcription factors, protein phosphatases and kinases, receptors, and proteins that mediate the trafficking of vesicles in the secretory pathway. The laboratory also studies cholesterol and triglyceride metabolism. These studies include genes that affect serum cholesterol levels as well as genes that affect the accumulation of excess triglyceride in the liver, termed hepatic steatosis. The laboratory uses systems genetics approaches to integrate data from transcriptomics, proteomics, and metabolomics with physiological phenotypes.

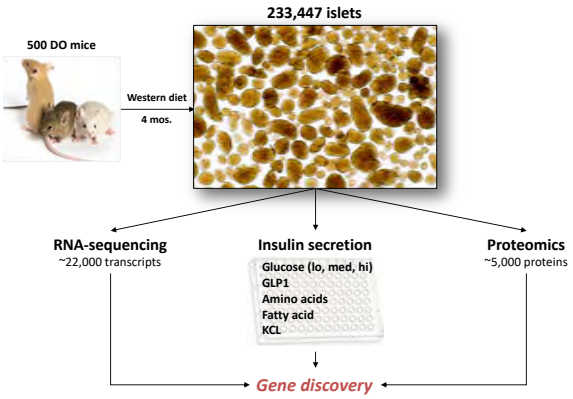
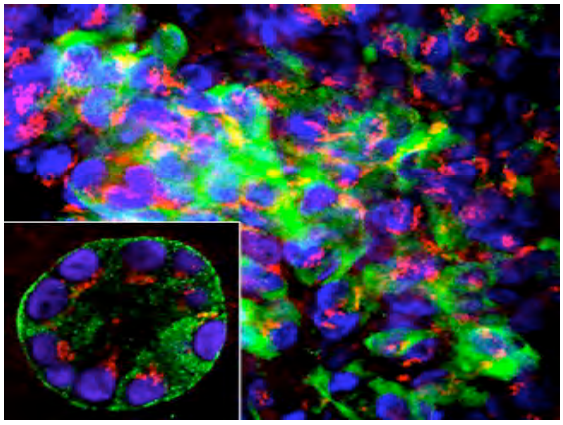


Figure: We screened a diverse population of outbred mice derived from 8 inbred mouse strains for the ability of their islets to secrete insulin *ex vivo* in response to several nutrient stimuli. We also carried out RNA sequencing and proteomics of the islets. Through extensive SNP genotyping, we reconstructed the full genome sequence of every mouse. We mapped the gene loci contributing to RNA and protein expression and insulin secretion.

Vincent Cryns MD
Professor of Medicine
Targeting Metabolic Stress in Cancer


Breast epithelial cells grown in three-dimensional culture display a glandular architecture (insert) that is disrupted by oncogenic transformation, resulting in chaotic, hypercellular tumor-like structures.

Dr. Cryns focuses on understanding how tumors adapt to and survive metabolic stress in the tumor microenvironment. The lab is particularly interested in translating these insights into improved biomarkers and therapies for cancer. We have demonstrated that the cell stress protein αB-crystallin contributes to the aggressive behavior of triple-negative breast cancer (TNBC) by inhibiting caspase-3 activation and stabilizing mutant p53. We have also developed unique mouse models of metastatic TNBC and demonstrated that αB-crystallin plays a key role in brain metastasis, a devastating complication with few treatment options. Much of the current work in the lab focuses on investigating the oncogenic mechanisms of B-crystallin in innovative cellular and mouse models. More recently, the Cryns lab developed a novel therapeutic paradigm to metabolically prime TNBC to proapoptotic therapy using dietary methionine restriction (MR). We demonstrated that dietary MR enhances the antitumor activity of proapoptotic TRAIL receptor agonists by increasing cell surface expression of TRAIL receptor-2 in tumors. These laboratory discoveries have led to two clinical trials of dietary MR to examine its tumor and metabolic effects in newly diagnosed TNBC (NCT03186937) and its activity in combination with a novel TRAIL agonist (ONC201) in patients with metastatic TNBC (NCT03733119). In this way, we hope to develop specific dietary interventions that enhance the efficacy of cancer drugs.

Dawn Davis MD, PhD
Associate Professor of Medicine
Stress responses and regulation of pancreatic beta cell mass

The **Davis Lab** is interested in pancreatic islet biology. The pancreatic beta cells are terminally differentiated cells responsible for insulin production to regulate glucose levels. When faced with insulin resistance and increased demand for insulin in the setting of obesity, the beta cell will divide and overall beta cell mass is increased. Conversely, one of the defects in type 2 diabetes is a loss of overall beta cell mass leading to insufficient insulin production. Numerous stressors (including cytokines and endoplasmic reticulum stress) lead to increased beta cell apoptosis in type 2 diabetes. We are also studying the ways that the pancreatic islet adapts to stressors and promotes beta cell survival. Two current projects in the laboratory approach the regulation of pancreatic beta cell mass and also the adaptation of the islet to the obesity environment. 1) **Tcf19**: Tcf19 is a novel protein, known as Transcription Factor 19. We initially identified *Tcf19* as a gene that was upregulated in response to obesity in mouse islet with expression that correlated with that of many known cell cycle genes. Our overall goal is to use cellular, molecular and animal studies to understand how genetic variations contribute to diabetes

pathogenesis and also to identify novel approaches to address deficiencies in beta-cell mass. 2) **Cholecystokinin**: The hormone cholecystokinin (CCK) is classically known for its production in the intestine and its role in digestive function. However, CCK is also produced in the pancreatic islet. We seek to understand the regulation of GLP-1 and CCK within the pancreatic islet and their role in protection from beta cell apoptosis.

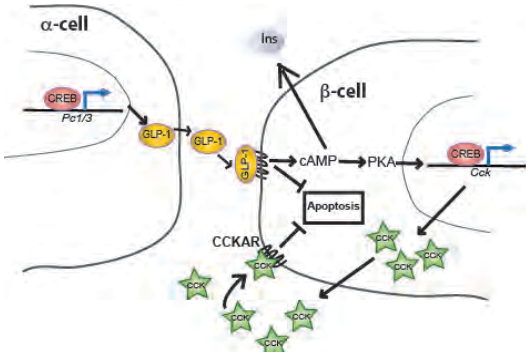


Figure: An intra-islet signaling network of incretin-like hormones GLP-1 (yellow) produced in the pancreatic alpha cells and stimulation the production of CCK (green) in the pancreatic beta cells. Both hormones can then signal back on the beta cell to prevent apoptosis.

John Denu PhD

Professor of Biomolecular Chemistry

Epigenetic chromatin changes that regulate cell signaling and metabolism

Dr. Denu's group investigates the molecular mechanisms and biological roles of reversible protein modification on controlling diverse cellular pathways. This focus has been applied to understand the molecular basis of metabolic-based diseases, cancer, aging mechanisms and dysregulated epigenetic states. This work involves integrating diverse approaches that cover mechanistic enzymology, quantitative proteomics, cellular biochemical pathways, mammalian model organisms, and human samples. Major projects include i.) understanding how metabolism is linked to the regulation of the epigenome ii.) revealing the molecular role of NAD-dependent deacylases in aging, metabolic disease and cancer, iii) understanding how dysregulation of the epigenome affects age-associated diseases, cancer, and brain health; and iv.) understanding how gut microbial metabolites affect host phenotypes.

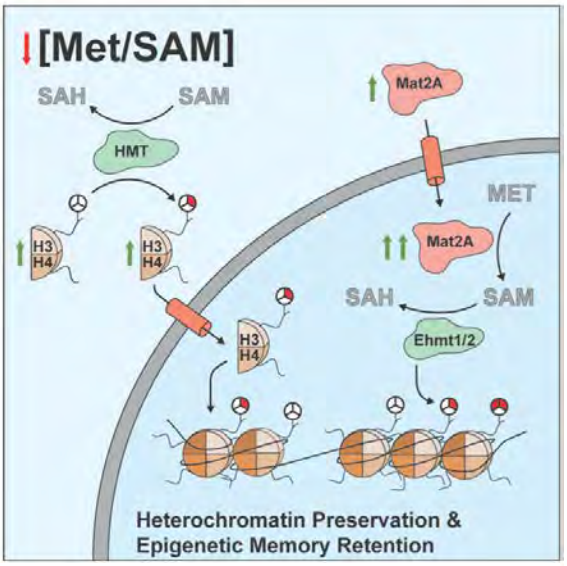


Figure: SAM producing and consuming pathways dictate histone methylation.

David Eide PhD

Professor of Nutritional Sciences

Genetics of zinc metabolism

Dr. Eide studies the genetic responses of eukaryotic organisms to the stresses caused by mineral nutrient deficiency. His studies are primarily focused on zinc using yeast (*Saccharomyces cerevisiae)* as the model system. Dr. Eide's most recent work has examined the zinc proteome and protein homeostasis during zinc deficiency. His lab has shown that zinc-deficient cells experience a crisis of protein misfolding and that the Tsa1 protein chaperone plays a critical role in the cell's ability to tolerate that stress. Moreover, they have discovered several novel mechanisms of gene regulation that also aid in this process. For example, expression of ubiquitin, an essential component of protein homeostasis, from the *UBI4* gene is induced during zinc deficiency by a novel

intragenic zinc-responsive promoter. His lab has also discovered a role for autophagy in zinc-limited growth. Finally, they have conducted a quantitative analysis of the zinc proteome in zinc-replete and deficient cells. This work is building a comprehensive and integrated picture of the many responses to metal-limited growth in simple eukaryotes and human cells.

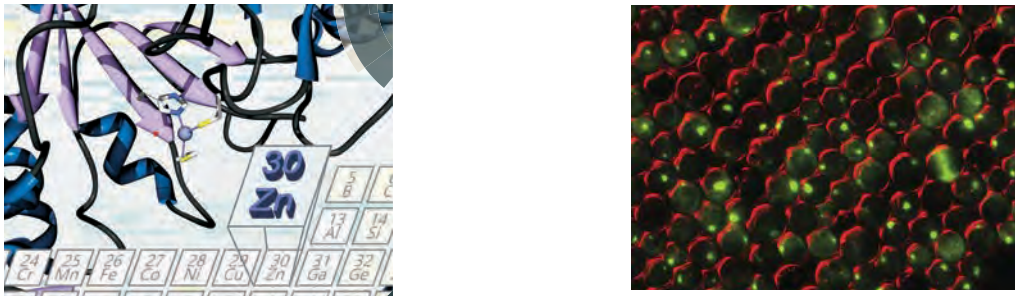


Figure: Zinc is a critical structural and catalytic cofactor for many proteins. For example, binding of zinc to a site in aldolase (left panel) is critical for folding and function of this key glycolytic enzyme. Therefore, zinc-deficient cells require mechanisms to prevent misfolding and aggregation of zinc-binding proteins that lack their metal cofactor. The Eide lab has shown that the Tsa1 peroxiredoxin protein chaperone is required to prevent protein aggregation during zinc deficiency. Zinc-deficient tsa1 mutant cells (right panel, outlined in red) accumulate foci of aggregated proteins (green) indicating the essential role of Tsa1 in maintaining protein solubility under these conditions. The mechanisms and regulation of these processes are a major focus of ongoing research in the Eide lab.

Rick Eisenstein PhD

Professor of Nutritional Sciences

Iron and oxygen sensing to control erythropoiesis and its dysregulation in disease

The **Eisenstein laboratory** investigates how erythropoiesis and iron metabolism are controlled and coordinated including how dysregulation of molecular sensors of iron and oxygen causes disease. Their focus is on iron regulatory proteins (IRP) and the mRNA targets they regulate. IRP are iron-regulated mRNA binding proteins that dictate the fate of at least 10 mRNA in vertebrates. Included among these targets is hypoxia inducible factor 2-α (HIF-2α) mRNA which encodes a transcription factor critical for the adaptive responses to hypoxia (i.e. anemia). HIF-2α drives expression of erythropoietin (Epo), the primary cytokine that promotes erythropoiesis. In adults, Epo is primarily made in rare interstitial fibroblast like cells in the kidney, renal Epo producing cells (REPC). A range of approaches using cell culture and genetically modified animals are being employed to elucidate the pathways through which iron metabolism is controlled in, and sensed by, REPC in order to modulate Epo. A long-range goal of our work is to elucidate how interorgan iron metabolism is coordinated with erythropoiesis and how dysregulation of iron sensing may contribute to the suppression of Epo expression in disease states such as renal failure.

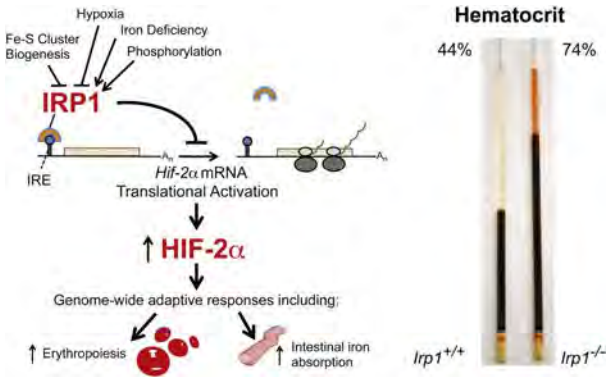


Figure: IRP1 is a translational repressor of HIF-2α mRNA. HIF-2α is a transcriptional activator of erythropoietin, the key cytokine driving erythropoiesis, and it also promotes expression of iron absorption genes in the intestine. Mice lacking IRP1 overproduced HIF-2α leading to overproduction of Epo and polycythemia (erythrocytosis).

Feyza Engin PhD
Assistant Professor of Biomolecular Chemistry
Organelle homeostasis in chronic inflammatory diseases.

Dr. Engin studies how aberrant cellular stress responses, and organelle dysfunction play a role in development and progression of chronic inflammatory diseases. The endoplasmic reticulum (ER) is a cellular compartment that regulates protein and lipid synthesis, folding and trafficking, as well as calcium homeostasis. Our lab is interested in a) understanding the metabolic biology of the ER and how this organelle adapts or fails to adapt under specific stress conditions in pancreatic beta cells, b) identifying the interactions between metabolic and immune responses in chronic inflammatory diseases. Using biochemical, genetic, pharmacological and physiological studies, and utilizing single cell genomic tools and computational modeling we aim to discover novel pathways and develop preventive therapeutic approaches against diabetes and other disorders that share similar aberrant ER stress responses in their etiology.

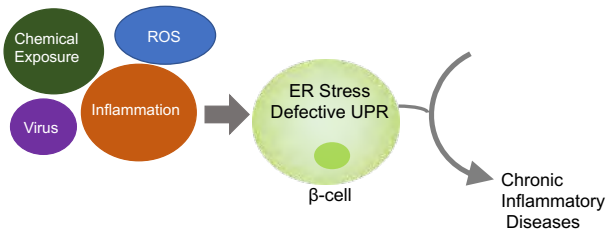


Figure: Pancreatic beta cell ER stress and abnormal unfolded protein response plays a significant role in T1D etiology.

Corinne Engelman MSPH, PhD
Associate Professor of Population Health Sciences
Genomic epidemiology

The **Engelman Lab** focuses on the study design and data analysis of genetic, demographic, socioeconomic, behavioral, physiological and environmental factors of complex diseases, including biomarkers and preclinical traits related to Alzheimer's disease. We use epidemiological, statistical, and bioinformatic approaches to analyze large-scale 'omic data, including that from whole genome array genotyping; whole-genome sequencing; DNA methylation beadchip; and metabolomic, lipidomic, and proteomic mass spectrometry. We integrate 'omic and questionnaire data to understand, predict, prevent, and/or treat health conditions. We are especially interested in identifying interactions with modifiable factors (e.g., social, behavioral, and environmental) to inform precision medicine and health. We study multi-ethnic populations in collaboration with the Wisconsin Registry for Alzheimer's Prevention (WRAP), Wisconsin Alzheimer's Disease Research Center (W-ADRC), and Survey of the Health of Wisconsin (SHOW).

Figure: Roles for Genetics and Lifestyle in the Incidence of Chronic Diseases

Luis Fernandez MD
Professor of Surgery
Interplay Between Complement and Mitochondrial Dysregulation in Acute Kidney Injury after Kidney Transplantation

Complement activation in the donor, the graft and the recipient before, during and after transplantation is a major cause of damage to the kidney transplant. Our goal is to understand and develop an effective therapeutic strategy to eliminate ischemia-reperfusion injury/delayed graft function in recipients of donation after cardiocirculatory death (DCD) kidney transplants using an ABO compatible, fully mismatched MHC disparate kidney rhesus macaque model. The primary hypothesis is that the inhibition of complement at the level of C1 can reduce the incidence of delayed graft function in DCD kidney transplant recipients. We are also exploring the role of mitochondrial (mt) DNA as a Damage Associated Molecular Pattern (mtDNA DAMPs) in acute kidney injury (AKI), the potential development of somatic mDNA variance as a result of AKI, and the therapeutic benefit of increasing mitochondrial health by increasing its repair capacity after the administration of fusion protein targeting mtDNA repair.

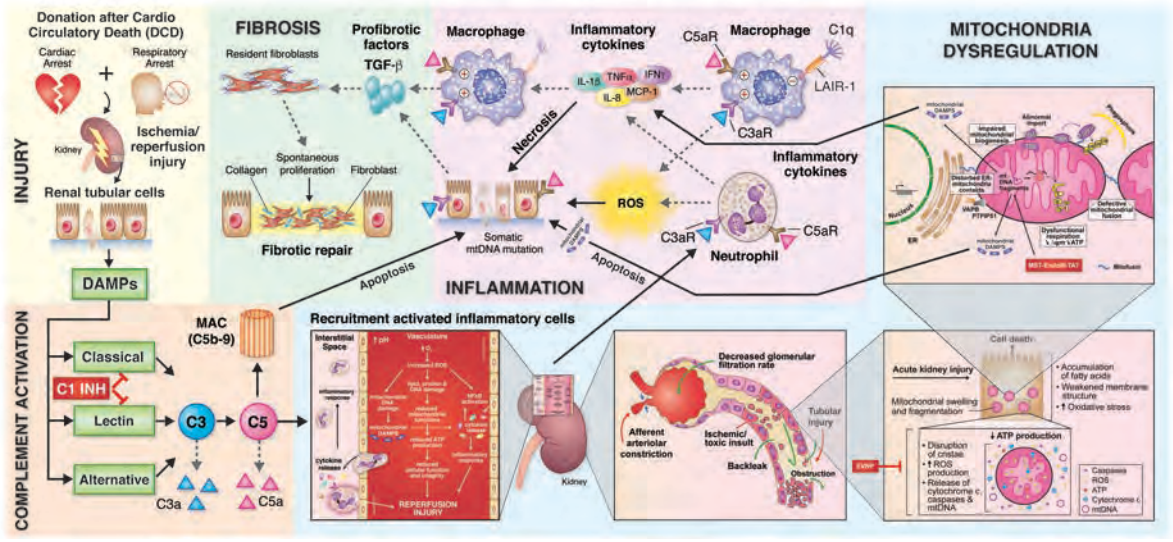


Figure: Role of complement in renal ischemia-reperfusion injury, inflammation, and progression to kidney fibrosis. Ischemia-reperfusion injury activates the complement system by release of endogenous ligands (DAMPs) from acutely injured tissue. The formation of the membrane attack complex (MAC) results in direct injury to the kidney by inducing apoptosis in epithelial tubular cells. In addition, the cleavage of C3 and C5 and subsequent release of anaphylatoxins (C3a and C5a) promotes inflammatory cell recruitment and release of pro-inflammatory cytokines/chemokines and reactive oxygen species, intensifying the immune response and further amplifying the level of tubular necrosis and apoptosis. Activated endothelium, monocytes and injured tubular epithelium have all been shown to secrete pro-fibrogenic factors such as TGF-β and PDGF in response to C3aR and C5aR ligation by C3a and C5a, respectively, which in turn activates local fibroblasts inducing collagen deposition and tissue repair. Dysregulated activation of complement and the subsequent inflammatory response ultimately results in maladaptive tissue repair and fibrosis.

Luke Funk MD, MPH
Associate Professor of Surgery
Identifying and Addressing Population-Level Trends in Obesity Care

Our research group identifies and addresses population-level trends in obesity and the care provided to individuals with obesity, particularly the 20+ million U.S. adults with severe obesity (defined as a body mass index of >=35 kg/m2). We are also interested in addressing disparities

in care, particularly as they pertain to social determinants of health and obesity. We are currently using a mixed-methods approach (observational data analysis and qualitative research methods) to investigate disparities in bariatric surgery outcomes related to socioeconomic status. Our group also conducts behavioral intervention clinical trials aimed at improving outcomes for patients with obesity.

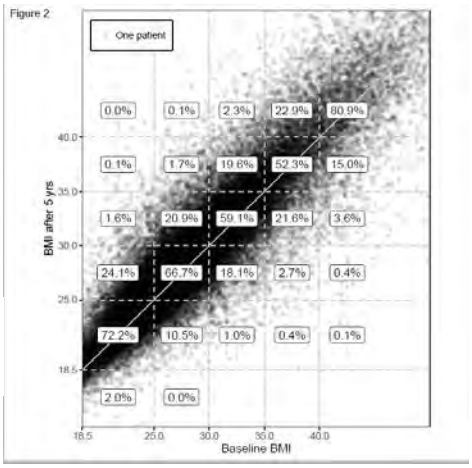


Figure: Each dot represents one patient. The x-axis represents baseline BMI and the y-axis represents BMI after 5 years.

James Gern MD

Professor of Pediatrics

Early life environment exposures and allergic diseases of childhood

Dr. Gern's research focuses on identifying how viral respiratory infections and other environmental exposures in early life promote the development of asthma, and in children with established disease, acute asthma attacks. To accomplish this goal, he has conducted birth cohort studies in a variety of different environments including disadvantaged urban neighborhoods, Wisconsin farm country and suburban neighborhoods. These NIH-funded studies include the Wisconsin Infant Study Cohort (WISC) in Central Wisconsin, the Urban Environment and Childhood Asthma birth cohort study in four US urban neighborhoods, and a new cohort ("CANOE") that will combine urban and suburban populations in four US cities. He is also collaborating with investigators at other institutions to pool data from 12 US birth cohorts to identify environmental exposures that promote childhood asthma. Current areas of investigation include understanding how microbial exposures and dietary factors influence the gut microbiome in early life, early immune development and allergic diseases such as asthma.

Figure: Environmental factors influence the development of allergic diseases and asthma.

Guy Groblewski PhD

Professor of Nutritional Sciences

Membrane trafficking in digestive epithelia: pathogenic mechanisms in pancreatic disease.

Dr. Groblewski studies the molecular control of membrane trafficking events in digestive epithelial cells using the acinar cell of the exocrine pancreas as a model. These studies aim to define potential targets for therapies against the diseases pancreatitis and pancreatic cancer. Dr. Groblewski's laboratory uses molecular and genetic approaches in isolated acinar cells and transgenic animals to explore membrane trafficking events regulating secretory granule biogenesis, endosomal trafficking, autophagy, ER stress and cellular secretion. We have established functional roles for various SNARE

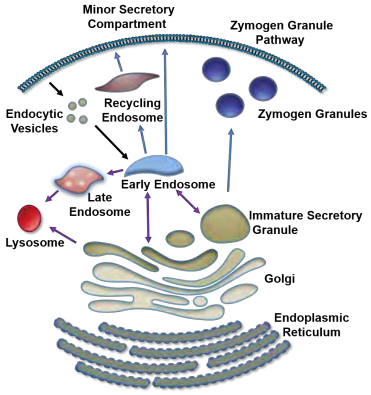


Figure: Overview of membrane trafficking pathways in the pancreatic acinar cell.

proteins, small Rab G-proteins and inositol phospholipids in controlling acinar cell secretory function. New evidence indicates that genetic manipulation of these regulatory molecules in rodents strongly impacts the onset and progression of pancreatitis which if left unchecked leads to pancreatic cancer.

Laura Hernandez PhD
Associate Professor of Dairy Science
Peripartal SSRI use impacts the mammary gland-bone axis

We study the contribution of serotonin to the regulation of maternal and mammary gland calcium homeostasis during the peripartal period. We have demonstrated that serotonin is increased in the circulation during lactation, and that it causes increased transport of calcium into milk. We have demonstrated that this occurs through regulation of parathyroid hormone related protein in the mammary gland. The increase parathyroid hormone related protein by the mammary gland leads to increased bone metabolism of calcium to restore maternal calcium homeostasis. Our initial data suggest that the increase in parathyroid hormone related protein is due to hypomethylation of the parathyroid hormone related protein promoter. Additionally, we have demonstrated that the use of selective serotonin reuptake inhibitors (**SSRI**s) during the peripartal period results in increased bone turnover during lactation, and long-term decreases in bone trabecular volume of the dam, as well in the pups that were exposed to SSRIs. We are currently characterizing the molecular mechanisms underpinning these phenomena in both mouse and cow models.

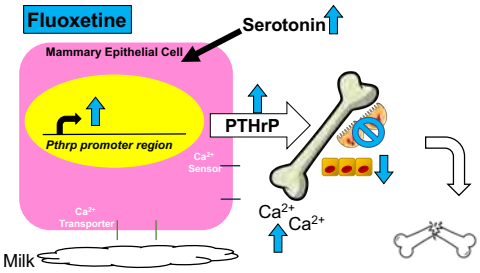


Figure: During lactation Pthrp production during lactation drives calcium resorption from the bone to support synthesis of milk and maternal calcium homeostasis. Fluoxetine increases serotonin activity in the mammary epithelial cell, which exacerbates the normal liberation of calcium from bone. This occurs through a decrease in the methylation of the Pthrp promoter, leading to increased Pthrp transcription and activity by the mammary gland. Increased Pthrp released into the circulation then increases bone activity leading to increased bone resorption and increased calcium into the circulation and into the mammary gland for milk synthesis.

Michelle Kimple PhD
Associate Professor of Medicine
Identifying New Therapeutic Targets for Diabetes

Research in the Kimple lab is focused on how the endocrine cells of the pancreatic islet of Langerhans coordinate to regulate hormone secretion in response to glucose and other stimuli; impacting whole-body fuel metabolism. The Kimple Lab is especially interested in elucidating how G protein signaling networks regulate alpha-, beta-, and delta-cell function and their response to insults such as hyperglycemia, dyslipidemia, and inflammation (coincident with insulin resistance and type 2 diabetes) or immune infiltration (coincident with type 1 diabetes). The premise behind research in the Kimple

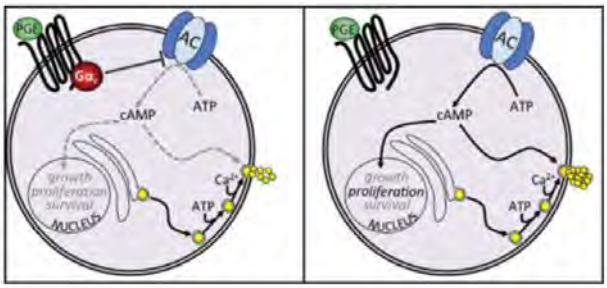


Figure: How control of cAMP production by $G\alpha_z$ impacts β-cell function & mass

lab is G protein-coupled receptors and their associated ligands, G proteins, and downstream effectors play key roles in early islet cell adaptation and resilience to external stressors, and that certain G protein signaling pathways become dysfunctional in the diabetic state, actively contributing to the pathophysiology of the disease and impacting the ability of certain classes of diabetes therapeutics to properly control blood glucose levels. It is the long-term goal of the Kimple Lab research program to identify and validate novel therapeutic targets to prevent or ameliorate the islet cell dysfunction of diabetes, improving the care and treatment of individuals with diabetes or preventing the disease in individuals with an underlying susceptibility.

HuiChuan Lai PhD

Professor of Nutritional Sciences, Pediatrics and Population Health Sciences

Precision Nutrition in Cystic Fibrosis

Precision Nutrition in Cystic Fibrosis Dr. Lai studies how nutrition affects treatment, quality of life and survival in people with cystic fibrosis (CF), one of the most common genetic diseases in the US. The ultimate goal of Dr. Lai's research is to develop personalized nutrition therapy and evidence-based clinical practice guidelines to improve clinical care and health outcomes of CF. Currently, Dr. Lai is conducting a prospective multi-center clinical study in six CF centers referred to as FIRST, located in five states (WI, IL, IN, MA and UT), that follows a birth cohort of 180 children with CF from the neonatal period to 6 years of age (2024). FIRST has expanded to include many ancillary studies such as breast milk composition, gut microbiome with sibling control, probiotic supplementation, chest computed tomography and lung clearance index, and nutrigenomics and pharmacogenomics using whole genome sequencing-derived genotype data. The goals of FIRST are to identify optimal feeding regimens during infancy, to predict non-responders of vitamin D supplementation, to resolve the longstanding controversy of essential fatty acid supplementation, and to advance our understanding of the gut microbiome and its relationship to obesity, malnutrition, diabetes and liver diseases in children with CF.

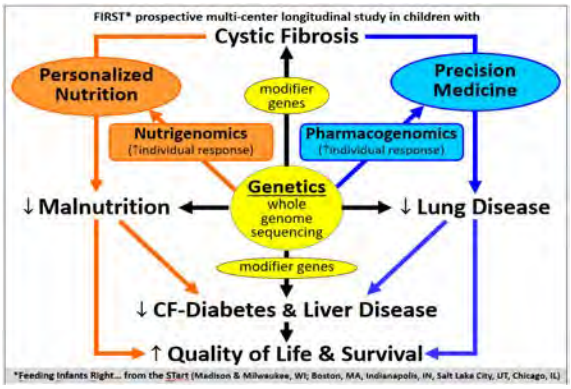


Figure: Outline and goals of the FIRST study (Feeding Infants Right… from the STart)

Dudley Lamming PhD
Assistant Professor of Medicine
Molecular Physiology of Aging and Age-Related Diseases

Our laboratory is focused on understanding how what, when, and how much we eat can regulate metabolic health and aging. We discovered that low protein diets promote metabolic health – improving blood sugar control and reducing adiposity – in humans and mice, and we have identified dietary branched-chain amino acids (BCAA) as key regulators of these effects. We currently study the mechanisms that mediate these beneficial effects, with an emphasis on understanding the role of the amino acid responsive kinase mTOR (the mechanistic Target of Rapamycin). We also study if altering mTOR signaling with rapamycin, novel rapamycin derivatives, and other geroprotective agents can be used to treat or prevent age-related diseases.

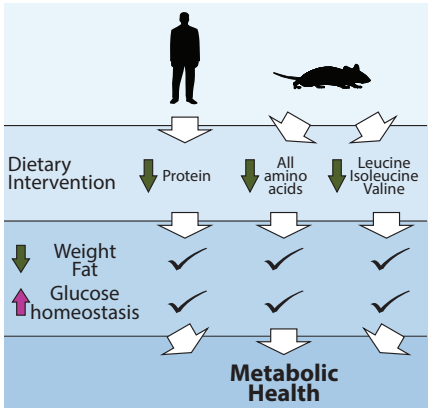
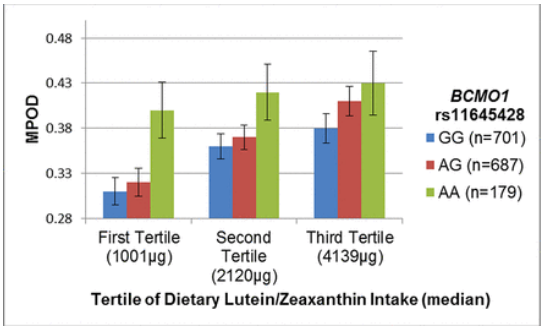


Figure: Decreased consumption of branched chain amino acids (Leu, Ile, Val) improves metabolic health.

Julie Mares PhD
Professor of Ophthalmology and Visual Sciences
Carotenoids and eye disease

The primary goal of **Dr. Mares's** research program is to evaluate relationships of diet and nutritional status to eye and brain health. This includes the study of the onset and progression of diseases that become common in old age such as cataract, glaucoma and macular degeneration. They conduct studies in several large population groups using epidemiological approaches.

The Mares group evaluates many interrelated aspects of diet and healthy lifestyles singly and jointly. In some studies, we use a non-invasive flicker photometry test to evaluate levels of plant pigments (the carotenoids lutein and zeaxanthin) that accumulate in eye tissues and comprise macular pigment. We measure blood levels of vitamin D which reflect vitamin D from both diet and sunlight exposure.



Relationship between macular pigment optical density (MPOD), dietary intake of lutein and zeaxanthin and signal nucleotide polymorphisms in the carotenoid cleavage enzyme (BCMO1) gene. Meyers K., et al Invest Ophthalmol Vis Sci. (2013) 54:2333-45

They are currently studying genetic predictors of the status of carotenoids that accumulate in the eye and genetic predictors of vitamin D status. We will next use these findings to study how nutritional and genetic factors are jointly related to lower risk for developing age-related deterioration of eye and brain health in different study populations. Ultimately these data will be used to understand and communicate modifiable aspects of diet and lifestyle that could promote eye and brain health as we age.

Kristen Malecki PhD
Assistant Professor of Population Health Sciences
Molecular Epidemiology and Environmental Health: Understanding human susceptibility and vulnerability to the environment.

As an environmental epidemiologist, I study the intersection between social and environmental stressors as a root cause of health disparities. Diet plays a key role driving both environmental exposures and metabolic processes underlying multiple chronic disease. My lab develops novel methods for understanding cumulative environmental risk using novel biological markers of exposure and response including epigenetic and the microbiome. As Director and PI of the SHOW cohort, I have overseen collection of detailed data on behavioral health, diet, and biological samples. I recently used these data to examine differential gene expression from smoking exposure among obese vs. non-obese. My lab also examines how diet serves as both a mediator and protective factor in chronic disease etiology, via alterations to metabolism of xenobiotic chemicals, associations with inflammation and altered gut microbiome and with mental health. Much of this work stems from increased understanding of the links between food insecurity and risk for chronic disease emerging from population based research.

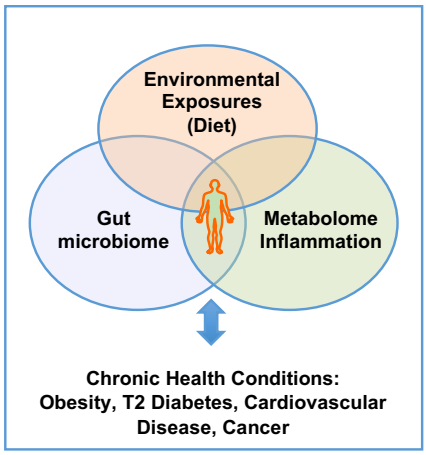


Fig 1: Malecki Laboratory Model . Interactions between environmental exposures, dietary factors, gut microbiome and the host's metabolism and immune system and associations with chronic disease.

Matthew Merrins PhD
Assistant Professor of Medicine and Biomolecular Chemistry
Enzymatic regulation of nutrient metabolism and hormone secretion in pancreatic islets

Research in our laboratory is focused on metabolic signaling in pancreatic islets of Langerhans. As metabolic sensors for the organism, islets regulate blood glucose by releasing the hormones insulin and glucagon. Our main interests lie in two features of nutrient metabolism in islet cells, (1) the ability to trigger pulses of insulin release, and (2) the ability to fine-tune hormone secretion through cell-cell communication. To understand how these processes adapt to environmental stress, we utilize mouse models of obesity/diabetes in combination with biochemistry, patch clamp electrophysiology, and quantitative imaging. A central focus of the lab is the use of fluorescence microscopy (3D light-sheet imaging, optogenetics, and 2-photon microscopy) to monitor biochemical reactions as they occur in living cells.

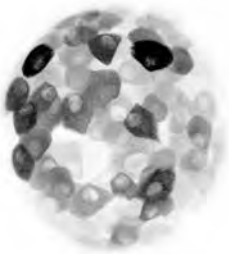


Figure: 3D Imaging of cAMP in β cells of the Islets of Langerhans.

Joshua Mezrich PhD
Associate Professor of Medicine
How the Outside Environment Influences Immune Responses

We focus on the Aryl Hydrocarbon Receptor (AHR) as a sensor that modulates the immune system in response to endogenous and exogenous ligands. We examine the role of dietary ligands in the presence and function of cells of the gut immune system in normal physiology and colitis, as well as the role of pollution in altering the immune system through the AHR, which is the receptor for toxicants including TCDD, polycyclic aromatic hydrocarbons and natural dietary constituents. We seek to understand mechanisms for how diet and pollution aggravate diseases from cancer to autoimmunity to chronic rejection

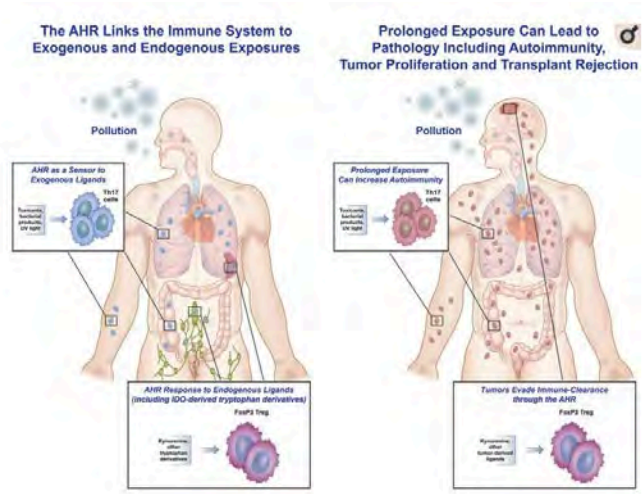


Figure: The AHR as friend and foe. This figure represents the hypothesis that the AHR can be both protective and pathologic in responding to endogenous and exogenous ligands.

Denise Ney PhD
Professor of Nutritional Sciences
Nutrition and inherited metabolic disease

Dr. Ney studies the nutritional management of phenylketonuria (PKU) by conducting studies in human PKU (www.clinicaltrials.gov NCT 01428258) and the murine model of PKU (*Pah*^{enu2}). PKU is caused by a deficiency of hepatic phenylalanine hydroxylase (PAH, EC 1.14.16.1) activity that catalyzes the conversion of phenylalanine (phe) to tyrosine. With normal protein intake, phe accumulates in the brain leading to profound cognitive impairment. A lifelong low-phe diet that includes amino acid formula is required to protect brain development. Dr. Ney has developed a more physiologic approach for the nutritional management of PKU using glycomacropeptide (GMP), a low-phe protein isolated from cheese whey. Skeletal fragility, characterized by low bone mineral density and fractures, is a chronic complication of PKU of unknown etiology. Skeletal fragility in murine PKU is attenuated with the GMP diet, compared with an amino acid diet. Studies are underway to characterize the pathophysiology of skeletal fragility in human and murine PKU.

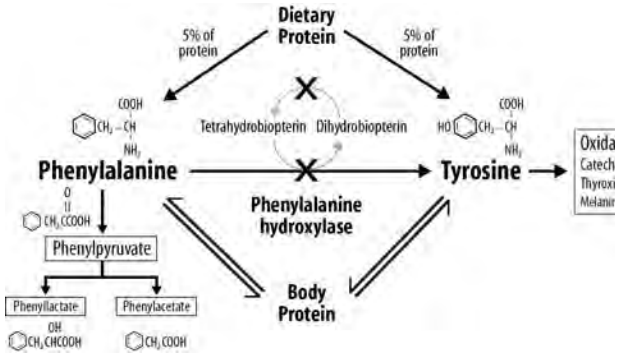


Figure 1. Phenylalanine (phe) metabolism in phenylketonuria (PKU). As indicated by the "X", PKU results from mutations (over 800 have been identified) that affect the hepatic phe hydroxylase (PAH) enzyme needed for the hydroxylation of the indispensable amino acid phe to tyrosine. PKU may also result from mutations in the recycling of the essential PAH cofactor tetrahydrobiopterin. Due to these mutations which reduce the conversion of phe to tyrosine, phe accumulates in blood and is transaminated and decarboxylated into many compounds which appear in blood and urine; three of the compounds which are measured clinically are shown. Tyrosine, a precursor for multiple biological products, becomes an indispensable AA and must be provided by the diet for those with PKU. Under physiological conditions PAH catalyzes about 75% of the phe input from the diet and protein catabolism.

David Pagliarini PhD

Associate Professor of Biochemistry

Mitochondrial proteins, pathways, and pathogenesis

Figure: EM images of mouse liver, heart and kidney mitochondria (respectively).

Dr. Pagliarini studies mitochondria — complex organelles whose dysfunction underlies a broad spectrum of human diseases. Mitochondria house a wide range of metabolic pathways, and are central to apoptosis, ion homeostasis and reactive oxygen species production. As such, to maintain cellular homeostasis cells must exert careful control over their mitochondrial composition and function.

How do cells custom-build mitochondria to suit their metabolic needs? What mechanisms do cells use to efficiently control mitochondrial processes? Which mitochondrial processes are disrupted in diseases and how might these be targeted therapeutically? What are the functions of disease-related orphan mitochondrial proteins?

The Pagliarini lab takes a multi-disciplinary approach to investigating these questions. By integrating classic biochemistry, molecular biology and genetics with large-scale proteomics and systems approaches, they aim to elucidate the biochemical underpinnings of mitochondrial dysfunction in human disease.

Brian Parks PhD

Assistant Professor of Nutritional Sciences

Leveraging genetics to discover drivers of metabolic disease

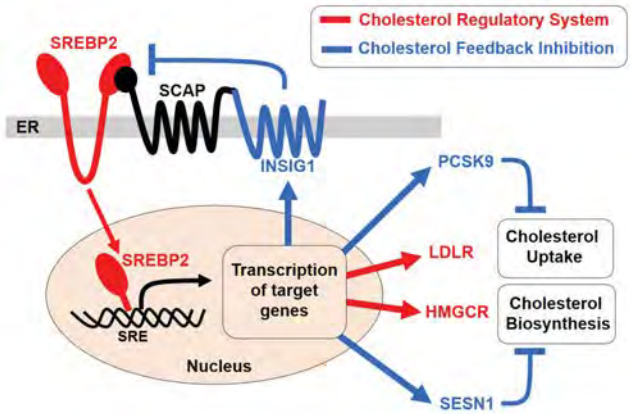
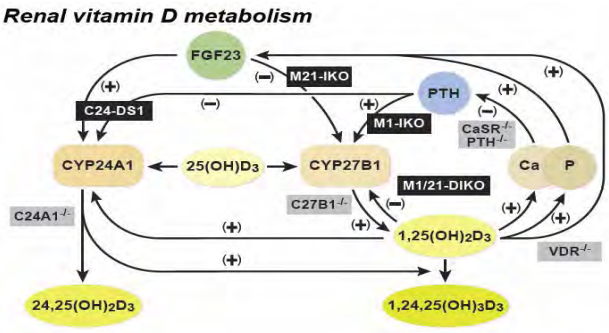


Figure: Cholesterol biosynthesis is controlled by a feedback inhibition mechanism primarily through the action of Insig1 (Insulin induced gene 1). Under cholesterol depletion, SREBP2 is activated for transcriptional activated of cholesterol biosynthesis by HMGCR and/or cholesterol uptake by LDLR, termed as cholesterol regulation (red line). Insig1, which is a target gene of SREBP2, is up-regulated, leading to retention of the Scap-SREBP complex and causing SREBP2 inactivation. This is called cholesterol feedback inhibition (blue line). In our study, Sesn1, which is found to be a target of SREBP2, can also inhibit cholesterol biosynthesis through activation of AMPK signaling. Our finding establishes Sesn1 as another regulator of cholesterol feedback inhibition.

Dr. Parks studies the underlying genes and biological pathways that contribute to cardio-metabolic diseases in humans. Using genetic, computational, and biochemical approaches the laboratory seeks to discover genes and the pathways through which they confer disease predisposition. The main areas of focus include; a) cholesterol and lipid biosynthesis regulation, b) regulation of blood insulin levels during obesity, and c) utility of genetic interaction analysis (epistasis) for biological discovery. Recent work has focused on the cholesterol biosynthetic pathway. Using genome-wide computational networks and human genetic data for plasma cholesterol, we identified Sestrin1 (SESN1) as a direct negative regulator of cholesterol biosynthesis. We are now working on understanding molecular mechanism through which Sestrin1 can regulate cholesterol biosynthesis and the mechanism through which it modifies blood cholesterol levels in humans.

J. Wesley Pike PhD
Professor of Biochemistry
Transcriptional mechanisms of vitamin D production and action

The **Pike** laboratory studies the mechanisms through which steroid hormones and other genomic regulators selectively modulate the transcription of genes. A special emphasis over the years has been on the details through which the vitamin D hormone and its nuclear receptor control the expression of genes in the intestine, kidney and bone. We use contemporary methods to explore the mechanisms and to identify the genomic targets of the vitamin D hormone as well as those for the peptide hormones PTH and FGF23 that control mineral homeostasis. These studies have identified not only the genes that are involved, but the genomic control regions that mediate the regulation of these genes as well. Many of these methodological advances have allowed us to explore this regulation in the mouse in vivo, enabling the study of hormonal regulation across diverse tissues in a wide range of physiological and pathophysiological states. Our most recent studies have focuses on the molecular mechanisms through which PTH, FGF23 and the vitamin D hormone itself control the production of key vitamin D metabolites, from the kidney. These studies have revealed not only the mechanisms through which blood levels of the vitamin D hormone are controlled in response to extracellular phosphate and calcium, but also the nature of separate mechanisms through which vitamin D controls distinct biological events in the skin, the cardiovascular system and in immune cells.



Federico Rey PhD
Associate Professor of Bacteriology
Gut microbiome, diet and cardiometabolic disease

Human studies have revealed consistent alterations in the gut microbiomes of patients with cardiometabolic and aging-associated diseases. A major focus of the Rey lab is to understand how variations in the gut microbiome modulate the effects of diet and host's susceptibility to cardiometabolic disease. To address these issues, we use a combination of hypothesis-generating, sequencing-centered analyses of microbiomes from humans and mice, followed by proof-of-principle/proof-of-mechanism studies in gnotobiotic mouse models of disease and classic bacteriology experiments. Our recent studies have revealed between dietary plant polysaccharides (i.e., fiber) and bacteria that lower inflammation and slow progression of atherosclerosis.

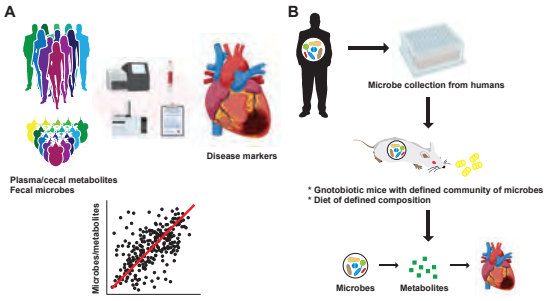


Figure: Identifying microbes and metabolites that contribute to CVD. **A.** Discovery pipeline starts with hypothesis-generating screen (plasma/cecal metabolites, fecal microbes) of humans/rodents with desired cardiovascular phenotypes. **B.** Features that show strong correlation with disease are further tested in gnotobiotic mice harboring communities that vary in specific microbes and/or microbial functions.

Scott Reeder MD
Professor of Radiology
Quantitative MRI Biomarkers of Metabolic Diseases

As the Director of the University of Wisconsin Liver Imaging Research Program (UW-LIRP), I lead the development of quantitative imaging biomarkers of metabolic diseases such as ectopic fat deposition in the liver and central adiposity, as well as biomarkers of abnormal iron deposition. Our work is focused on quantifying liver fat deposition in non-alcoholic fatty liver disease and iron in the genetic disorder hemochromatosis. The UW-LIRP performs fundamental image acquisition and reconstruction techniques, particularly using MRI, as well as validation in human clinical trials (https://lirp.radiology.wisc.edu).

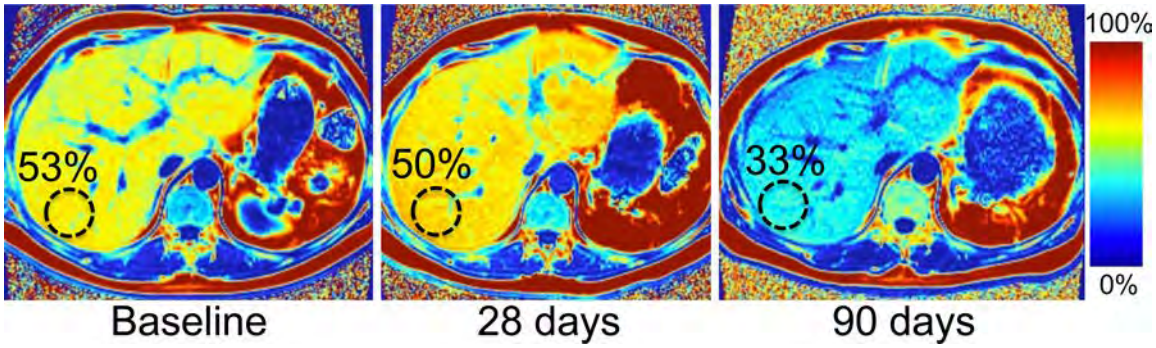


Figure: Serial MRI proton density fat fraction (PDFF) maps in a patient with recalcitrant hypertriglyceridemia (>10,000 at baseline) treated with plasmapheresis. Serial studies demonstrate not only a significant drop in the concentration of liver fat from 53% to 33% but also a decrease in the overall size of the liver. This example demonstrates the ability of MRI to monitor this patient during treatment, within a single 20 second breath-hold, no ionizing radiation and no contrast.

William Schrage PhD
Professor of Kinesiology
Cardiovascular control during dietary, environmental, or exercise challenges

We study the causes of obesity-related alterations in blood vessels perfusing skeletal muscles and brains, and the mechanisms responsible. In other words, how do our bodies regulate blood flow, and how does this change with obesity or prediabetes? We pursue the mechanisms responsible for this, including signals from nerves, contracting muscles, substances in the blood, adipose tissue, from immune cells, and the vessels themselves. While much of our research focuses on the cardiovascular response to a single stressor (acute exercise or hypoxia), we also consider these responses before and after long-term interventions. We quantify blood flow with doppler ultrasound, or magnetic resonance imaging, and use acute drug interventions to test mechanisms that may have gone awry in obesity-related conditions.

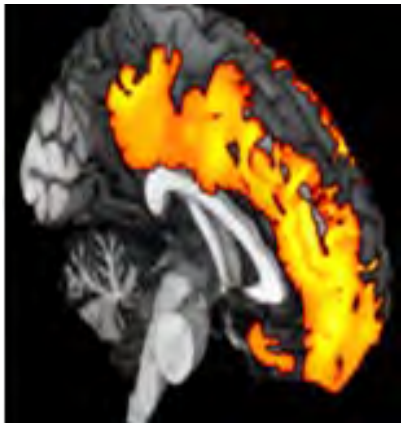
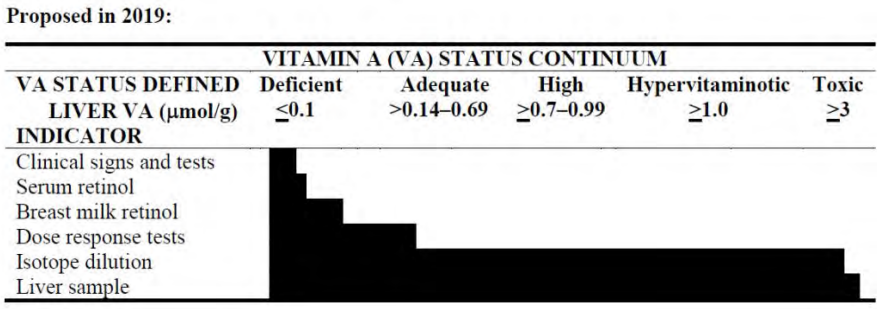


Figure: Composite analysis of microvascular brain perfusion using Arterial Spin Labeling (ASL) MRI scans. The distribution and amount of perfusion (and thus oxygen delivery) changes in aging and cardiovascular diseases.

Sherry Tanumihardjo PhD
Professor of Nutritional Sciences
The Vitamin A Status Continuum

Dr. Tanumihardjo has two major research foci: methods to assess vitamin A and carotenoid status. Special emphasis is on provitamin A carotenoids in foods to improve vitamin A status in humans world-wide. Dr. Tanumihardjo has developed many unique techniques to assess vitamin A status. The Tanumihardjo laboratory uses animal models to develop and test hypotheses, i.e., rats, gerbils, pigs, and monkeys. Ultimately, her methods are applied to humans for evaluation. Her trainees have developed and simplified methods, e.g. the modified relative dose response test and breast milk retinol determinations, which can be used in labs lacking sophisticated equipment. Dr. Tanumihardjo developed a stable isotope method that is very sensitive and provides enhanced accuracy over prior methods. It is currently being used to determine human vitamin A requirements and will be used to investigate interactions with other nutrients and diseases. Her carotenoid studies have examined the uptake and clearance of carotenoids from specialty carrots and staple crops through chronic and acute feeding.



Amy Trentham-Dietz PhD
Professor of Population Health Sciences
Epidemiology of cancer risk, detection, and survivorship

Obesity and physical inactivity are established risk factors for several cancers including breast cancer. We focus on 1) improving our understanding of the relationships between diet, body weight and weight gain with mammographic breast density, an intermediate risk marker of breast cancer; 2) incorporating diet and other risk factors into prediction models to tailor cancer screening recommendations and improve outcomes of screening programs; and 3) extending our knowledge of the impact of diet, obesity and physical activity on cancer survivorship.

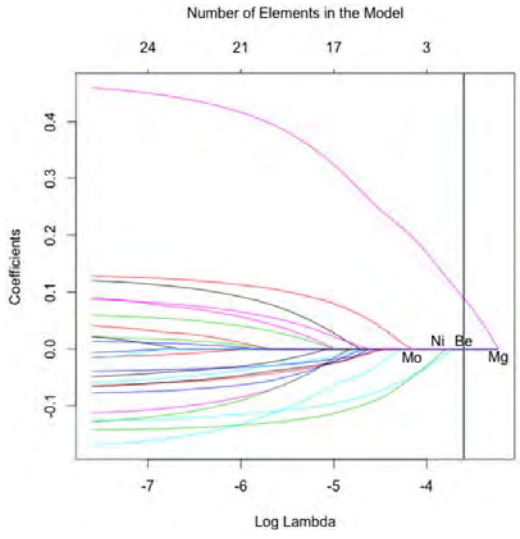


Figure: Automated variable selection for a regression model of heavy metals and other elements in relation to breast density. Logistic regression coefficients for each element and the number of elements in the regression model shown as a function of the LASSO penalty parameter (log lambda). The model on the far left corresponds to the unconstrained maximum likelihood estimate (all elements); the model on the far right corresponds to the null model (no elements). The vertical line corresponds to the optimal model by cross-validation with a single element, magnesium. Every model includes all potential confounders. Abbreviations: LASSO, least absolute shrinkage and selection operator; Be, beryllium; Mg, magnesium; Mo, molybdenum; Ni, nickel.(Mora-Pinzon *Nutr Cancer* 2018)

Eric Yen PhD
Associate Professor of Nutritional Sciences

Intestinal regulation of systemic metabolism

Dr. Yen studies the roles of intestine in mediating metabolic responses to diet. The intestine is the location where diet, gut microbiota, and host interact. In addition to assimilating diet, the intestine signals and modulates the availability incoming nutrients to the rest of the body and thus controls systemic metabolism. Dr. Yen's group is interested specially in the roles of intracellular lipid processing of enterocytes. One current focus is on acyl CoA:monoacylglycerol acyltransferase 2 (MGAT2). Using tissue-specific gain- and loss-of-function models, Dr. Yen's group showed that intestinal MGAT2 enhances metabolic efficiency and promotes weight gain – mice lacking the enzyme exhibit delayed fat absorption, increased energy expenditure, and resistance to diet-induced obesity and related metabolic disorders. These findings helped prompt the development of several MGAT2 inhibitors as potential therapeutics. In addition, using genetically engineered mice, his MANTP-funded pre-doctoral trainee Mitchell Lavarias identified intestinal fatty-acid oxidation as a major contributor to maintaining systemic lipid homeostasis. Dr. Yen's group is now combining biochemical and systems biology approaches to understand the intracellular mechanisms and inter-organ communication, by which intestinal lipid processing regulates systemic metabolism.

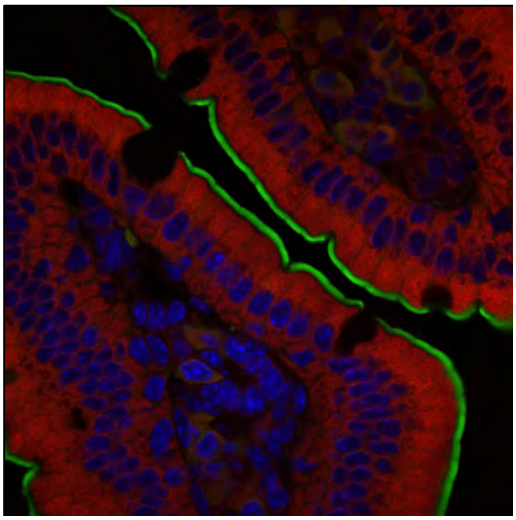


Figure: MGAT2 in the enterocytes. Immunofluorescence micrograph. MGAT2 (Red); Villin, which binds microvillar actin and marks apical membrane of enterocytes; (Green); DAPI stained Nuclei (Blue)