The increasing prevalence of obesity and type 2 diabetes poses a significant health problem worldwide.......
interests are centered on the role of protein tyrosine phosphatases (PTPs) in metabolism, with a particular focus on central nervous system (CNS) signal transduction pathways that control body weight and glucose homeostasis.

Mind over matter? CNS signaling and control of energy balance

The increasing prevalence of obesity and type 2 diabetes poses a significant health problem worldwide. Understanding the cellular signaling pathways underlying these pathological states is critical for the future development of therapeutics designed to treat these conditions. The brain is a master regulator of body mass control, with many neural pathways contributing to the control of food intake and energy expenditure. Circulating factors such as the adipocyte-secreted hormone leptin, insulin and certain cytokines, regulate energy balance via neuronal circuits (see Figure 1). Notably, leptin initiates an intracellular signaling cascade that leads to changes in ion channel activity and gene expression that ultimately keep energy balance in check. All of these signaling pathways are tightly controlled by tyrosine phosphorylation, and Dr. Bence’s lab focuses on how these pathways are regulated by protein tyrosine phosphatases (PTPs).

Figure 1. Model of PTP regulation of energy balance pathways in the brain. PTP1B and SHP2 may have leptin-dependent and leptin-independent effects in neuronal control of energy balance.

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SEARCH TOOLS to find funding opportunities and reports........

SMARTS: Free Access with valid Penn Key; SPIN is an up-to-date listing of funding opportunities from national and international governmental and private funding. Go to https://www.pennera.upenn.edu/

To set up SMARTS, at the PennERA portal page, click “Find Funding” in the left menu, then click “SMARTS.”

You must select and configure the “Preferences” and “Keywords” sections (which are listed in the left menu under SMARTS). It is recommended that, at least initially, you leave the other sections in their default settings state (more restrictions on search criteria may unnecessarily limit your SMARTS matches). You must have a valid e-mail address in your PennERA profile to obtain SMARTS funding updates.

NEW NIH Tool: CRISP is being retired. The NIH has released to the public a beta version of its new Research Portfolio Online Reporting Tool Expenditures and Results (RePORTER) tool. This new tool retains all of the features of CRISP while providing additional query fields, hit lists that can be sorted and downloaded to Excel, NIH funding for each project (expenditures), and the publications and patents that have acknowledged support from each project (results). RePORTER also provides links to PubMed Central, PubMed, and the US Patent & Trademark Office Patent Full Text and Image Database for more information on research results. New features will be added to RePORTER in several releases throughout fiscal year 2010. This site provides access to reports, data and analysis on NIH research activities. Go to this link to reach the query form: http://projectreporter.nih.gov/reporter.cfm
FAREWELL TO GERRY

Gerhard A. “Gerry” Schad, 81, Professor of Parasitology in the Department of Pathobiology for more than 35 years, died after a long battle with cancer on April 25, 2009. He was interested in neurological aspects of the developmental biology of parasitic nematodes using the free living nematode, Caenorhabditis elegans, as a model. Dr. Schad gained worldwide recognition as an authority on the population biology of helminth parasites and their behavioral neurobiology, and made significant discoveries about the epidemiology of hookworm, a major tropical disease. In the last 10 years of his work, Dr. Schad focused his research on the sensory biology of parasites that may help better control parasites in the future. Of his many awards and accolades, Dr. Schad was most proud of the American Society of Parasitologists’ Clark Read Mentor Award in recognition of his leading role in training young scientists. He was also proud of his McGill University regalia, especially the black velvet hat shown in his portrait painted in 2008. A departmental memorial service for Dr. Schad is being planned.

ED PEARCE TO JOIN TRUDEAU INSTITUTE

The Penn Vet community wishes Dr. Edward Pearce and his family well as they relocate to the Trudeau Institute in Saranac Lake, NY. Dr. Pearce joined Penn Vet in 2001 as an associate professor and was quickly appointed Director of the Veterinary Center for Infectious Disease Research. Under his leadership, the Center rapidly instituted a Research Initiative Fund, to provide funds for urgent new infectious disease-related research projects at the School, and a Infectious Disease Research Fellowship Program, to provide salary and research support for qualified veterinarians to gain hands-on experience in infectious disease research at the School. As an obviously integral member of the Department of Pathobiology, Dr. Pearce was appointed Professor in 2004.

Dr. Pearce is a parasitologist by training and his research focuses on the biology of the helminth Schistosoma mansoni, and on the host immune response to this parasite during infection. Schistosomes infect hundreds of millions of people in developing countries, causing the neglected disease schistosomiasis. Disease develops when schistosome eggs intended for release instead become trapped in target organs such as the liver, where they induce immune-mediated pathologic changes. The Pearce laboratory is actively engaged in three lines of research; 1) the molecular cell biology of schistosomes, 2) regulation of the immune response during chronic schistosome infection, and 3) the role of dendritic cells in pathogen recognition and induction of the adaptive immune response. His numerous publications in journals such as The Journal of Immunology, PLoS Pathogens, Nature Medicine, The Journal of Clinical Investigation, and The Journal of Experimental Medicine attest to his success. As Dr. Pearce wormed his way into Immunology, he has also wormed his way into the collective hearts of his colleagues and he will surely be missed.
125th Anniversary Symposium
Over 250 faculty, Postdoctoral Fellows, Residents, Students and Staff attended the 125th Penn Vet Anniversary day-long Research Symposium on June 17, 2009. Celebrating a long history of bettering the lives of animals and humans, the theme of Animal Diseases in Translational Research was carried out in presentations by Dr. Steven Walkley, Albert Einstein College of Medicine; Dr. Francis Golder, Clinical Studies PHL; Dr. Andrew Lackner, Tulane University; Dr. Thomas Parsons, Clinical Studies NBC; Dr. Dennis Hickstein, National Cancer Institute (NIH); Dr. Dorothy Cimmino Brown, Veterinary Clinical Investigation Center, Penn Vet; Dr. Randall Prather, University of Missouri, Dr. Kurt Hankenson, Department of Animal Biology; Dr. Gustavo Aguirre, Department of Clinical Studies PHL; Dr. Margaret Sleeper, Department of Clinical Studies PHL; and Dr. Ranier Storb, Fred Hutchinson Cancer Research Center Seattle. Over 80 posters were on display from all Penn Vet departments, centers and institutes. At the end of the presentations, Dr. David Artis, Department of Pathobiology, was presented with the Pfizer Award for Research Excellence. Event chair, Dr. John Wolfe, Department of Pathobiology and director of the Walter Flato Goodman Center for Comparative Medical Genetics, School of Veterinary Medicine, thanked the faculty and staff committee for their commendable participation and organization.

Recent Papers


Notify us when your manuscripts, clinical or basic, have been accepted for publication to: resnews@vet.upenn.edu and to Jordan Reese, jreese@upenn.edu Penn Science
Penn Vet Imaging Facility continued from page 1.

The facility currently serves more than 20 laboratories in the Schools of Veterinary Medicine, Medicine, and Arts and Sciences at the University of Pennsylvania. Research performed in the facility has already contributed to numerous publications and images generated in the facility have been used on the covers of *Nature Immunology* and *PLoS*. Studies performed in the facility have contributed substantially to at least eight R01 and S10 grant applications. In addition to providing state-of-the-art instrumentation, the facility hosts workshops on the uses and advanced applications of the instruments and analysis software and a monthly imaging user group meeting. The facility faculty director Dr. Bruce Freedman, V.M.D., Ph.D., Associate Professor of Pathobiology, has extensive cell signaling and imaging experience. He has been instrumental in implementing many of the advanced imaging capabilities of the imaging facility. The facility’s technical director, Dr. Lingli Zhang obtained a Ph.D. in Neuroscience from the University of Pennsylvania. She has a solid background in quantitative cellular imaging, confocal, two-photon imaging and FRET imaging.

Research in imaging is currently focused on three general applications: (1) *In vivo* and intravitral deep tissue microscopy, including real-time imaging of pathogen infection and immune responses in the brain, intestine, skin, and secondary lymphoid organs, (2) dynamic cellular imaging, including a) FRET based approaches to track the localization, interactions, and activity of signaling molecules in response to receptor stimulation, b) photo-activation to generate signaling intermediates instantaneously *in situ*, c) live imaging of calcium and mitochondrial function, and d) real time imaging of mitosis, and (3) high-quality confocal fluorescence imaging for morphological studies.

Penn Vet Faculty benefitting from the technology and excellence of the Imaging Facility include Drs. William Beltran and Gustavo Aguirre from the Department of Clinical Studies PHL. A research paper was recently published in *Investigative Ophthalmology and Visual Science* entitled “Age-Dependent Disease Expression Determines Remodeling of the Retinal Mosaic in Carriers of RGPR Exon ORF15 Mutations” and includes the figure shown above.

Another paper utilizing the Imaging Facility entitled “Dynamic Imaging of CD8+ T Cells and Dendritic Cells during Infection with *Toxoplasma gondii*” was authored by Beena John, Harris TH, Tait ED, Wilson EH, Gregg B, Ng LG, Mrass P, Roos DS,

Dzierszinski F, Weninger W, and Hunter CA (Department of Pathobiology) and was published in *PLoS Pathogens*. The image shown above was acquired on the Leica SP5 2-photon microscope equipped with a picosecond laser and tunable internal detectors by Beena John and is featured on the cover of *PLoS Pathog.* 2009 Jul;5 (7):e1000505. Epub 2009
Two PTPs have recently been implicated in the regulation of metabolic pathways in the brain: protein tyrosine phosphatase 1B (PTP1B) and Src homology 2-domain containing tyrosine phosphatase (SHP2). Dr. Bence and colleagues found that mice with global CNS deletion of PTP1B are lean (due to leptin hypersensitivity and increased energy expenditure) and have improved ability to utilize glucose [1]. On the other hand, deletion of SHP2 in the brain results in mice with early-onset obesity, leptin resistance, and fatty liver [2]. As these PTPs clearly have important in vivo roles in regulating energy balance, the Bence lab went on to determine their precise neuronal site(s) of action. In a recently submitted manuscript, Bence and colleagues found that PTP1B- or SHP2-deficiency in a subset of hypothalamic neurons (POMC neurons; Figure 2) results in reciprocal effects on body weight, energy expenditure, and high-fat diet-induced fatty liver. These findings shed new light on how PTPs function in specific neuronal populations to control body weight. In future studies the Bence lab hopes to identify additional brain regions that mediate the metabolic effects of PTPs, and determine which signaling pathways within these brain regions are affected by altered PTP activity.

Dr. Bence is also working in collaboration with Dr. Harvey Grill and Dr. Matthew Hayes in the Department of Psychology to examine the signaling mechanisms that underlie hindbrain control of food intake. In a recent publication, the groups found that hindbrain 5’ adenosine monophosphate-activated protein kinase (AMPK) activity contributes to energy balance control through regulation of food intake and energy expenditure [3]. This work highlights the previously unrecognized importance of the hindbrain in energy balance control and gives researchers new clues about the signaling pathways utilized by neurons to integrate information about hunger and satiety.

PTP1B in liver: an ER stress-reliever?

In addition to its important role in regulating CNS metabolic pathways, PTP1B is a key regulator of metabolism in peripheral tissues. A common feature of obesity and type 2 diabetes is the development of insulin resistance, a pathological state which prevents the body from responding normally to insulin and glucose. Insulin resistance is associated with activation of endoplasmic reticulum (ER) stress pathways, which may exacerbate these conditions. PTP1B acts as a negative regulator of insulin signaling by directly inhibiting the function of insulin receptor. In a recent paper from the Bence lab, the liver was shown to be an important site of PTP1B action in the regulation of insulin sensitivity and lipid metabolism [4]. Specifically, when fed a high-fat diet, mice with a liver specific deficiency in PTP1B expression showed enhanced insulin sensitivity, improved lipid profiles, and resistance to high-fat diet-induced ER stress. This study highlights the potential therapeutic potential of PTP1B inhibitors for the treatment of type 2 diabetes and associated insulin resistance.

Obesity and cancer risk

Epidemiological studies indicate that obesity contributes to increased incidence of many types of cancer, including breast, endometrial, colon, kidney, esophagus, pancreatic, liver, gallbladder, and gastric cancers. In fact, it is estimated that increased adiposity may be responsible for 15-20% of all cancer deaths in the United States. The cellular and molecular events linking these two prevalent diseases remain largely unknown. As the incidence of obesity continues to rise around the world in both human and our pet populations, there is renewed urgency to define a causal role of obesity in the progression of various types of cancer. Recently, altered regulation of specific protein tyrosine phosphatases (PTPs) has been implicated in promoting metastasis, a major factor in cancer mortality. The Bence lab is currently investigating a novel link between eating a diet high in fat and upregulation of PTPs involved in elevated cancer risk. Dr. Bence and colleagues hope that identification of specific PTPs linking these two diseases may lead to improved diagnostic indicators and/or novel treatment options in high-risk patients.

Dr. Bence’s research continued from page 2

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**Figure 2.** Immunohistochemistry for α-MSH (alpha-melanocyte stimulating hormone) shows the location of POMC neurons in mice injected intracerebroventricularly with colchicine. 3V, third ventricle. ARC, arcuate nucleus of the hypothalamus. Scale bars: 50 µm.
Dr. Bence’s research is funded by the NIH/NIDDK (R01DK082417), the USDA, and the American Cancer Society. Her laboratory is located in Old Vet 228E and her office in 223E (inside suite 220E).

Dr. Bence’s article continued ........

Dr. Bence’s research is funded by the NIH/NIDDK (R01DK082417), the USDA, and the American Cancer Society. Her laboratory is located in Old Vet 228E and her office in 223E (inside suite 220E).

References

Three Students Named 2009 Hayre Fellows in Public Outreach Projects to Advance Understanding of Animal Research in Medicine.

Americans for Medical Progress is pleased to announce the recipients of the 2009 AMP/Michael D. Hayre Fellowship in Public Outreach: Gillian Braden-Weiss, University of Pennsylvania School of Veterinary Medicine; Breanna Caltagarone, University of Pennsylvania School of Veterinary Medicine; and Megan Wyeth, David Geffen School of Medicine, University of California Los Angeles.

Some Recent Grants Awarded...

Gudrun Philomena Debes, DVM
Regulation of T cell egress from inflamed skin
NIH R01 grant
7-1-09--5-31-2014
$1,125,000

Marie Fecteau DVM, Ray Sweeney VMD & Robert Whitlock
DVM/PhD: Johne’s disease in Alpacas
Alpaca Research Foundation
9-1-09--8-31-10
$15,700

Chris Hunter, PhD
Regulation of early immune response to toxoplasma gondii
NIH/NIAID
7-1-09--6-30-2014
$1,250,000

Cynthia Otto, DVM/PhD
Intermittent hypoxia: cardiac protection or risk?
American Heart (Great Rivers Affiliate)
7-1-09--6-30-2011
$120,000

David Artis PhD
Immuno-regulation of GI nematode infection
NIH/NIAID
7-1-09--6-30-2014
$1,250,000

Brett Kaufman, PhD
Determining the mechanism underlying TFAM-mediated cardiomyocyte protection during heart attack
McCabe Fund
7-1-2009-6-30-2010
$40,000

Peijing Jeremy Wang, MD/PhD
Regulation of Chromosome Synapsis in Mice
NIH/NIGMS
12-1-2009--11-30-2014
$1,250,000

Rabindranath De La Fuente
Epigenetic Control of Heterochromatin Formation
NIH/NICHD
7-27-2009--6-30-2011
$499,637

To date, many Penn Vet Faculty are receiving funding and supplements resulting from grant submissions for American Recovery and Reinvestment Act (ARRA) programs. Among those have been Drs John Wolfe, Phillip Scott, Michael May, Peter Felsburg, Robert Greenberg, Michael Atchison, Chris Hunter, Sam Chacko, Peijing Wang, and Anna Kashina. Stay tuned, more awards may be coming!
Through the generous gift of Mindy Halikman Heyer, C’79, W’79, WG’80, and Andrew R Heyer W’79, WG’79, the beginnings of a one million dollar endowment for the VMD-PhD Program has been initiated. Mindy Heyer currently serves as the Chair of the Board of Overseers for Penn Vet and Andy Heyer is a member of the University Board of Trustees. This endowment will enable us to secure the VMD-PhD Program at Penn, and to initiate new and innovative research and educational experiences for our students.

The Program wishes to welcome three new students this year; Meghan Noelle Knight, a Dartmouth graduate with a degree in Biology, will join the Biochemistry and Molecular Biology Graduate Group; Jonathan Madara, a University of Pennsylvania alumnus with a Bachelor’s in Biochemistry, joins the Cell and Molecular Biology-Microbiology, Virology and Parasitology Graduate Group; and Feini (Sylvia) Qu comes to us from Duke University with a BSE in Biomedical Engineering and a BS in Biology to pursue her PhD with the Bioengineering Graduate Group. All three students will be funded by the Medical Scientist Training Program grant.