Vassilis Pachnis, M.D., Ph.D., is the 2011 Vanderbilt Digestive Disease Center (VDDRC) Retreat Keynote Speaker. His presentation entitled “Enteric Nervous System development: recent progress and future challenges” will be delivered on Monday, January 24, 2011 at 4 pm in the Board of Trust room located in the Student Life Center.

Dr. Pachnis earned his M.D. from University of Athens Medical School in 1980 and earned his Ph.D. in genetics at the University of Pennsylvania in 1986. He is currently Head of the Division of Molecular Neurobiology at the National Institute for Medical Research in London, England.

Dr. Pachnis’ research team focuses on the mechanisms that control the development of the enteric nervous system of the gut; how enteric neurons and their progenitors migrate during embryogenesis and how they differentiate to form complex networks that regulate gut motility and secretions. His group also studies the mechanisms that control neuronal differentiation in the forebrain. They have identified signals that mediate cellular interactions, molecules that underlie the functional interconnection of neurons and transcription factors underlying neuronal cell fate decisions. These studies provide novel insight into the development and function of the nervous system in normal and disease conditions.

Pilot/Feasibility Projects for 2011

Holly Algood, Ph.D.
The Role of IL-21 in H. pylori immunopathogenesis

Kate Ellacott, Ph.D.
The Effect of Diet-induced Obesity on Enteric Glia

Alfred George, M.D.
Intestinal Microbiota as a Risk Factor in Necrotizing Enterocolitis

James Goldenring, M.D., Ph.D.
Mapping the cell lineages of the normal and obese human stomach

Danyvid Olivares-Villagomez Ph.D.
Impact of the microbiota on naïve T cell responses

Dengping Yin, M.D., Ph.D.
Gastric bypass regulates liver inflammation in mice

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POINTS OF INTEREST:

• 2011 VDDRC Retreat Keynote Lecture - Vassilis Pachnis, M.D., Ph.D.
• Six P&F Recipients 2011
• Spotlight, Young Investigator Award Recipient – Kate Ellacott, Ph.D.
Young Investigator, Kate Ellacott, Ph.D.

Dr. Kate Ellacott completed her Ph.D. at the University of Manchester, UK in 2002. She completed her post-doctoral training in Neuroendocrinology in 2006 at the Vollum Institute/CSWR, Oregon Health and Science University in Portland, OR.

The focus of her lab is how obesity influences nervous system function. Obesity is associated with chronic low-grade inflammation which negatively influences the function of a number of organ systems contributing to the development of insulin resistance, hepatic steatosis, atherosclerosis and cardiovascular disease. The effects of obesity-associated inflammation on nervous system physiology are poorly understood. Individuals with obesity are more susceptible to the development of neurodegenerative disease and severe complications following traumatic brain injury or ischemic insult; however, the mechanisms underlying this increased central nervous system (CNS) vulnerability are not clear. Her group is using a combination of in vivo, neuroanatomy and molecular biology approaches to examine how obesity changes CNS physiology with an emphasis on the blood-brain barrier and glia.

Dr. Ellacott’s pilot project will focus on glial cells of the enteric nervous system (ENS). This will represent a new direction for the lab which has previously focused primarily on the CNS; however, there are many parallels between the CNS and ENS and her experience with CNS glia means that her laboratory has many of the tools and techniques required already in place.

As Director of the Energy Balance Subcore of the Vanderbilt Mouse Metabolic Phenotyping Center, Dr. Ellacott has extensive experience with in vivo studies relating to obesity in mice. She has generated and used both genetic and diet induced obesity models in mice and is familiar with their pathophysiology.

Holly Algood, Ph.D.

Dr. Holly Algood is a Research Instructor at Vanderbilt University and a Research Scientist at the VA Tennessee Valley Health Care System (TVHC) where she has been investigating H. pylori with funding from a Career Development Award (CDA). Dr. Algood obtained her Ph.D. at the University of Pittsburgh in Microbiology. She did her post-doctoral fellowship in the Department of Medicine at Vanderbilt and the TVHS and has been studying the immune response to H. pylori.

H. pylori is a Gram-negative bacterium that colonizes the stomach in an estimated 50% of the population and is associated with an increased risk of gastric cancer and peptic ulcer disease. The immune response to H. pylori is ineffective in clearing the infection, but in most cases, it successfully restricts bacterial proliferation, and most H. pylori infected persons remain asymptomatic. The immune response to H. pylori involves a mixed T helper-1, T helper-2 and T helper-17 response. It has been suggested that T cells contribute to the gastric inflammatory response during infection, and that Th1 and Th17 cell subsets may be required for control of H. pylori colonization in the stomach. The relative contributions of these subsets are still under investigation. Meanwhile, new populations of CD4+ T helper cells are being defined, including the follicular helper T cells (Tfh). One common link between Th17 cells and follicular T helper cells is their production of IL-21. IL-21 plays a role in both B cell stimulation and T cell differentiation. While the role of IL-21 has not been investigated in models of H. pylori, Dr. Algood has preliminary data that suggests IL-21 contributes to the control of infection and severity of gastritis. H. pylori-infected IL-21 deficient mice have significantly higher levels of H. pylori in their stomachs and significantly less gastritis compared to H. pylori-infected wild-type mice. The role of IL-21, in the context of Th17 responses, Th1 responses, T regulatory cells and follicular T helper responses will be investigated. These experiments will contribute to the understanding of the immune pathology associated with mucosal infections at epithelial cell surfaces and immune-mediated diseases, such as inflammatory bowel disease.
Alfred George, M.D.

Dr. Alfred George has more than 20 years of experience investigating the structure, function and molecular genetics of human ion channels. He has been Scientific Director of the Vanderbilt DNA Sequencing Facility for 10 years and has 15 years of experience with automated DNA sequencing technologies. He has experience with next-generation sequencing using the Roche 454 and Illumina Genome Analyzer platforms. His research has focused on inherited disorders of heart and brain ion channels that predispose the sudden cardiac death and epilepsy in childhood and early infancy.

Dr. George’s translational pilot project will use the expertise of another independent physician-scientist from a different discipline (Dr. Hendrik Weitkamp) to translate basic science observations regarding microbial colonization of the human intestinal tract, the intestinal microbiome, to understand the risk of a life-threatening condition that arises in infancy, Necrotizing Enterocolitis (NEC). NEC is the most common surgical emergency in preterm infants. Bacteria are believed to be important in the pathogenesis of NEC; however no specific pathogen has been identified through conventional microbial culture techniques. Recent advances in DNA sequencing technologies have created new opportunities to investigate the human microbiome and to test hypotheses regarding the contribution of microbiota to the pathogenesis of human disease.

The major goals of his translational pilot project are to: 1) prospectively ascertain NEC cases and non-NEC controls; 2) collect paired DNA samples from feces and resected tissue from each case and control subject; 3) generate bacterial 16S rRNA sequence data from each DNA sample; and 4) perform comparisons of microbial diversity within and among groups. He will test two complementary hypotheses: 1) Microbial communities in feces and resected intestinal tissue from the same patient share greater similarities in microbial diversity than comparison among patients; and 2) NEC infants harbor distinct intestinal microbiota as compared to control subjects.

James Goldenring, M.D., Ph.D.

Dr. James Goldenring is a leader in the study of preneoplastic changes related to gastric cancer and the roles of mucosal stem cells in generating metaplasia and cancer. His work has refined concepts of the origin of metaplasia and altered views of the plasticity of differentiated cells, which manifest properties of cryptic progenitor cells. In recognition of this work, Dr. Goldenring received the 2004 AGA Funderburg Research Award in Gastric Biology Related to Cancer. He has extensive experience in the characterization of gastric cell lineages and has recently developed the present research related to the role of endocrine cells and luminal sensing brush cells in gastric injury and obesity.

Treatment of obesity has increasingly come to rely on surgical procedures that either restrict the size of the stomach or provide for partial bypass of the stomach. Gastric bypass patients experience postoperative relative anorexia as well as reversal of metabolic syndrome and Type II diabetes. Most recently several reports have indicated that gastric sleeve resection can provide equivalent benefits compared with gastric bypass operations. While a number of studies have suggested that bariatric surgery disrupts signaling between the stomach and the brain, the identity of the cells signaling to afferents to the vagus nerve remain obscure. Given the success of the sleeve resection, it would appear that key signaling cells must reside in the greater curvature of the stomach, which is removed in the sleeve resection. Unfortunately, there are no detailed data examining the normal distribution of cell lineages within the gastric mucosa and similarly there are little data on alterations in cell lineages that might occur along the greater curvature of the obese stomach. Dr. Goldenring’s group has hypothesized that regional distributions of endocrine and sensory (brush) cells within the gastric mucosa may account for the changes observed after gastric sleeve resection. Therefore he will first create a geographical map of lineages in the entire stomach in total stomach specimens arrayed from normal, non-obese organ donors. Second, he will compare the geographic distribution of cell lineages in the greater curvature of sleeve resections from obese patients to that in the normal stomach. These studies will establish the distribution of gastric lineages in the normal stomach and will provide the first in depth analysis of lineages in the greater curvature of the stomach. These investigations may lead to new insights into specific cell lineages that could be targeted directly for the treatment of obesity.
Danyvid Olivares-Villagomez, Ph.D.

Dr. Danyvid Olivares-Villagomez received his Ph.D in Immunology from New York University in 2000. He received his M.S. degree in Science in 1996 at Vanderbilt and his B.S. degree from the National and Autonomous University of Mexico in 1991. He currently is a Research Assistant Professor in the Department of Microbiology and Immunology at Vanderbilt.

Dr. Olivares-Villagomez’s research will investigate the influence of the intestinal microbiota in the adaptive immune response. Recent evidence has indicated that the microbiota shapes the proportion of CD4+ T cells in the lamina propria, which are capable of triggering Th17 and/or IL-17 immune responses important for the maintenance of commensal bacteria homeostasis and protective immune responses against pathogenic microorganisms. Additionally, his group has observed that development of colitis in the adoptive transfer of spleen-derived naive T Cell (CD4+CD45RBhi) murine model, depends on the origin of the donor cells, i.e., cells obtained from mice from commercial sources behave differently than cells derived from his own colony. Considering these previous reports and observations, his group hypothesizes that different microbiota modifies the non-mucosal adaptive immune response, and subsequently influences the susceptibility to inflammatory bowel disorders. His pilot project will be developed over a period of two years, which should yield relevant information to pursue a more comprehensive approach for this line of research.

Dengping Yin, Ph.D.

Dr. Dengping Yin received his Medical License from Three Gorges University, China in 1983 and received his Ph.D. in Surgery from Tongji Medical University, China in 1992. He is an Assistant Professor within the Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery.

Dr. Yin began his research at Stanford University Medical Center in transplantation immunology and in the development of microsurgical models in mice. After passing the ECFMG (USMLE) examination he continued his research as a surgical resident/fellow at the University of Illinois Hospital. He was awarded a JDRF research grant and came to Vanderbilt in 2006 to continue his transplant research.

Dr. Yin became interested in bariatric surgery over the last two years in collaboration with Drs. Wasserman, Abumrad and Cone. Bariatric surgery is one of the best approaches for obesity and diabetes. However, a reliable mouse bariatric surgery model is lacking. His model is important to explore the mechanisms of bariatric surgery in the treatment of obesity and diabetes. Dr. Yin recently developed expertise that provides a unique opportunity to examine the effects of bariatric surgery on the cellular and molecular events of inflammatory responses that accompany obesity and insulin resistance. The pilot project will analyze glucose metabolism, hormone action and immune responses. Dr. Yin’s expertise in transplantation immunology, using a variety of animal models, and expertise in microsurgery will provide the scientific foundation for the development of strategies that advance the treatment of obesity and T2DM based on the metabolic and immunological mechanisms of bariatric surgery.

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
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