**ZNI Faculty Profile**

Janos Peti-Peterdi MD PhD  
Professor, Zilkha Neurogenetic Institute and Department of Physiology and Biophysics

Dr. Janos Peti-Peterdi is dedicated to finding a cure for chronic kidney disease. His laboratory in the Zilkha Neurogenetic Institute examines kidney and cardiovascular pathophysiology – more specifically the mechanisms of the healthy kidney that control the maintenance of body fluid, electrolyte balance and blood pressure – and how they are changed in the disease state. The main goal of his laboratory is to identify the key molecular players in various renal pathologies as potential therapeutic targets, with the aim of developing new approaches for the treatment of kidney and cardiovascular diseases. The Peti-Peterdi lab is contributing to ZNI’s expertise in vascular barrier functions in multiple organs including the kidney and brain.

Their ongoing collaboration with the Zlokovic lab focuses on studying structural-functional similarities between the blood-brain barrier and the glomerular filtration barrier, and their regenerative processes.

Dr. Peti-Peterdi’s group played an important role in identifying the cellular and molecular processes of a key anatomical site within the kidney – the juxtaglomerular apparatus or JGA – which controls the amount of blood flow and filtration through the kidneys.

During the past decade, the laboratory pioneered several applications of intravital (live animal or in vivo) multiphoton microscopy, allowing researchers to quantitatively visualize the most basic (patho) physiological parameters of kidney and nephron function, including tissue activity of a hormone called renin, which regulates the body’s mean arterial blood pressure. The Peti-Peterdi lab is using this imaging technology to examine complex regulatory and disease mechanisms in intact kidney tissue in various animal models, exploring chronic kidney disease, acute kidney injury, nephrotic syndrome (which causes excessive release of protein in urine), focal segmental glomerulosclerosis (scar tissue in the filtering unit of the kidney which can lead to nephrotic syndrome), hypertension and diabetes.

Dr. Peti-Peterdi established the NIH-funded Multi-Photon Microscopy Core at USC for high-resolution intravital imaging.

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Leaky Blood Vessels May Lead to Alzheimer’s Disease

In a well-received Neuron paper published in January of 2015, Berislav Zlokovic MD PhD notes that leaky blood vessels in the hippocampus of the brain may facilitate the development of dementia and Alzheimer’s disease. The hippocampus – located in the medial temporal lobe of the brain – is responsible for the creation of short and long-term memories. The blood-brain barrier, a protective boundary within the brain to stave off bacterial infections, has been found to grow weaker and leakier with age, which can cause cognitive impairment associated with Alzheimer’s disease. More importantly, Zlokovic’s report noted that by deploying MRI technology to detect leaky blood vessels, it may be possible to more effectively diagnose early on-set Alzheimer’s disease, slowing down the neurodegenerative effects.

This discovery opens the door to a better understanding of the vascular mechanisms of the brain, which hopefully leads to improved screening for cognitive impairments and the development of preventive measures that can be taken by those at risk for Alzheimer’s disease. With early detection comes a more varied and effective field of treatments for the disease.

Zlokovic’s research findings were made in collaboration with USC colleagues, Helena Chui MD, Meng Law, MD, Arthur Toga, PhD, and members of his lab including Axel Montagne, Melanie Sweeney and Abhay Sagare and others.

Importance of GLUT1 in Slowing Down Effects of Alzheimer’s Disease

Berislav Zlokovic MD PhD and members of his ZNI laboratory published a paper in the 2 March 2015 issue of Nature Neuroscience noting that the insufficiency of GLUT1, a protein transporter of glucose into the brain, may cause symptoms associated with Alzheimer’s disease. Previously, the deficiency of GLUT1 in the brain has been seen as a side effect of having Alzheimer’s disease rather than having a role in creating symptoms. Zlokovic and his team, which includes Ethan Winkler, Abhay Sagare and Yoichiro Nichida and others, have found that GLUT1 is a crucial component in maintaining a healthy blood-brain barrier and blood flow within the brain. The preservation of GLUT1 levels in the brain may inhibit cognitive impairment caused by Alzheimer’s disease.

These findings could lead to new methods in preventing or slowing down of Alzheimer’s disease, especially in individuals who are genetically at risk for the disease. If they are able to accurately target the GLUT1 protein, scientists may be able to slow down the progression of Alzheimer’s disease.

The full Nature Neuroscience paper can be found at http://www.nature.com/neuro/journal/vaop/ncurrent/full/nn.3966.html.

Glucose transporter-1 deficiency leads to early blood-brain barrier breakdown in the brain of a mouse model of Alzheimer’s disease as indicated by leakage of blood-derived fibrin (red) from brain microvessels (white). Above are representative images from an Alzheimer’s disease mouse with normal (left) or reduced (right) levels of glucose transporter-1.

Immune Response Can Clear Brain of Plaques Causing Alzheimer’s Disease

In the 4 February 2015 issue of Neuron, Terrence Town PhD and his group published an article noting that by prohibiting interleukin-10 – an anti-inflammatory cytokine – an immune response is triggered in the brain that enables the clearing of sticky plaque build-up known to cause neurodegeneration and memory loss. The build-up of this plaque has been cited as a cause of Alzheimer’s disease, and thus with the successful blocking of this substance, there may be a restoration of memory loss and brain damage. This finding has considerable implications for potential treatment of Alzheimer’s disease and will likely lead to further research on innovative drug therapies aimed at suppressing interleukin-10.

Town, who joined ZNI and USC in 2013, is interested in developing treatments for Alzheimer’s disease through the research and analysis of the human immune system. The co-authors of the Neuron paper are laboratory members Marie-Victoire Guillot-Sestier, Kevin Doty, David Gate, Javier Rodriguez and Brian Leung.

The full Neuron article can be found at http://www.sciencedirect.com/science/article/pii/S089662731401201X.

Caption: 3D reconstruction of an immune cell (red) containing β-amyloid (blue) within an intracellular degradation compartment (yellow). Deletion of the anti-inflammatory cytokine, Il10, activates innate immune cells to clear the brain of toxic b-amyloi.

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Stroke is the leading cause of serious, long-term disability in the United States. Each year, approximately 795,000 people suffer a stroke. About 75% of these are first attacks and 25% are recurrent attacks. Nearly three-quarters of all strokes occur in people over the age of 65.

Dr. William Mack is an associate professor of neurosurgery (Clinical Scholar), a faculty member of the Neuroscience Graduate Program, and the director of the Cerebrovascular Laboratory at the Zilkha Neurogenetic Institute.

He and his team are working to develop new technologies, techniques and therapies to directly improve the clinical care administered to stroke patients. His research program seeks to improve patient care by establishing a novel delivery mechanism for the rescue of threatened brain tissue that can be administered rapidly following acute stroke. Through distal endovascular access – catheters advanced through the blocked arteries to the region of brain tissue damage – the team has devised a technique that allows rapid measurement and delivery of neuroprotective agents to brain tissue affected by a stroke.

A brain (cerebral) aneurysm is a bulging, weak area in the wall of an artery that supplies blood to the brain. In most cases, a brain aneurysm causes no symptoms and goes unnoticed, unless it ruptures. Cerebral vasospasm (vessel narrowing) following rupture of a brain aneurysm results in stroke in approximately 30% of patients. Dr. Mack’s team is utilizing data obtained from advanced MRI perfusion imaging sequences to investigate the association between an enzyme – an inflammatory mediator, Matrix Metalloproteinase (MMP 9) – and the breakdown of the blood brain barrier (BBB) following aneurysm rupture. Dr. Mack and his group want to examine the relationship between compromised BBB integrity and the occurrence of stroke. A positive correlation would suggest a potential role for MMP 9 as an early diagnostic biomarker, and BBB permeability as a therapeutic target, in the management of stroke following the rupture of brain aneurysms.

Building on Progress: 2nd Annual Zilkha Symposium on Alzheimer Disease & Related Disorders

Following the success of last year’s inaugural Zilkha Symposium, Drs. David Holtzman, Rudolph Tanzi and Berislav Zlokovic will host the 2nd Annual Zilkha Symposium on Alzheimer Disease & Related Disorders. The all-day symposium on 10 April 2015 will feature 12 leading researchers in the field of neurodegenerative diseases like Alzheimer Disease. Speakers will present new findings and unpublished research, sharing the latest information with their colleagues from around the world.

The confirmed speakers include: David Holtzman MD (Wash U); Rudolph Tanzi PhD (Harvard); Sangram Sisodia PhD (Univ Chicago); Maiken Nedergaard MD DMSc (Univ Rochester); Costantino Iadecola, MD (Well Cornell); Christier Betsholtz MD PhD (Uppsala University); Cheryl Wellington PhD (University British Columbia); Dominik Paquet PhD (Rockefeller); Justin Ichida PhD (Broad Stem Cell, USC); Judy Pa PhD (LONI, USC); Daniel Nation PhD (Psychology, USC) and Berislav Zlokovic MD PhD (ZNI, USC).

The chairs will include Maria Carrillo PhD (Alzheimer’s Association); Rod Corriveau PhD (NINDS/NIH); Helena Chui MD (Neurology, USC) and Caleb Finch PhD (Gerontology, USC).

There will be opportunities for attendees of the symposium to interact with the speakers via Q&A sessions following the presentations and throughout the day. The symposium will be held in the Herklotz Seminar Room and open to students, faculty and members of the USC community.
of intact organs – kidney, liver, spleen, pancreas, skin, eye – in small laboratory animals. Over the past 5 years he has trained more than 30 investigators from around the world on the use of intravital imaging of the mouse kidney. His recent imaging studies addressed and solved a critical technical barrier in kidney research, allowing researchers for the first time to quantitatively visualize the function of cellular and molecular elements of the kidney filter (glomerulus) in vivo, to examine their roles in the development of disease.

Most recently, the Peti-Peterdi lab deployed serial multiphoton microscopy to track the fate and function of individual cells in the same region of the living intact kidney over several days, during disease development. This approach has led to significant advances in understanding the highly dynamic kidney tissue and glomerular environment, and the mechanisms of glomerular injury and regeneration. Ongoing work in the laboratory is studying the fate and function of renal stem cells, and their role in endogenous kidney repair. Based on targeting the molecular mechanisms that control a newly discovered tissue repair process, the Peti-Peterdi lab is currently developing a new regenerative therapeutic approach for the treatment of chronic kidney disease.

Two new grants from the National Institute of Diabetes and Digestive and Kidney Diseases will allow the Peti-Peterdi lab to use novel intravital imaging approaches to study the function of critical cell types in the glomerular filter. One cell type is called podocyte, which localizes around blood vessels (glomerular capillaries) in the kidney filter and help maintain the normal structure and function of the glomerular filtration barrier. The other chief cell type is called macula densa (MD) cells, which are strategically positioned at the vascular entrance of the glomerulus. MD cells can sense changes in the tissue environment (e.g. salt, fluid flow, cell metabolism) and release chemical mediators that control other glomerular cells to maintain body fluid and electrolyte balance and blood pressure.

A newly established research collaboration between the Peti-Peterdi lab and Amgen Inc. aims to validate another calcium signaling pathway, the calcium channel TRPC6 in podocytes as a target in glomerular pathology.

Another research project, funded by the American Heart Association, is studying the role of MD cells in the development of high blood pressure-related kidney injury and disease.

Also, a new grant from the American Diabetes Association will allow the Peti-Peterdi lab to investigate a new mechanism of tissue remodeling in the diabetic kidney, which may be targeted in future therapeutic development for diabetic patients.

In recognition of his pioneering work and cutting edge research on kidney disease, Dr. Peti-Peterdi was recently elected to two prestigious honor societies, the American Society for Clinical Investigation (ASCI), and the European Academy of Sciences and Arts (EASA).

Janos Peti-Peterdi and his colleagues have developed a new multiphoton microscopy technique that allows scientists to visualize the migration patterns of single podocytes, a type of visceral epithelial cell involved in glomerular function in the kidney. The method should advance studies of glomerular injury and regeneration.

http://www.nature.com/nm/journal/v19/n12/abs/nm.3405.html

ZNI New Grants Increase in FY14

To anyone familiar with the federal budget, it will come as no surprise that NIH funding is highly competitive and new awards are increasingly difficult to obtain. What is sensational is that even in these challenging times, ZNI investigators have been successful in securing new grants.

In early FY12, two epidemiologists conducting genome-wide association studies of breast and prostate cancer, relocated their laboratories from ZNI to the USC Norris Comprehensive Cancer Center. This long-planned move combined with the move of another senior investigator to CHLA, paved the way for the Institute to concentrate on neuroscientists investigating the biology and genetics of Alzheimer’s and other neurogenetic diseases. Nonetheless, ZNI’s grant portfolio took a hit.

The chart at left diagrams how, despite the loss of three major PIs in FY12, ZNI researchers nonetheless were able to recover and increase the number of new grants awarded to the Institute.