Alyssa Hasty is an Associate Professor in the Department of Molecular Physiology and Biophysics. Dr. Hasty is also the Director for the Gastrointestinal Physiology, Obesity, and Metabolism Program of the Vanderbilt Digestive Disease Research Center (VDDRC). She received her PhD in Pathology from Vanderbilt University in 1998 and completed her post-doctoral fellowship at Tokyo University. Dr. Hasty’s group now studies the role of adipose tissue macrophages in the metabolic consequences of obesity.

It has been less than 10 years since the report that macrophages, cells of the innate immune system, infiltrate adipose tissue in obesity. This was a ground-breaking discovery as adipose tissue macrophages were thought to contribute to local and systemic inflammation, which could explain the increased risk of metabolic diseases in obese individuals. Since then, over 1000 papers have been published on this topic. Most of the published research since these original discoveries has focused on the following: 1) how do macrophages and adipocytes interact with one another, 2) what are the factors that mediate the recruitment of macrophages to adipose tissue, 3) what is the polarization or inflammatory status of the adipose tissue macrophages, and 4) what other immune cell types enter adipose tissue. The discovery that B and T lymphocytes also enter adipose tissue significantly advanced our understanding that both innate and adaptive arms of the immune system converge in adipose tissue, opening up the exciting possibility that complex immune responses can occur there. During the past 7 years, the Hasty laboratory has focused on different chemokines and chemokine receptors that may recruit macrophages to adipose tissue. Furthermore, they have become intrigued by the presence of unique populations of myeloid cells in the adipose tissue that have a different inflammatory profile compared with traditionally studied macrophages. Finally, they have become interested in whether macrophage numbers in adipose tissue can be reduced, either by apoptosis or by emigration from the tissue. If the number of inflammatory macrophages in adipose tissue can be reduced, it might be able to dissociate obesity from its metabolic consequences.
October 26, 2010 Seminar Series Speaker:
Keith Sharkey, Ph.D.
Professor and Al-HS Medical Scientist
Crohn’s and Colitis Foundation of Canada Chair in IBD Research
University of Calgary - Physiology & Pharmacology

The focus of Dr. Sharkey’s lab is the role of nerves in the gastrointestinal (GI) tract in intestinal inflammation. The GI tract has a dual autonomic innervation and its own, enteric nervous system. The relative roles the different neural components of the gut make to physiological and pathophysiological processes in the intestine are only now being fully understood. Dr. Sharkey’s studies seek to explore the role of nerves in the function of the GI tract in health and in inflammatory diseases of the GI tract.

A synopsis of Dr. Sharkey’s presentation:
The enteric nervous system (ENS) controls all the functions of the gut. Specific populations of enteric neurons have been identified that regulate motility, secretion, etc. Enteric glia are intimately associated with neurons in the ENS, and are thought to be supportive to neurons. Enteric glia display morphological and molecular similarities to central nervous system astrocytes. The expression of neurotransmitter receptors by enteric glia suggests that, like astrocytes, they are active participants in neuronal communication. Dr. Sharkey discussed how enteric glia participate in functional responses to nerve signaling and may be involved with neurons in regulating the workings of the gut.

November 2, 2010 Seminar Series Speaker
Jay Solnick, M.D., Ph.D.
Professor of Medicine and Microbiology & Immunology
University of California, Davis

Dr. Solnick is a microbiologist and infectious disease physician whose research seeks to understand the pathogenesis of Helicobacter pylori, a bacterium that causes peptic ulcers and gastric cancer. There are two major lines of investigation in his laboratory. First, how does the bacterium modify outer membrane proteins and other surface structures to avoid host immunity and persistently colonize the gastric epithelium? Second, what is the role of defensins and other innate immune effectors in the chronic colonization by H. pylori? These and related questions are addressed using a wide range of molecular and biochemical methods, as well as primate and murine animal models.

A synopsis of Dr. Solnick’s presentation:
Strains of H. pylori that cause clinical disease are more likely to express a functional cag pathogenicity island (PAI) and the outer membrane adhesin, BabA, than are strains that simply cause asymptomatic gastritis. Our studies in rodent and non-human primate models have elucidated mechanisms by which H. pylori modifies the cag PAI and outer membrane proteins, a strategy that likely contributes to persistent infection.
December 7, 2010 Seminar Series Speaker
Justin Sonnenburg, Ph.D.
Assistant Professor of Microbiology & Immunology
Stanford University School of Medicine

Dr. Sonnenburg’s research program aims to elucidate the basic principles that govern interactions within the intestinal microbiota and between the microbiota and the host. Specifically, we are exploring how perturbations in the intestinal environment, such as changes in host diet, microbial community composition, pathogen exposure, host genotype, and microbiota-targeted small molecules alter microbiota structure and function, and how these changes, in turn, influence host biology. To pursue these aims, we study germ-free (gnotobiotic) mice colonized with simplified, model microbial communities, apply systems approaches (e.g. functional genomics) and use genetic tools for the host and microbes to gain mechanistic insight into emergent properties of the host-microbial superorganism.

One major challenge in obtaining a basic and mechanistic understanding of the microbiota is teasing apart relationships within this excessively complex community. Germ-free mice serve as an ideal platform for creating a defined community of microbial species amenable to controlled experimental investigation using tools emerging from the ongoing genomic revolution. Recent molecular enumerations of the human microbiota have established that greater than 90% of bacterial cells in the distal gut microbiota are members of one of two dominant divisions (phyla): the Bacteroidetes and the Firmicutes. Therefore, the microbiota can be reasonably modeled in the intestines of gnotobiotic (ex-germ-free; gnoto = known, bios = life) mice using a simplified community composed of species that represent the prevalent microbial taxa.

January 17, 2011 Seminar Series Speaker
Mark Knepper, M.D., Ph.D.
Chief, Laboratory of Kidney & Electrolyte Metabolism
National Heart Lung & Blood Institute
National Institutes of Health (NIH)

Vasopressin is a peptide hormone that regulates water balance in the body by controlling the rate of urinary water excretion. Several disorders of water balance ascribe to failures in this process. It has long been recognized that vasopressin binds to receptors on the basolateral plasma membrane of collecting duct cells and increases the permeability of the cells to water, allowing water to be reabsorbed from the urine to blood. We are investigating the mechanisms of the water permeability increase on a cellular and molecular basis. Our experiments have demonstrated the presence of water-selective channels called “aquaporins” in collecting duct cells. One of these aquaporins (aquaporin-2) is regulated by vasopressin. We have demonstrated that aquaporin-2 water channels are present in intracellular vesicles that, in response to a rise in intracellular cyclic AMP, fuse with the apical plasma membrane, increasing the water permeability of this membrane. We have also shown that vasopressin positively regulates transcription of the aquaporin-2 gene. Current studies focus on the molecular apparatus responsible for trafficking water channel-laden vesicles as well as the mechanisms involved in regulation of aquaporin-2 gene transcription. These studies utilize a wide variety of technical approaches including: 1) shotgun and targeted proteomics using protein mass spectrometry; 2) oligonucleotide expression arrays (Affymetrix); 3) knockout mouse models; 4) in vitro perfusion of microdissected renal tubule segments from kidneys to measure water transport; 5) mutational and siRNA knockdown approaches in cultured collecting duct cells; 6) immunochemical approaches to assess the abundance, intracellular distribution, and post-translational modification of physiologically important transporters; 7) biochemical analysis of microdissected renal tubule segments; and 8) computational methods including differential-equation-based mathematical modeling.

Current emphasis is on: 1) the molecular basis of regulated vesicular trafficking of the molecular water channel aquaporin-2 in the renal collecting duct; 2) the mechanisms involved in control of expression of the aquaporin-2 gene by vasopressin; 3) development of methods for quantitative proteomics and phosphoproteomics; and 4) development of computational methods for systems biological study of vasopressin signaling in the renal collecting duct.
Christian Jobin, Ph.D.

"Interaction between inflammation, microbial composition and colorectal cancer"

April 7, 2011 Seminar Series Speaker

Christian Jobin, Ph.D.
Associate Professor
University of North Carolina Department of Medicine

Dr. Jobin’s research program focuses on an important medical problem: the pathological consequences of a dysregulated immune host response to the intestinal non-pathogenic commensal microflora. Dr. Jobin has a longstanding interest in characterizing the mechanism governing host response to the intestinal microflora in respect to intestinal inflammation and colon cancer. This research involves the study of signaling pathways (TLR, Nod, NF-kB) regulating innate host response to bacterial colonization in the intestine. To selectively address the interplay between the host and bacteria, we utilize axenic mice (germ free) derived at the National Gnotobiotic Rodent Resource Center at UNC-Chapel Hill. Dr. Jobin is the principal investigator of two NIH RO1 projects investigating the role of immunosuppressive molecules in IBD and the role of bacteria in colitis-associated colon cancer. Overall, this research program is an example of translational molecular medicine where fundamental disease-selective mechanisms could be utilized to design novel therapeutic strategies to alleviate inflammation, restore healing and prevent development of inflammation and colon cancer.

John M. Miles, M.D.

"Trafficking of dietary and endogenous lipid fuels: a new old role for lipoprotein lipase?"

April 26, 2011 Seminar Series Speaker

John M. Miles, M.D.
Professor of Medicine
Mayo Clinic, Rochester, MN

Dr. Miles conducts in vivo research in human lipid fuel metabolism, including free fatty acids and triglyceride-rich lipoproteins. He has developed several novel tracer techniques that involve the intravenous infusion of radiolabeled substrates. The primary objective of his research is to characterize the systemic and regional partitioning of free fatty acids and triglycerides between storage and oxidation pathways. He is currently applying these techniques to the study of the deranged metabolism of the metabolic syndrome and type 2 diabetes. Studies of regional metabolism in the forearm, in adipose tissue and in the splanchnic bed are underway. A preliminary study of myocardial triglyceride and free fatty acid metabolism, utilizing coronary sinus blood sampling, has also been started.

"The art of healing comes from nature, not from the physician. Therefore the physician must start from nature, with an open mind."

~Philippus Aureolus Paracelsus
The VDDRC News Digest is the official publication of the VDDRC. Each issue features an area of research interest and highlights research activities. The Digest also includes news, a feature publication by a VDDRC member, and upcoming events. If you have suggestions for a future issue of the VDDRC News Digest, please contact us.

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The Vanderbilt Digestive Disease Research Center

**Mission and Goals**

The DDRC is a multidisciplinary center at Vanderbilt University Medical Center developed to serve the following purposes:

1. Promote digestive diseases-related research in an integrative, collaborative and multidisciplinary manner
2. Enhance the basic research capabilities of established DDRC investigators
3. Attract investigators not involved in digestive diseases-related research to pursue these lines of investigation
4. Develop and implement programs for training and establishment of young investigators in digestive diseases-related research
5. Facilitate the transfer of basic research findings to the clinical area