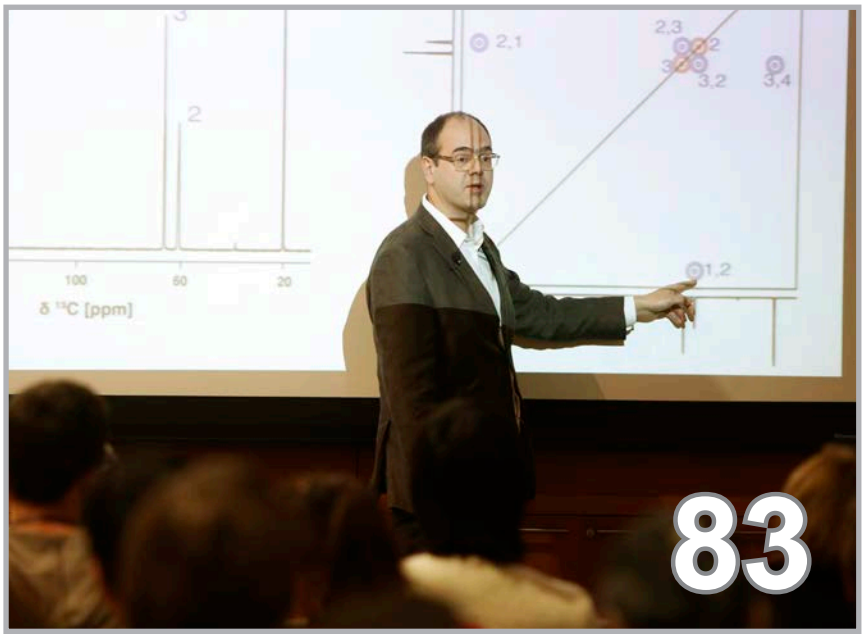
Zilkha Neurogenetic Institute

ANNUAL REPORT 2015 | 2016

Keck School of Medicine of USC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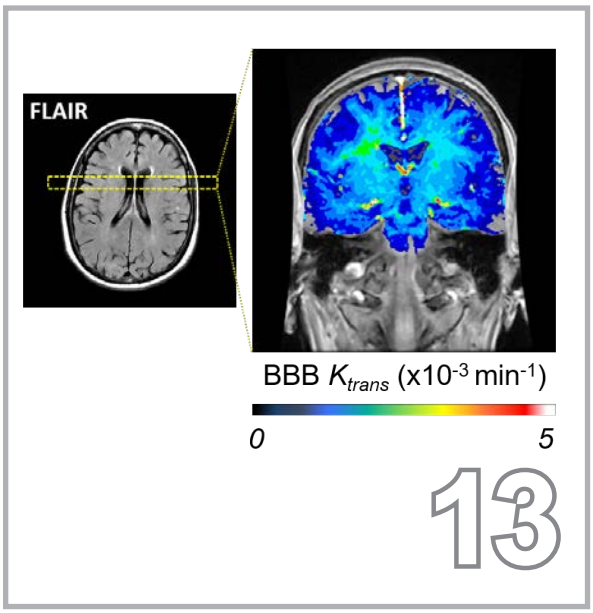
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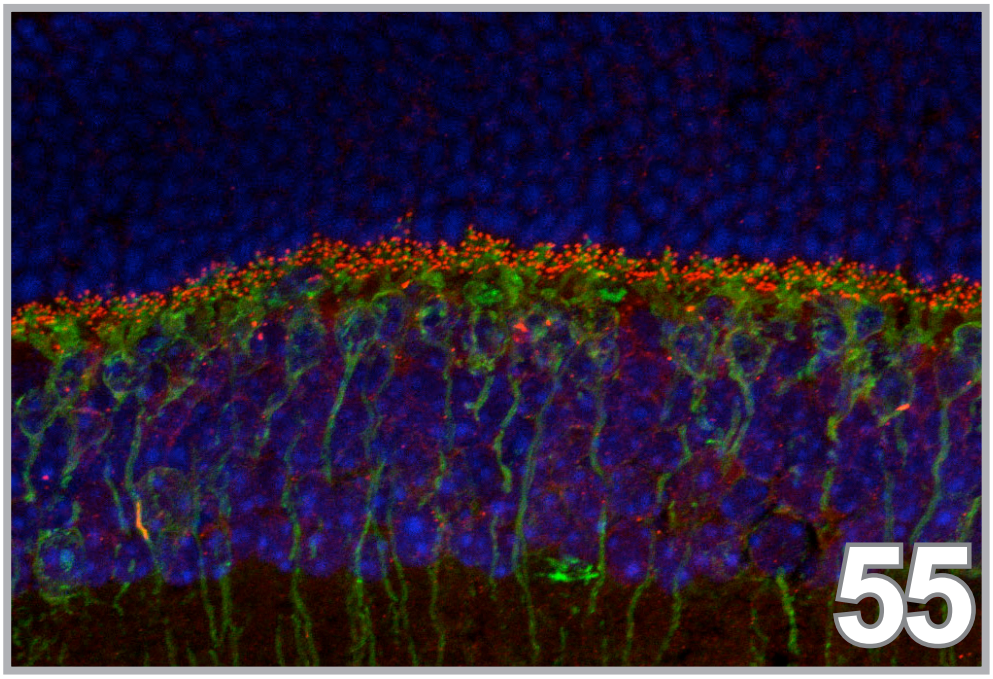
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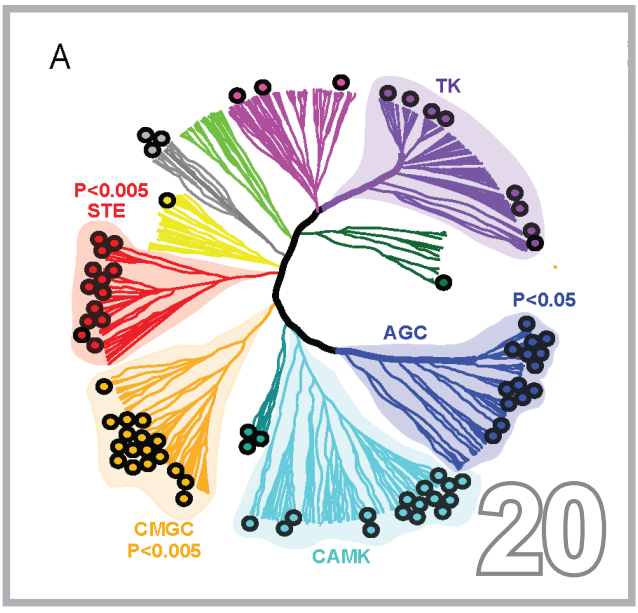
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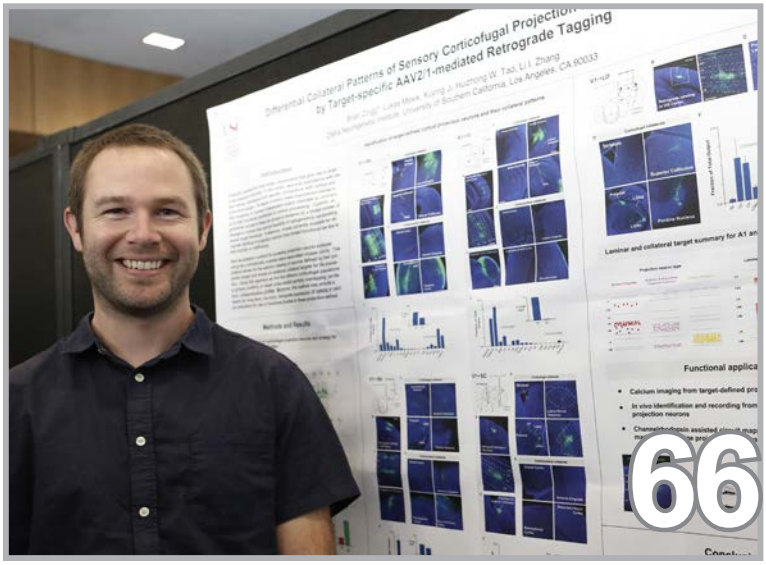
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director's letter

In this report we present a variety of facts and diagrams, statistics and pictures that provide evidence of the work we are doing at the Zilkha Neurogenetic Institute (ZNI), specifically our accomplishments from July 2015 through June 2016 (FY16). However, with more than 52 graduate students and 37 postdocs at ZNI and a grants portfolio that exceeds $23M a year—larger than many freestanding independent research institutes—it is challenging to encapsulate all that we do in a single report, much less this introductory letter.

Faculty excellence is paramount to our efforts. Our faculty have taken on leadership roles in multi-Principal Investigator, multi-center grants, projects that push the boundaries of collaborative science. They publish in high-impact journals while training the next generation of scientists. Their passion, expertise, and enthusiasm are matched by physician-scientists and researchers in other areas throughout the Keck School of Medicine of USC, as well as colleagues across the University. These partnerships are helping transform ZNI into a premiere research institute.

Neuroscience research grants reflect 37% of the Keck School of Medicine of USC sponsored projects portfolio, and I am proud to say that ZNI is a significant contributor to this success.

At ZNI, we strive to make an impact in discovery science every single day, by encouraging researchers at all levels to challenge and expand their creative boundaries. Whether an undergraduate working at the bench, a graduate student rotating through a lab, or a postdoctoral fellow conducting independent experiments under the mentorship of an established investigator, researchers at ZNI have the resources of a dynamic medical research campus at their disposal, where experts in established fields such as Alzheimer's disease, neurodegenerative disorders, cerebrovascular (stroke) research, neurogenetics and informatics, protein structural studies, audio and visual studies, connectomics and model organisms integrate and interact with researchers in neuroimaging, neuroimmunology, neurovirology and those studying the vascular contributions to dementia.

We are thankful to be part of such a vibrant scientific community. ZNI would not be the world-class institute it is without the tireless dedication of our staff, students and fellows, as well as our loyal community partners. Their financial and other support help us to continue pushing the envelope of progressive science, year after year.

The vision for the Zilkha Neurogenetic Institute is to harness and focus the resources necessary to make us a worldwide leader in neuroscience and a vital part of the Keck School of Medicine of USC. I invite you to be a part of it!

All the best,

our mission

The Zilkha Neurogenetic Institute provides a home for a program of interdisciplinary research that builds on USC's existing strengths in neuroscience and genetics, as well as the clinical expertise of the physician-scientists in the Keck School of Medicine's clinical departments.

Established in 2003 by a generous gift from Selim Zilkha and Mary Hayley and further support from the WM Keck Foundation, the Zilkha Neurogenetic Institute is an integral part of a larger USC Neuroscience Initiative, encompassing scientists throughout the University. An organized research unit of the Keck School of Medicine at the University of Southern California, the ZNI is housed in a five-story, 125,000 sq. ft. building on the Health Sciences Campus, a state-of-the-art facility that allows basic scientists and physician-researchers to concentrate and collaborate.

Investigators at ZNI hold active federal grants from more than a dozen different institutes across the National Institutes of Health, plus the National Science Foundation, Department of Defense, the Department of Public Health Services, foundations and industry partners. ZNI is home to over 300 researchers, staff and students, including 37 postdoctoral fellows and 52 graduate students.

Faculty, postdocs, staff and students from a large and diverse array of USC departments, institutes, divisions and centers participate in collaborative interactions between researchers working at ZNI, including the Alzheimer's Disease Research Center, department of Neurology, the Broad Center for Regenerative Medicine and Stem Cell Research, Dornsife College, Stevens Institute for Neuroimaging and Informatics, Departments of Neurosurgery, Psychiatry & the Behavior Sciences, Cell & Neurobiology, Biochemistry & Molecular Biology, Division of Bioinformatics (department of Preventive Medicine), USC Science Initiatives, Viterbi School of Engineering, and the departments of Otolaryngology, Molecular Microbiology and Immunology.

Areas of research at ZNI chiefly include Alzheimer disease, dementia and related diseases; but also amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease); Huntington disease; Parkinson's disease; Down's syndrome; stroke/vascular health; psychiatric genetics and genomics (OCD, schizophrenia, bipolar); human and animal neurovascular imaging; brain circuits (systems neuroscience), brain mapping; fetal brain development; brain injury, cancer; as well as vision/eye; hearing/ear; diabetes; genomics, statistical methodologies; kidney, renal health; and autism and the environment.

As ZNI continues to expand our network of partnerships internal and external to USC, we will further develop our world-class research programs. It is only by working together that we will have a positive impact identifying, preventing and treating a range of neurological disorders.

faculty

Alexandre Bonnin, PhD
Assistant Professor
Cell & Neurobiology

Daniel B. Campbell, PhD
Assistant Professor
Psychiatry & the Behavorial Sciences

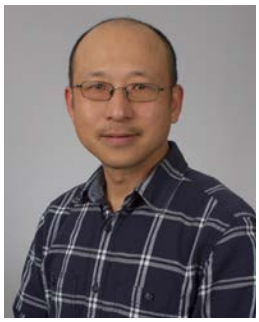
Karen Chang, PhD
Assistant Professor
Cell & Neurobiology

Jeannie Chen, PhD
Professor
Cell & Neurobiology

Robert H. Chow, MD, PhD
Professor
Physiology & Biophysics

Marcelo Coba, PhD
Assistant Professor
Psychiatry & the Behavioral Sciences

David V. Conti, PhD
Professor
Preventive Medicine



Hong-Wei Dong, MD, PhD
Associate Professor
Neurology

Oleg Evgrafov, PhD
Associate Professor of Research
Psychiatry & the Behavioral Sciences

Rick A. Friedman, MD, PhD
Professor
Otolaryngology

Radha Kalluri, PhD
Assistant Professor of Research
Otolaryngology

James A. Knowles, MD, PhD
Professor
Psychiatry & the Behavorial Sciences

Ralf Langen, PhD
Professor
Biochemistry & Molecular Biology

William Mack, MD
Assistant Professor
Neurological Surgery

Takahiro Ohyama, PhD
Assistant Professor of Research
Otolaryngology

Mariangela Nikolakopoulou
Assistant Professor of Research
Physiology & Biology

Janos Peti-Peterdi MD, PhD
Professor
Physiology & Biophysics

Ahbay Sagare, PhD
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Derek Sieburth PhD
Associate Professor
Cell & Neurobiology

Ansgar Siemer PhD
Assistant Professor
Biochemistry & Molecular Biology

Huizhong W. Tao, PhD
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Terrence Town, PhD
Professor
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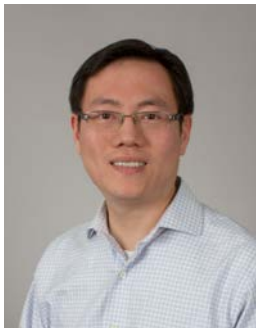
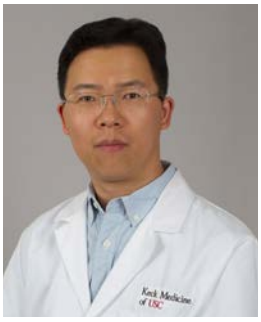
Tobias S. Ulmer, PhD
Associate Professor
Biochemistry & Molecular Biology

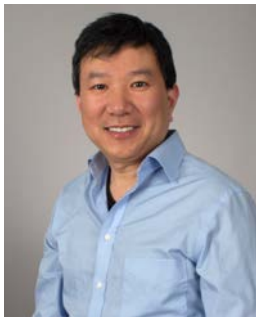


Kai Wang, PhD
Assistant Professor
Psychiatry & the Behavioral Sciences

Gabriel Zada, MD
Assistant Professor
Neurological Surgery



Zhen Zhao, PhD
Assistant Professor of Research
Physiology & Biophysics



Li Zhang, PhD
Professor
Physiology & Biophysics

Berislav V. Zlokovic, MD, PhD
Director, Zilkha Neurogenetic Institute
Professor & Chair
Physiology & Biophysics

faculty news

Some notable advances by ZNI faculty over the past year:

A publication by **Dr Ralf Langen** was awarded the paper of the year for biophysical papers in the **Journal of Biological Chemistry**. In it, Dr Langen shows how a peptide involved in diabetes disrupts biological membranes. The more general importance comes from the fact that similar mechanisms are likely at work in Alzheimer's disease and Parkinson's disease. Thus the work provides a new insight into potential therapeutic avenues.

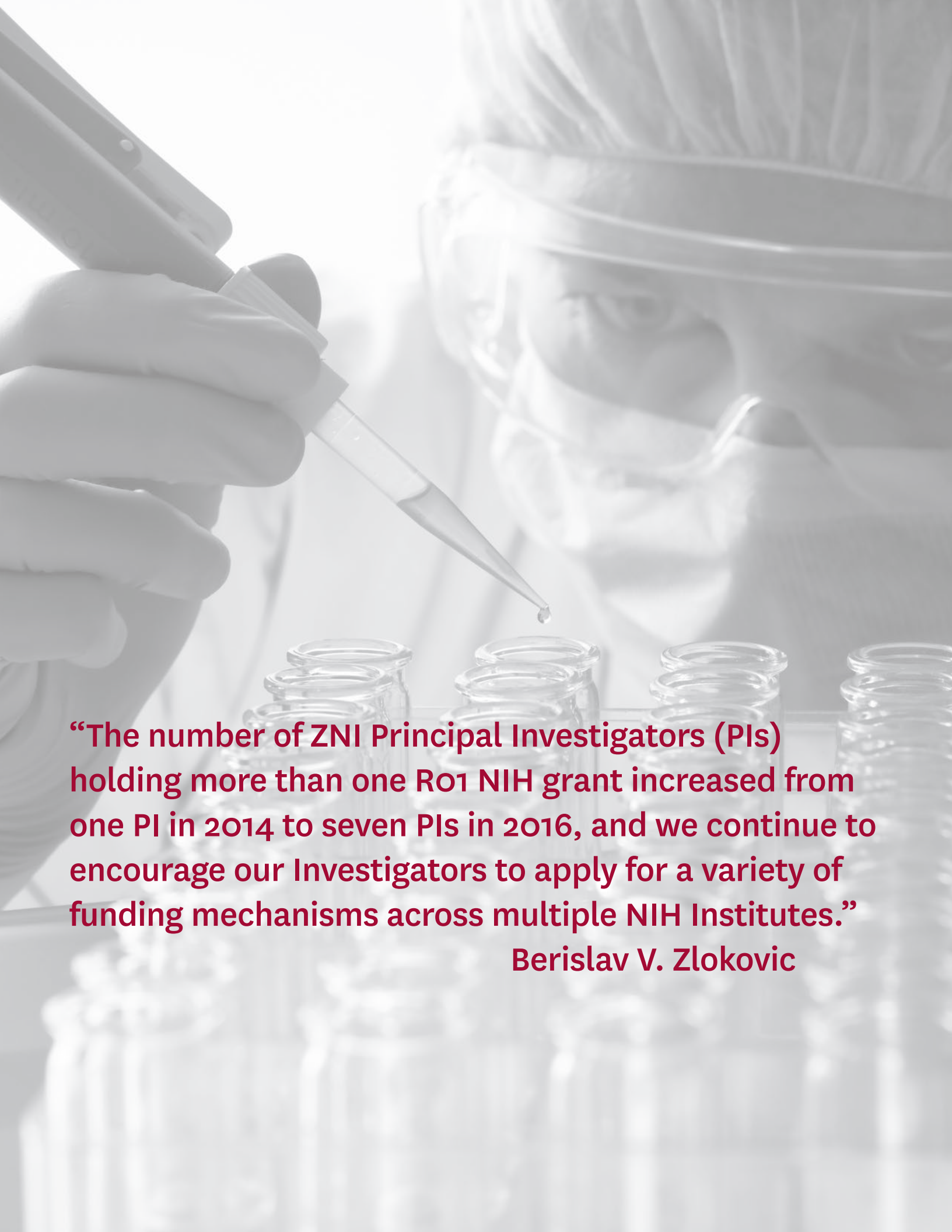
Another paper by Dr Ralf Langen's group was published in **Nature Chemistry**. The work shows that certain naturally occurring protein modifications in the Parkinson's disease protein alpha-synuclein prevent the formation of toxic, misfolded forms of the protein. Thus, enhancing these modifications might be a potential therapeutic strategy for combatting Parkinson's disease.

In the context of ongoing worldwide Zika virus epidemic, **Dr Alexandre Bonnin's** findings of a novel mechanism by which maternal infections during pregnancy affect fetal brain development provide potential new preventative or therapeutic directions. Dr Bonnin's work was published in the **Journal of Neuroscience** and received considerable attention in both the national and international press.

Cross modality (e.g. auditory-visual) interaction is beneficial for sensory perception and quick reactions to environmental challenges. A study by **Dr Huizhong (Whit) Tao** and **Dr Li Zhang** for the first time revealed the micro-neural circuit and synaptic mechanisms underlying the auditory-visual cross modality interaction in the visual cortex. The work was published in **Neuron**.

A study by **Dr Berislav Zlokovic**, published in **Nature Medicine**, demonstrates the ability of a novel combination therapy (neural stem cell transplantation and co-treatment with 3K3A-APC) in repairing damaged host neural circuits and enhanced long-term functional outcomes in experimental model of stroke in mice, suggesting that 3K3A-APC, an FDA-approved investigational protein, potentially can be used to improve stem cell therapy in stroke patient.

Working with Dr Helena Chui in the Department of Neurology, **Dr Berislav Zlokovic** and Arthur Toga helped update the approach and enhance the scientific direction for the **USC Alzheimer's Disease Research Center (ADRC)**, adding CSF biomarker studies and imaging biomarkers of the cerebrovascular system and blood-brain barrier integrity. Both Drs Zlokovic and Toga were added to the administrative core and along with other PIs, direct projects of their own. The ADRC grant received a good score, was awarded, and is just now completing its first year.



“The number of ZNI Principal Investigators (PIs) holding more than one R01 NIH grant increased from one PI in 2014 to seven PIs in 2016, and we continue to encourage our Investigators to apply for a variety of funding mechanisms across multiple NIH Institutes.”

Berislav V. Zlokovic

The ADRC-ZNI pilot program was also launched in 2016, providing additional opportunities for individual PIs across disciplines to obtain funds for novel projects holding promise for further external funding. By combining forces, the ADRC-ZNI program funded three pilot studies in fall 2015 and four additional projects in Spring 2016. All awardees presented their work in a half-day symposium at ZNI, attended by researchers across the health sciences campus. The ADRC receives $11.5M over five years from the National Institute for Aging (NIA).

The number of ZNI Principal Investigators (PIs) now holding more than one R01 NIH grant increased from one PI in 2014 to now seven PIs in 2016, and we continue to encourage our Investigators to apply for a variety of funding mechanisms across multiple NIH Institutes. The ZNI grants portfolio for FY16 included 52 federal grants across 12 different institutes within the NIH, as well as projects sponsored by NSF, DoD, some industry partners and many private foundations.

Kai Wang PhD was promoted to Associate Professor in Psychiatry & the Behavioral Sciences. While at USC, Dr Wang developed the program ANNOVAR, which was the first easy to use, and the most publically available, program used to "annotate" human (or any species) genomes. Knowing that a person has a base pair change at position 138,345, 698 of chromosome 3 is not really very useful information. Knowing that change occurs in the protein coding region of a gene and changes an amino acid codon to a stop codon is extremely useful information. That is what ANNOVAR does. It takes the essentially raw file of all the base pair changes in a subject's genome and converts them into biological knowledge. No open source program to do this existed prior to ANNOVAR. This is the reason for its overwhelming success in the field. Dr Wang had the further insight to make it easily extensible to other species and new types of genomic data, as well as an investigator's private data, so we suspect it will remain the standard genome annotation program for years to come. His recent work, focusing on interpretation of whole genome and other next generation sequencing data, is an example of state-of-the art human genetics. This included the development of a new platform, Phenolyzer, published in **Nature Methods**, as well as a web tool for integration of GWAS with other biological data called Enlight, published in **Bioinformatics**.

In Fall of 2016, for personal reasons, Dr Wang relocated his laboratory from ZNI to Columbia University in New York. He will, however, retain the collaborations he developed with several researchers at USC and retain an adjunct appointment at the Keck School of Medicine.

In recognition of his pioneering work and cutting edge research in the areas of Alzheimer's disease and related disorders, **Berislav Zlokovic MD, PhD** was elected in December to the Academia Europaea (Academy of Europe. Founded in 1988 as an international, nongovernmental association of individual scientists and scholars from all disciplines, the group invites a limited number of individuals to join each year, all experts and leaders in their own subject areas as recognized by their peers. Membership in the Academy is limited to 2,600 scholars, 54 of whom are current Nobel prize winners.

In January 2016, **Dr. Berislav Zlokovic** coordinated the preparation and resubmission of a large, multi-center P01 grant with three cores, "Vascular Contributions to Dementia," which was preapproved as a special new program of the NIA. As we go to press, it was announced that the USC Center wwill receive $1.5M in direct costs each year for five years. Partners and Co-Is on the grant include Helena Chui MD, Lon Schneider MD, Meng Law MD, Daniel Nation PhD, Art Toga PhD, Paul Thompson PhD, Judy Pa PhD, Terrence Town PhD, Hong-wei Dong PhD (all USC); Michael Harrington MD (Huntington Medical Research Institute); John Ringman MD (formerly UCLA, now USC); John Morris MD, Anne Fagan PhD, Tammie Benzinger MD PhD, Randy Bateman MD (all Washington Univ at St Louis); Eric Reiman MD (Banner Institute); Richard Caselli MD (Mayo Clinic); and Russell Jacobs (formerly at Caltech, now USC).

Early in 2016, **Russell Jacobs PhD** accepted an offer from the Keck School of Medicine of USC and as of July 2016 became Professor of Research in the department of Physiology and Biophysics and in Fall 2016 he will move his laboratory from Caltech to ZNI. Dr Jacobs has more than 30 years of experience in the theory, hardware/software development and application of high resolution preclinical MRI. He uses animal models to understand the human conditions they approximate, including embryonic development, multiple sclerosis, Alzheimer's Disease, cancer, and substance abuse. He has also been involved in several multimodal imaging efforts including contrast agent development, implementation of a simultaneous dual PET/MRI scanner, and quantitative analysis of PET and MR images using an array of modeling, computational warping and statistical techniques.

The addition of Dr Jacobs will complement well previous recruitments and development in the areas of imaging, and is a strong fit for the ZNI, the Department of Physiology & Biophysics and the Keck School of Medicine in general, where there is a clear unmet need in preclinical imaging. Although small animal model systems only recapitulate some of the characteristic of the human situation(s), valuable insights are gain through the examination of these model systems. MRI and PET are techniques that apply equally to small animals and humans – precisely the same experimental protocols and agents are used in the laboratory and the clinic. Having a robust small animal imaging center within the clinical environment and available to researcher/clinicians is one near ideal way to translate laboratory findings into clinical practice.

The newly formed pre-clinical imaging resource at the ZNI will take advantage of state-of-the-art preclinical MRI/PET instrumentation provided by MR Solutions. Simultaneous acquisition of PET and MR images is a newly emerging technology that marries the exquisite sensitivity of PET with the high spatial resolution and soft tissue contrast of MRI. Applications in collaboration with a number of researchers at the Keck School of Medicine of USC are wide ranging. Among them are elucidating disease etiology in mouse and rat models of Alzheimer's Disease; imaging assays of in vivo effects of several neuroprotection schemes in stroke; refinement of methodologies to delineate neuronal pathways and how they go wrong in disease and with aging; and the development and testing of novel cancer immunotherapies.

Over the past few years, the ZNI has experienced a continuous growth in funding and has drawn a new baseline to concentrate on basic, translational and clinical neurosciences research. This includes studies on the biology and genetics of Alzheimer and other neurodegenerative diseases, the effects of vascular factors on brain function as well as well as continued studies in genomics of psychiatric disorders, brain connectivity and neuroimaging, and developing further studies on the visual and auditory system during development, normal physiology and disease.

Alzheimer & Related Disorders

The Protein Structure group (**Drs. Ralf Langen, Ansgar Siemer and Tobias Ulmer**) investigate the structure of proteins involved in debilitating diseases. A number protein misfolding diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease, type 2 diabetes) are thought to be caused by the misfolding of proteins into abnormal and toxic structures. How this misfolding occurs on a molecular level, how it can be prevented therapeutically and how risk factors can promote misfolding is only poorly understood. A main goal of the Langen lab is to address these questions using a combination of biophysical and cell biological tools. The Siemer lab investigates the atomic structure of amyloid fibrils that are found in (neurodegenerative) diseases and amyloid fibrils that are found in non-disease contexts also called functional amyloids. Comparing the atomic structure and biochemical properties of these two classes of amyloids, will not only help find a cure for amyloid disease, but also widen our understanding of amyloids in biology beyond disease. In particular, the Siemer lab is working on two amyloid fibril forming proteins. Huntingtin, the first protein, can cause Huntington's Diseases if it is mutated. Orb2, the second protein, is an important factor for the development of long-term memories in fruit flies.

Dr. Karen Chang's lab is investigating the cellular and molecular mechanisms underlying neuronal dysfunctions seen in various neurological disorders. There two main areas of research: 1) identification of the genotype to phenotype correlations in Down syndrome (DS), and 2) mechanisms regulating synaptic development and plasticity. DS is the leading genetic cause of mental retardation, and DS individuals have numerous clinical manifestations, including early onset Alzheimer's disease (AD). The exact mechanisms underlying those anomalies, however, remain unclear. They believe that Drosophila, with its powerful genetics, is an ideal model system for identifying the network of genes responsible for mental retardation and AD in DS, as well as for elucidating fundamental mechanisms regulating synaptic functions.

Dr. Terrence Town and his team focus on developing a treatment for Alzheimer's disease by targeting the body's immune system. Most therapies targeting the disease are thwarted by the blood-brain barrier, a natural mechanism that protects brain cells from entry of peripheral substances, and by the fact that immune responses in the brain are typically muted. However, in laboratory mice programmed to develop Alzheimer's-like disease, Dr. Town's group has shown that certain immune cells can be coaxed into the brain from the circulation, where they attack the damaging sticky plaque buildup that is a defining feature of Alzheimer's disease. Earlier this year, Dr. Town's lab revolutionized the field of Alzheimer's disease research by conducting non-invasive neuro-imaging studies on the first rat model of the disease that manifests all of the clinico-pathological hallmarks of the human syndrome. These transgenic rats over-express two mutant human transgenes that are each independently causative of familial early-onset Alzheimer's disease. With these state-of-the-art neuroimaging results, this makes this exciting rat model an invaluable tool for understanding Alzheimer's disease etiology and for testing cutting-edge therapeutics pre-clinically.

Dr. Berislav Zlokovic's laboratory has a long standing interest in understanding the role of cerebral blood vessels and blood-brain barrier (BBB) in pathogenesis of Alzheimer's disease (AD), related neurodegenerative disorders and stroke, as foundations for development of new therapies for these diseases. Using animal models and studying post-mortem and living human brain, his laboratory has shown that dysfunction in the blood-brain barrier (BBB) and brain microcirculation can accumulate before neuronal dysfunction and contribute to the onset and progression of different neurological symptoms including cognitive impairment. His research team has identified the cellular and molecular mechanisms in cerebral blood vessels causing disruption of the neurovascular unit, which leads to neurodegeneration in models of Alzheimer's disease, pericyte-deficient rodents and stroke. His group has also developed new neuroimaging and molecular biomarkers in the living human brain that are currently being studied in individuals at genetic risk for AD and those with vascular risk factors. His group has also identified molecular mechanisms at the BBB that maintain clearance of Alzheimer's toxin amyloid-beta from the brain into the circulation, and its influx or re-entry from the circulation into the brain, reflecting an important physiological function of the BBB in maintaining brain amyloid-beta homeostasis. Discoveries of his research team have contributed to the development of clinical trials for Alzheimer's disease based on clearance of amyloid-beta or inhibition of its re-entry into the brain that are currently being tested in Phase 2 and Phase 3 studies in Alzheimer's patients, respectively. They also developed a new therapy for stroke based on activated protein C treatment that is currently under clinical assessment in stroke patients as a neuroprotective agent in Phase 2 studies.

Hong-Wei Dong's research focuses primarily on the Mouse Connectome Project (MCP) (www.MouseConnectome.org). The lab has well-established state of the art tract-tracing technologies to systematically reveal and map neuronal networks of the whole mouse brain, and have developed a high-throughput pipeline for data production, collection, and informatics. To date, they have collected over 100 TB of high-resolution, high-quality data from 700 mice (an aggregation of >1200 neuronal pathways). About one third of these raw imaging data have been made freely accessible to the neuroscience community and general public. To facilitate their use, they have also developed a powerful visualization tool that enables users to visualize and annotate these data. This type of open resource will guide hypothesis-driven neuroscience research on brain function and behavior. In addition, they will begin to apply their connectomics approach to systematically characterize connectopathies in mouse models of several neurological and neuropsychiatrical diseases, such as Huntington's and Alzheimer's diseases.

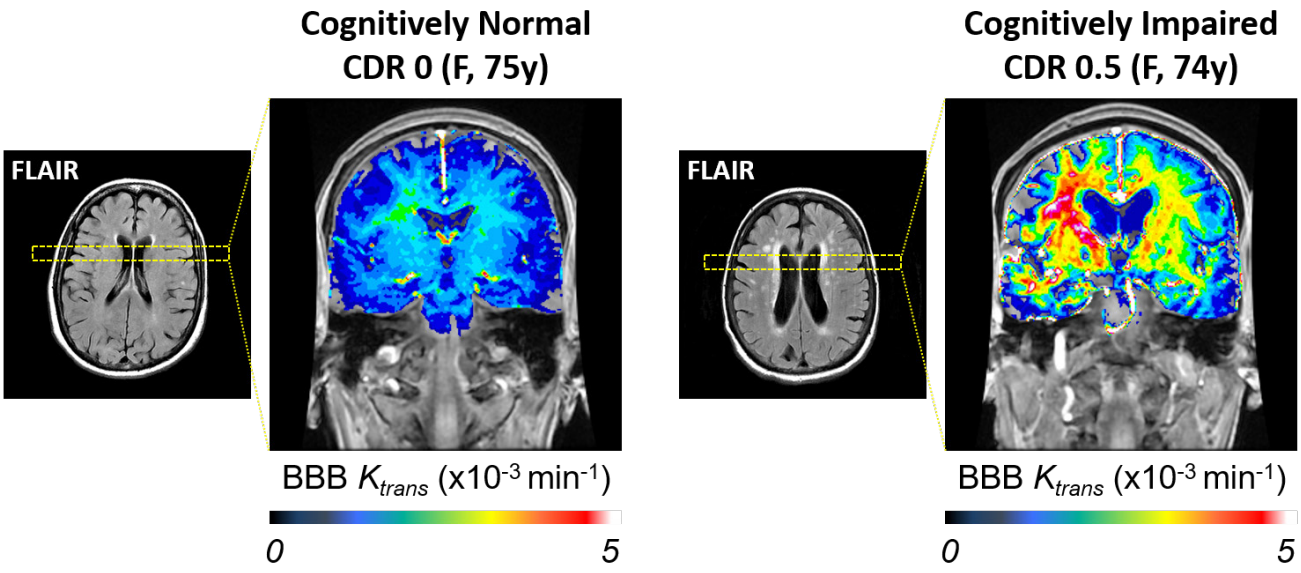


Photo credit: Zlokovic/Montagne

Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) images showing white matter damages in a cognitively impaired (CDR 0.5) 74 year old female (right panel) compared to a healthy brain from a cognitively normal (CDR 0) 75 year old control female (left panel). In addition, coronal blood-brain barrier (BBB) permeability, K_{trans}, heat maps in the same cognitively normal (left panel) and cognitively impaired (right panel) individuals using our newly developed high-resolution dynamic contrast-enhanced (DCE)-MRI technique. These illustrate that increased BBB breakdown may contribute to cognitive decline.

Psychiatric Genetics

The Center for Genomic Psychiatry investigates the role of genetic risk factors in disorders of the mind. Human genetic studies have uncovered several genes associated with complex psychiatric and developmental disorders. Human synapses and synaptic proteins have been in many of these disorders. Dr. Marcelo Coba uses a systems biology approach to understand how the disruption in the communication between neurons at the synapse might play a role in psychiatric disease. He uses a combination of state of the art proteomic assays, together with mouse genetics, CRISPR technology, hiPSC derived neurons, computational biology, and synaptic physiology. These methods are used to investigate how mutations associated to psychiatric disease impairs synaptic function by modifications in protein signaling networks. This aim is to define protein-network maps that will allow us to stratify patients by their correspondent mutations signatures.

Dr. Dan Campbell focuses on defining functional genetic variants that contribute to the etiology and treatment effectiveness of autism and schizophrenia. The long-term goals of these studies are to better understand the causes of the disorders and to improve the ability to treat them on an individualized basis. His continuing work seeks to determine how genetic variants influence expression of noncoding RNAs in the brain and what environmental factors contribute to altered noncoding RNA expression.

Dr. Alex Bonnin is working to understand how maternal-fetal interactions affect fetal brain development. The current focus is on the role of serotonin (5-HT) signaling in fetal programming or in other words, how serotonin signaling affects the mechanisms by which maternal and environmental factors shape the fetal brain and influence the development of adult diseases. These studies should ultimately provide new clues into the developmental origin of several mental health-related disorders in humans, such as autism and schizophrenia. These and other disorders of adult brain function have developmental components suggesting a crucial ontogenetic role of neurotransmitter systems. In particular the serotonergic modulation of axon guidance mechanisms is important for the refinement of neuronal circuits formation in utero, suggesting that serotonergic signaling is important for normal fetal brain wiring. They are pursuing a translational approach aiming at understanding and potentially reducing the effects of maternal infections during pregnancy as well as the use of therapeutic drugs, in particular antidepressants, on fetal brain development.

The overall interest of **Dr. James Knowles's** laboratory is the genetic basis of behavior, cognition and affect. Most of our studies search for the genetic factors that have an etiological role in psychiatric illness. Finding genes for the psychiatric disorders is by necessity a collaborative effort. These are large-scale studies that require multiple sites to collect the sample sizes necessary to have adequate power. These studies also require teams of clinicians, geneticists and statisticians working together to make progress. Dr. Knowles is the geneticist/molecular biologist on several such teams. In the past, his work with these investigators has focused on the anxiety disorders, depression and the addictive disorders. Currently, most of the lab's effort is focused on schizophrenia and OCD, along with several smaller projects.

Genomics

Dr. Kai Wang is working on creating an automated bigdata pipeline for whole exome/genome sequencing analysis on Mendelian diseases and cancer, and for RNA-Seq analysis of single neuronal cells. His lab also investigates DNA methylation, gene expression and somatic mutations in various cancer. A chief goal of the Wang lab is to develop data mining algorithms to extract more information from genomic data. He has developed several tools in wide use, including the PennCNV, GenGen and ANNOVAR software packages.

Dr. David Conti is working to elucidate the genetic contribution of complex diseases from population-based samples, using both applied genetic epidemiologic studies and the development of statistical methods. Presently, Dr. Conti's applied work focuses on elucidating the genetic contribution of candidate genes within the dopamine and serotonin pathways and their role in smoking initiation, progression, and cessation. His research in statistical methodology concentrates on the use of hierarchical modeling and Bayes model averaging as a general framework for the analysis of multiple genetic polymorphisms in genes involved in numerous pathways impacting disease.

Dr. Gabriel Zada utilizes next-generation genomic and epigenomic profiling (i.e. DNA Methylation analysis) to study the behavior of various brain tumors. In particular, he is interested in studying the process of local tumor invasion and developing molecular classification systems for various skull base tumors, including pituitary tumors and meningiomas. He is also working to develop novel treatment strategies for skull base tumors using intranasal therapy systems.

Vascular

Dr. William Mack is focused on translational efforts to treat stroke and cerebrovascular disease. He and his group are interested in inflammation and resultant microvascular failure in a range of experimental and clinical models. Dr. Mack has refined an experimental model of bilateral carotid artery stenosis to examine the role of inflammation in the setting of chronic cerebral hypoperfusion. This system has enabled his team to assess the impact of vascular disease on cognition and neurodegeneration. The group has identified the C5 complement protein as a critical effecter of injury through histological and behavioral outcome measures. These findings lend insight into the role of complement in progressive cognitive injury and neurodegenerative conditions such as vascular dementia and Alzheimer's disease. Dr. Mack's laboratory also studies biomarkers of cerebral vasospasm following subarachnoid hemorrhage and employs novel endovascular delivery platforms in the setting of acute stroke. He utilizes advanced MR permeability imaging sequences and serum analysis to quantify blood brain barrier breakdown in subarachnoid hemorrhage patients. Dr. Mack also currently leads a multicenter phase 2a safety and feasibility study of regional and distal intra-arterial Magnesium delivery during endovascular mechanical thrombectomy procedures for acute stroke.

Dr. Berislav Zlokovic's lab currently studies how genes that influence AD risk (e.g., APOE4, PSEN1, PICALM, CLU) affect the cerebrovascular system using transgenic models, human inducible pluripotent stem cell-derived neuronal and BBB in vitro models of human neurological disorders. He also studies how BBB function and cerebral blood flow changes influence cognitive functions and white matter connectivity. He remains interested in developing advanced approaches with activated protein C therapy for stroke and neurological disorders.

The broad interest of the **Janos Peti-Peterdi lab** is renal (patho)physiology, specifically the intrarenal mechanisms involved in the control of blood pressure and body fluid balance under normal and disease conditions (chronic kidney disease, hypertension, diabetes). A new research direction focuses on mechanisms of endogenous nephron repair and their augmentation in the development of new therapeutic approaches.

Circuits

The **Robert Chow** laboratory studies the function of electrically excitable cells, such as neurons and endocrine cells. The major projects involve (a) characterizing the function of synaptic proteins in nerve-nerve signaling; (2) correlating the physiology and transcriptomes of neurons in adult and fetal brain; (3) testing the role in cancer invasion/metastasis of novel non-coding RNAs derived from regulators of neural development; (4) evaluating the role of amyloid proteins in cell death in diabetes and neurodegenerative diseases.

Dr. Li Zhang's ultimate research goal is to decipher brain circuits, and to understand how perception and behaviors are generated and controlled, how the brain's cortex adapts in response to changes in the dynamic external environment, and how specific changes in cortical functions result in neurological and psychiatric disorders. To address these highly challenging questions, Dr. Zhang's approach is to resolve the neural circuitry (how neurons are wired in the brain), i.e. the structural basis underlying the brain functions. In the past years, Dr. Zhang and his collaborators have committed substantial efforts toward developing molecular/genetic and electrophysiological/imaging techniques for elucidating the neural circuits for both local neuronal computation and for controlling animal behavior. To this end, he and his group pioneered in applying in vivo whole-cell voltage-clamp recording, to reveal at the synaptic connection level, how the excitatory and inhibitory synaptic interplay determines the sensory response/processing properties.

Dr. Huizhong Tao's work mainly concentrates on the organization of neural circuits underlying visually evoked behavior and perception and how the circuits are established during development (please see Vision/Eye below). In recent years, her lab has developed various optogenetic tools to achieve selective activation and inactivation of visual structures and specific types of neuron in a visual structure, using different Cre-driver mouse lines. Her lab has also developed quantitative methods to measure behavioral outputs. They study local circuits with not only in vitro but also in vivo electrophysiology, assisted by newly developed retrograde and anterograde labeling techniques.

Derek Sieburth studies synaptic signaling pathways that regulate synaptic function, with the goal of understanding how these pathways contribute to the function of neuronal circuits controlling behavioral programs in the nervous system. His laboratory uses C. elegans as a model organism for studying synaptic biology, because of its simple neuronal circuitry, the ability to visualize synapses by fluorescent imaging in live animals, and its powerful genetics. He combines state of-the-art behavioral, genetic, cell biological, and in vivo neuronal imaging techniques in to study the cellular molecular mechanisms underlying secretion of synaptic vesicles and dense core vesicles.

Vision/Eye

Photoreceptor cells are light sensitive neurons in the retina that initiate the first step in vision. One of the main objectives of **Dr. Jeannie Chen's** laboratory is to understand the molecular cascade that underlie the ability of retinal photoreceptor cells to perceive light, and how defects in this cascade leads to human blindness. The sophisticated circuitry in the neural retina comprises of up to 20 different channels of information that encodes our visual scene. Death of photoreceptor cells leads to re-wiring of this circuitry. Another objective of Dr. Chen's laboratory is to understand how this pathological change of the retinal circuitry process visual information after the photoreceptor cells have been rescued by gene therapy or replaced by stem cell therapy.

Dr. Huizhong Tao is interested in the architecture of visual cortical circuits. To dissect the circuits that consist of excitatory and inhibitory neurons, Dr. Tao's lab applies in vivo electrophysiology, in particular two-photon imaging guided recording, to target different types of neurons in rodent visual cortex. From the response properties of individual neurons and the pattern of synaptic inputs to these neurons, they attempt to deduce the connectivity rules governing the construction of cortical circuits. The hope is that this work will lead to insights into how diverse visual processing functions are achieved by the cortical circuits. Dr. Tao is also interested in how functional visual circuits are established during development. The development of visual system not only depends on molecular and genetic programs, but also can be profoundly influenced by the pattern of neural activities along the visual pathways. Early synaptic connections in the developing brain can undergo substantial remodeling in response to patterned electrical activity of neurons. The Tao lab examines how neural activity of various patterns leads to modulations of synaptic connections and shapes the formation of visual circuits. The aim is to provide insights into how abnormal visual experience in early life, such as in the condition of strabismus and visual deprivation, can lead to abnormal wiring in the brain, and how we can correct it.

Hearing/Ear

The most common sensory abnormality in the world is age-related hearing loss. The second most common form of hearing loss is noise-induced. **Dr. Rick Friedman's** laboratory has demonstrated that both of these traits can be treated as common diseases and can be approached through association mapping. The primary objective of Dr. Friedman's laboratory is to study these common forms of hearing loss using a genome-wide association approach in mice. Dr. Friedman's laboratory has begun to define the genetic architecture of age-related hearing loss in mice and has identified several loci leading to susceptibility to noise-induced hearing loss. This work will provide important insights into the mechanisms underlying these common forms of hearing loss and studies in the mouse provide the power to begin to understand gene X environment interactions.

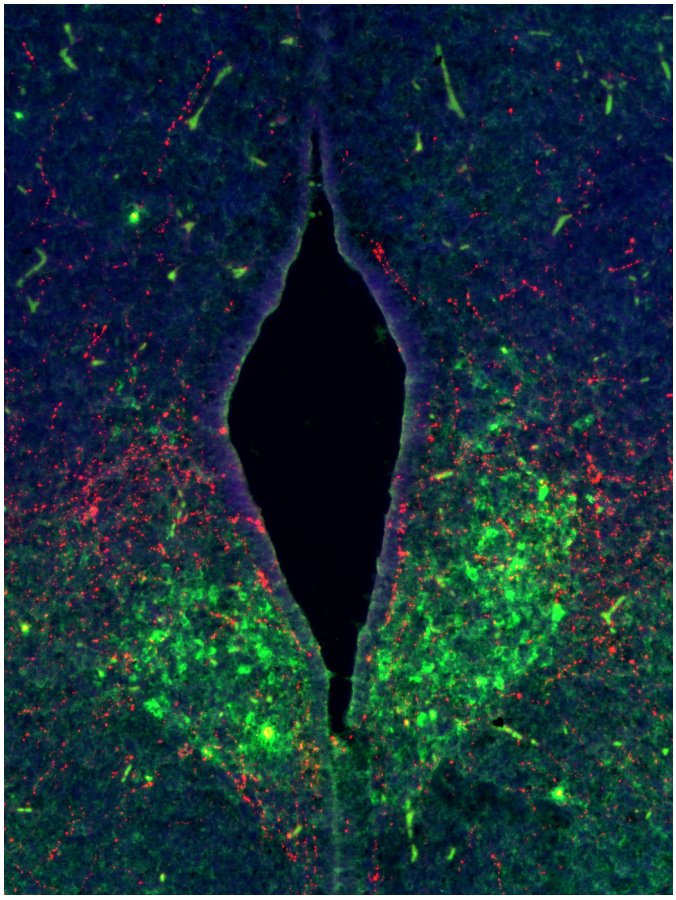


Photo credit: Bonnin

Serotonin axons (red) and S100a10 neurons (green) in mouse fetal hypothalamus.

The Kalluri lab is interested in understanding the biophysical mechanisms by which the auditory and vestibular sensory peripheries encode information about sound and head movements. They are specifically interested in how these functions develop and degrade with age and insult.

Hearing loss is one of the most common birth defects. Approximately one in five hundred newborns suffer from significant hearing impairment. In addition, once mechanosensory hair cells in the inner ear are damaged and lost by any of a variety of reasons such as aging and loud noises, they never regenerate. Thus, the majority of sensorineural hearing loss, such as age-related hearing loss and noise-induced hearing loss is permanent and will significantly affect the quality of one's life. Recently, stem cell research has shed light on the possibility of regeneration of hair cells in humans. The research goal of the **Takahiro Ohyama** lab is to understand the molecular mechanisms of inner ear development and to explore the possibility of regenerating sensory cells to treat hearing and balance disorders.

scientific advancements

In the following pages are some of the notable accomplishments by ZNI faculty over the past year.

Alexandre Bonnin

Research in the Bonnin lab focused on understanding how adverse events experienced during pregnancy increase the risk of developing mental disorders in the offspring. Efforts were centered around two common types of prenatal insults: 1) maternal infections during pregnancy, and 2) maternal stress/depression as well as exposure to antidepressant drugs. The Bonnin lab demonstrated that maternal infection directly affects the functioning of an important molecular pathway in the placenta which then specifically alters the development of serotonin neurons in the fetal brain. This is expected to have long term consequences on offspring brain function, such as increased anxiety or depression. These results were published in The Journal of Neuroscience. The Bonnin lab also characterized how maternal depression and the use of SSRI antidepressants during pregnancy directly affect fetal brain development. In addition, we started to characterize the role of a novel adaptor protein in fetal brain development. The results are under review for publication later this year.

Daniel Campbell

The rates of autism continue to rise, creating challenges for an increasing number of children and families. The Campbell lab contributed two important publications toward understanding and treating autism this year. First, we published a review of genetic predictors of quantitative social communication phenotypes relevant to autism. The review allowed us to propose practical measures to describe how our work can be translated to helping individuals with autism. Second, we published a paper showing the changes in expression of noncoding RNAs as human neurons differentiate. Noncoding RNAs are genes that do not code for a protein but instead regulate the expression of other genes during brain development. Using state-of-the-art RNA sequencing in human neural progenitor cells, we found that nearly half the genes expressed in differentiating neurons were noncoding RNAs. We found that genes that change expression as the neurons differentiate are enriched in genes implicated in autism. We also found that noncoding RNAs make up half of the genes that predict neuronal differentiation. These results indicate that noncoding RNAs are likely to hold key regulatory roles in gene networks underlying neuronal differentiation and neurodevelopmental disorders.

Karen Chang
The Chang laboratory discovered: 1) a protein upregulated in Down syndrome and mis-expressed in some cases of Alzheimer's disease plays an important role in preserving memory during aging in a fly model; 2) a novel activator of integrin is required to preserve the stem cell niche and synaptic development in Drosophila. They are continuing to investigate the biological functions of both of these proteins, mechanisms of their actions, and contribution to neurological disorders.

Jeannie Chen
Like other GPCRs, rhodopsin is deactivated through receptor phosphorylation and arrestin binding. Full recovery of receptor sensitivity is then achieved when rhodopsin is regenerated through a series of steps that return the receptor to its ground state. We show that dephosphorylation of the opsin moiety of rhodopsin is an extremely slow but requisite step in the restoration of rhodopsin to its ground state that is required for optimal dim light vision. We propose a model in which light-exposed retinae contain a mixed population of phosphorylated and unphosphorylated rhodopsin. Moreover, complete dark adaptation can only occur when all rhodopsin has been dephosphorylated, a process that requires >3 h in complete darkness.

Robert H. Chow
In the process of correlating physiology and transcriptomes of individual brain neurons, we believe we have identified a neuron in fetal brain that has never been described previously. Work is ongoing to further characterize the neuron, and we hope to publish a detailed description in spring 2017.

With Dr. I-Chueh Huang, we have performed the first study of Zika virus tropism in human fetal brain slices, and we have shown that drugs that modify cytosolic calcium also prevent viral replication. This work is currently under review for publication.

With Jim Weiland and Mark Humayun's laboratory, we published a paper identifying a new electrical stimulation protocol that improves the visual acuity of patients with the Argus II epiretinal implants. What makes this work exciting is that experiments conducted in the Chow laboratory using an in vitro model of the retinal implant were used to identify the stimulation protocol, which was tested and found successful in patients who had the retinal implant. This opens the way for further testing and refinements of the epiretinal prosthesis.

With Ralf Langen's laboratory, we published a paper showing that three molecules found elevated in blood of patients with type 2 diabetes may each accelerate amyloid peptide misfolding. Accumulations of amyloid peptides have been implicated in the pathophysiology of a range of cellular degenerative diseases, including Alzheimer's, Parkinson's, and, in this case, type 2 diabetes.

The Postsynaptic density Kinome

Photo credit: Coba

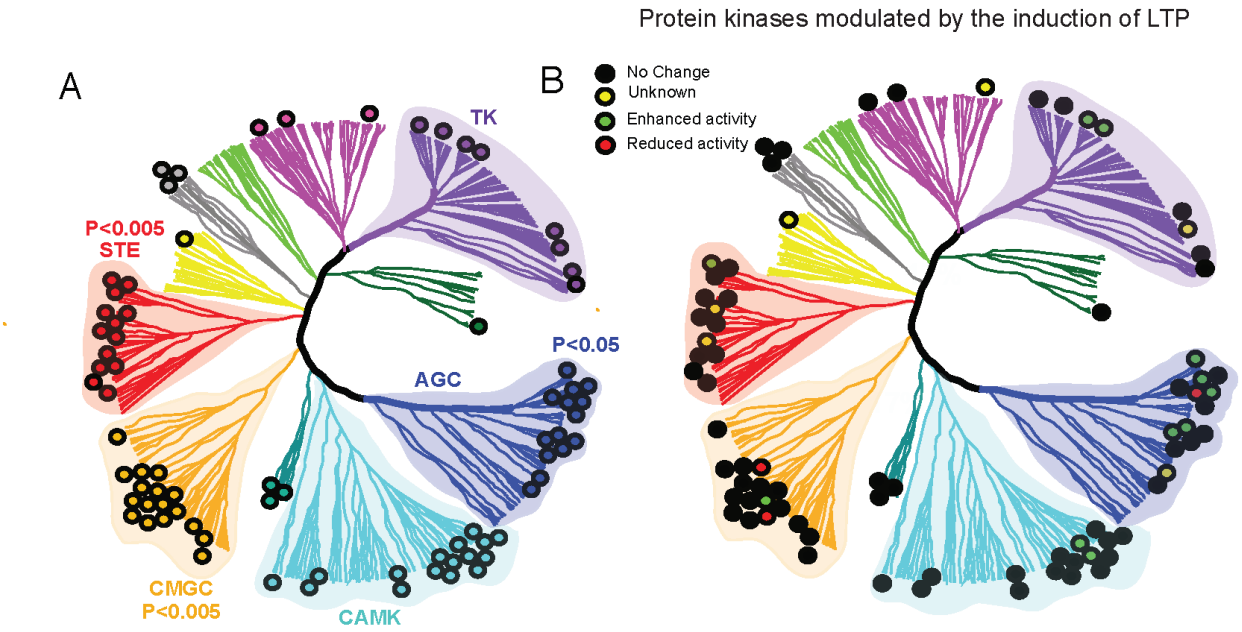


Fig. Modulation of the protein kinases present in the postynaptic site (PSD kinome) by the induction of synaptic plasticity

(A) Representation of the kinases present in the mouse PSD on the mouse kinome tree. Circles show kinases present in part of the kinome tree. Main groups are indicated: AGC, CMCG, TK, STE, and CAMK. P values indicate kinase groups that are enriched in the PSD. (B) Kinases modulated by the induction of long-term potentiation (LTP) mapped on the mouse kinome tree.

Marcelo Coba

We recently developed novel large-scale methods that allow the study of protein networks in the CA1 area of mouse hippocampus. The CA1 region of the hippocampus in the brain responses to high frequency stimulation by inducing a synaptic strengthening event call long-term potentiation (LTP). This is commonly considered an electrophysiological representation of memory and learning and involves changes in the abundance of receptor proteins at the postsynaptic side of the membrane and complex changes in the organization of the region beneath the postsynaptic membrane called the postsynaptic density (PSD), which contains more than 1500 proteins. Performing electrophysiology and proteomics assays, together with bioinformatics analysis, we have shown how modifications in specific groups of proteins work together at a cellular level. Additionally, we showed how these protein modifications, called phosphorylation, are potentially related to the risk for developing either autism spectrum disorders or schizophrenia. This work provides an important link between the wealth of genetic data that has accumulated over the past decade, with an understanding of how the brain works to form memories. As such, it is a prime example of how the promise of genetics may now be ready to be applied in understanding complex neurological diseases.

The data provided along with this medical association of disease risk should guide researchers and clinicians toward a better understanding of both the molecular changes that enable learning and memory, as well as complex neurological diseases involving proteins that are part of the PSD.

David V. Conti

Recently the Conti group has been focused on methodological advances in three main areas of research in genetic association studies: (1) fine-mapping, (2) integrated analysis, and (3) gene-environment interaction. Motivated by recent applied work in which we examined 67 prostate cancer risk regions in populations of European, African, Japanese and Latino ancestry, we have developed a new and scalable algorithm for the re-analysis of published marginal associations under joint multi-SNP models to better identify a small set of variants for further functional follow-up via laboratory experiments. To leverage the availability of various omics data, we have recently proposed an integrated analysis approach that models the causal relationships of the various data types, such as germline, omic and disease data, to estimate relevant clusters of individuals to better characterize the underlying disease mechanism. Finally, we have expanded our approach to better identify gene-environment interactions by using Bayes model averaging to: (1) balance the robustness of a case-control approach with the power of the case-only approach; (2) leverage marginal SNP effects; (3) allow for the incorporation of prior information; and (4) allow the data to determine the most appropriate model.

Hong-Wei Dong

The major direction of our research focuses primarily on the Mouse Connectome Project (MCP) (www.MouseConnectome.org), which aims to create a three-dimensional, Google Earth-like, digital Connectome atlas of the C57BL/6J mouse brain. We have constructed the first comprehensive and precise connectome of the entire cerebral hemisphere and thalamus. The first major milestone, Neural Networks of the Mouse Neocortex, was published in 2014 (Zingg et al., 2014, Cell, 156, 1096-1111). As another major achievement of our MCP project, recently, we constructed a mouse cortico-striatal projectome: a comprehensive projection map from the entire cortex to the dorsal striatum in the mouse brain (Hintiryan et al., Nature Neuroscience, 2016). In this study, we developed an innovative computational neuroanatomic method to systematically and quantitatively map and analyze large scale connectivity data, which allowed us for the first time to identify 29 distinct functional domains in any mammalian brain. Additionally, this connectomics approach was applied to characterize circuit-specific cortico-striatal connectopathies in mouse models of disconnection syndromes such as autism spectrum disorder and Huntington disease. This work was reported by many news media (see http://www.mouseconnectome.org/press/).

Rick A. Friedman

The Friedman lab has completed the first GWAS in mice for hearing loss, noise-induced susceptibility, and vestibular functional variation. They have identified Nox3 as a candidate gene and several new and novel loci. Also, they have begun the first GWAS for vestibular traits and identified Dcc as a novel gene affecting vestibular function. The Friedman lab has generated several transgenic lines and has begun validation of two novel genes for age-related hearing loss and a new candidate for susceptibility to noise.

Radha Kalluri

In the Kalluri lab we study the biophysical processes underlying sensory signaling at the first synapse between the sensory cells of the inner ear and their partner neurons. We use a combination of patch-clamp electrophysiology, modeling, and anatomical methods to study the connectivity patterns of sensory cells in developing auditory and vestibular sensory epithelia during a critical period of development when synapses are forming and stabilizing. We've made major advances in the following four directions:

1. Sensory-neural hearing loss is a waste-basket term for a wide range of hearing impairments. Using non-invasive measures of auditory function we have proposed a method for refining the classification of hearing loss. Ongoing experiments are testing this new approach for understanding the etiology of hearing impairments.
2. We have recently found that the synaptic features that typically serve as markers for functional specificity in the auditory periphery may be driven by developmental signals that are independent of true sensory experience.
3. We've identified candidate ion channels in the vestibular system whose differential expression within sub-groups of vestibular afferent neurons may serve as the substrate upon which vestibular sensory information is parsed into parallel channels.
4. In collaboration with the Segil, Ohyama, and Ichida laboratories we are characterizing the biophysical properties of reprogrammed inner ear hair cells and neurons using patch-clamp techniques.

James A. Knowles

The overall theme of the Knowles lab is the identification of genetic risk variants for the neuropsychiatric disorders. During the past year, significant progress has been made towards the discovery of risk genes for obsessive-compulsive disorder (OCD). The Knowles lab, as part of the Psychiatric Genomics Consortium (PGC) has recently completed a meta-analysis of the available OCD GWAS data and submitted this for publication. We are quite close to genome-wide significant findings and we have a substantial amount of additional data in the upcoming academic year, which will give us significant findings. We are continuing to study a mouse model of OCD (it lacks the gene encoding the transcription factor BTBD3) which has multiple compulsive behaviors. We have identified three regions of the thalamus that have decreased connectivity and are now performing human brain imaging to see if the same regions are altered in OCD patients (in collaboration with Drs. Art Toga and Yonggang Shi).

We have nearly completing a Transcriptome Wide Association study (TWAS) of schizophrenia (led by Dr. Oleg Evgrafov) using neuronal cell lines we have derived from individuals with schizophrenic, that is implicating about 120 transcripts in the neurodevelopmental aspect of the disorders and 90 of these code for proteins. Nine of these 90 have been previously implicated by other genetic studies (3 under SCZ PGC2 GWAS peaks, 2 in CNV regions and 4 have de novo mutations). Additional analysis of these cell lines is in progress with microRNAs (miRNA) and epigenetic marks (as part of the PsychEncode Consortium).

We have also nearly completed a study of Cajal-Retzius neurons, the first neurons in the developing human brain, in collaboration with the Chow laboratory. We have the first electrophysiological recording of human Cajal-Retzius neurons, and have used single-cell RNA sequencing to determine the transcriptome that defines Cajal-Retzius neurons, and have compared it to the transcriptomes of cortical plate and subplate neurons from the same stage period of brain development.

Ralf Langen
The Langen lab has on ongoing interest in the structural changes that occur in protein misfolding diseases such as Alzheimer, Parkinson, Huntington disease as well as type 2 diabetes. The overall focus has been on understanding the structural changes of proteins known to promote the aforementioned diseases with the goal of developing potential therapeutic molecules that can reverse or prevent these structural changes.

Huntingtin proteins with excessively high numbers of glutamine building blocks (>36 consecutive glutamines) are known to cause Huntington disease. How these large numbers of glutamine residues alter the protein structure and cause disease is not known. Such knowledge would be an essential first step for devising potential therapeutic treatments aimed at guiding the protein structures away from the toxic to the non-toxic forms. The Langen lab has now made significant advances by delineating how excessive numbers of glutamines affect the native structure of huntingtin and how they force the protein to misfold into non-native and toxic structures. With this information in hand, molecules can now be evaluated with respect to a potential therapeutic activity.

The Langen lab also provided direct evidence that factors associated with obesity can have a pronounced impact on protein misfolding. These findings provide a mechanistic link between obesity and misfolding diseases.

William Mack
The Mack laboratory completed the first year of a grant to study the effects of air pollution from vehicular exhaust in the setting of acute stroke. New R01- NIH/NIEHS ONES (Outstanding New Environmental Scientist): The proposed research program seeks to determine the impact of particulate matter (PM) exposure on white matter injury and neurocognitive decline. These associations are further examined in the setting of underlying cerebrovascular disease (chronic cerebral hypoperfusion). The team has demonstrated white matter changes in the setting of nanoparticulate matter exposure that are exacerbated by chronic cerebral hypoperfusion

Takahiro Ohyama
The Ohyama Lab is investigating how the cochlea, the auditory organ, develops during embryonic development. They discovered BMP signaling pathway is important for cell fate decision between sensory and non-sensory structure of mammalian cochlea. The Ohyama lab is also analyzing the mechanisms how migrating neural crest cells are incorporated into the non-sensory structure of developing cochlea, which is crucial for proper hearing functions. These projects aim to understand disease mechanisms of hearing impairment and develop translational research such as regeneration of auditory cells.

Janos Peti-Peterdi

The Peti-Peterdi lab investigated the cellular and molecular mechanisms of glomerular kidney diseases and renal tissue repair, and identified several new potential therapeutic targets for future further development. The main focus of our studies last year was the role of a special chief cell type in the kidney called macula densa, and their role in endogenous nephron repair. Our laboratory 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 physiological adaptive responses, and in 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 specific molecular mechanisms within macula densa cells 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. Another focus was the role of a pericyte-like cell type within the glomerulus called podocyte, in the development of glomerulosclerosis and chronic kidney disease. We identified purinergic calcium signaling mediated by the P2Y2 receptor, and the cell membrane calcium channel TRPC6 as the most significant mechanisms of podocyte cell-to-cell communication and propagation of podocyte injury. We are currently testing the effects of various pharmacological approaches that target these podocyte mechanisms, to investigate if they provide benefit in chronic kidney disease.

Derek Sieburth

The Sieburth lab is interested in understanding how behavior is controlled by the regulation of structural and functional properties of neurons. We use the nematode as a model system for studying neuronal function because of its simple nervous system and the ability to visualize proteins in synapses in behaving animals. This year the lab identified a new signaling pathway that controls when neurons become activated during a rhythmic behavior. The lab also discovered a neuroendocrine signaling pathway that protects organisms from the toxicity of oxidative stress through the stress-induced release of specific neuropeptides from neurons that activates the oxidative stress response in distal tissues.

Ansgar Siemer

The Siemer lab made great progress characterizing the structure of the functional amyloid protein Orb2A. Not only did they show that the N-terminus of this protein can form amyloid fibrils on its own, but also that the same part of the protein is able to bind specifically to lipid membranes. This dual function of the N-terminus might give interesting clues about how the behavior of Orb2 and thereby long-term memory is regulated. We are currently studying the structure of the full length Orb2 protein and compare it to the structure of the N-terminus alone.

Furthermore, the Siemer lab developed new methods to look at intrinsically disordered domains that are often found in amyloid fibrils. Using these method, they did an in depth characterization of the dynamic domains of Orb2A and huntingtin exon-1 (HTTex1). Especially for HTTex1 this new method allows them to study its dynamic N-terminus, which has been shown to be important for the toxicity of HTTex1 in Huntington's Disease in unpreceded detail.

Huizhong Tao

During FY16, Dr. Tao's lab made two major discoveries. First, in layer (L)2/3 of primary visual cortex (V1), they found that complex cells, identified by their overlapping On/Off response subfields, had significantly weaker orientation selectivity than simple cells identified by segregated On and Off subfields. They further revealed that although excitatory inputs to complex and simple cells exhibited a similar degree of orientation tuning, inhibition in complex cells was more narrowly tuned than excitation, whereas in simple cells inhibition was more broadly tuned than excitation. Interestingly, the differential inhibitory synaptic tuning correlated well with the spatial organization of the input. Their results thus demonstrate that orientation selectivity of complex and simple cells is differentially shaped by cortical inhibition based on its orientation tuning profile relative to excitation, determined partially by the spatial organization of receptive fields of presynaptic inhibitory neurons. Second, they discovered that orientation selectivity of L2/3, but not L4, excitatory neurons was sharpened in the presence of sound or optogenetic activation of projections from primary auditory cortex (A1) to V1. The effect was manifested by decreased average visual responses yet increased responses at the preferred orientation. It was more pronounced at lower visual contrast and was diminished by suppressing L1 activity. L1 neurons were strongly innervated by A1-V1 axons and excited by sound, while visual responses of L2/L3 vasoactive intestinal peptide (VIP) neurons were suppressed by sound, both preferentially at the cell's preferred orientation. Their results thus indicate that the cross-modality modulation can be achieved primarily through L1 neuron- and L2/L3 VIP-cell-mediated inhibitory and disinhibitory circuits.

Terrence Town

My lab's focus continues to be developing a treatment for Alzheimer's disease by targeting inflammation and the immune system. For the first time, we have shown that 're-balancing' the immune system in pre-clinical Alzheimer's rodent models halts learning and memory impairment and ameliorates pathological features of the human syndrome. This work was published this year in the top journal, Trends in Neurosciences. Furthermore, we had three additional papers on our work related to the role of the immune system in human disease.

Further, my lab has revolutionized the field of Alzheimer's disease research by generating the first rat model of the disease that manifests all of the clinico-pathological hallmarks of the human syndrome. Specifically, we made transgenic rats that over-express two mutant human transgenes that are each independently causative of familial early-onset Alzheimer's disease: "Swedish" mutant amyloid precursor protein and deltaE9 mutant presenilin-1. Unlike their transgenic mouse cousins that develop 'senile' plaques but fail to manifest 'tangles' and frank neuronal loss, these transgenic rats-for the first time-develop the full spectrum of Alzheimer pathologies. This year, we used the latest cutting-edge imaging techniques to longitudinally show progression of Alzheimer's disease in this exciting new rat model. This makes them an invaluable tool for understanding Alzheimer's disease etiology and for testing cutting-edge therapeutics—all in living animals. Using this exciting new Alzheimer rat, we are actively pursuing collaborations with academics and with industry around the world to understand basic mechanisms of Alzheimer's and to develop a cure for this devastating disease of the mind.

Tobias S. Ulmer

The Ulmer lab has associated the brain enzyme carnitine palmitoyltransferase 1C with spastic paraplegia in humans. Spastic paraplegia are a group of human neurological disorders with progressive spasticity and weakness of the lower limbs, which is likely a result of distal axonopathy in the corticospinal tract where axons reach lengths of >1 m. At present, the lab is aiming to elucidate the biochemical basis of carnitine palmitoyltransferase 1C action.

In extending the understanding of cell-cell adhesion, the Ulmer lab has developed new techniques to study the thermodynamic basis of integrin receptor activation. As a first application of our technological advance, they examined the role of membrane lipid composition on receptor activation and found that negatively charged lipids act to stabilize the receptor in its inactive state. Recently, they have revealed how the coupling of extracellular and membrane-embedded protein domains sets the activation threshold of integrins receptors. Moreover, the sequence motif responsible for modulating this coupling was predicted in 21% of all single-pass human transmembrane proteins, making it a universal motif involved in the signaling of a wide range of cell surface receptors.

Kai Wang

The Wang lab has developed several computational tools for genome analysis, including Phenolyzer for phenotype-driven detection of disease-causal variants and SeqMule for automated human genome/exome analysis and disease gene identification. Additionally, the Wang lab also used long-read sequencing technology and nanochannel technology to perform de novo human genome assembly, and analyze the complex alternative splicing in the transcriptome.

Gabriel Zada

The Zada lab focuses translational research pertaining to genomics and targeted, precision molecular therapies for brain tumors. Our lab research focuses on a variety of brain tumors including pituitary adenoma, meningioma, glioma, cerebral metastases, chordoma, and craniopharyngioma, among others. Research in 2014-2015 has focused on performing genome-wide DNA methylation and gene expression analysis of surgically-resected pituitary adenomas and meningiomas. Based on this research and prior work, several promising candidate gene targets have been identified that are now being incorporated in to tumor cell line models to test the effects of modulated gene expression on cell survival, invasion, and hormone production.

Collaborations in 2015 include leading a nationwide collaborative group called the Pituitary Adenoma Genomic and Epigenetic (PAGE) consortium and applying for national support for a consortium-based, multi-institutional study focusing on these tumors. In addition, we have launched a collaborative research study with Dr. Joshua Neman at USC focusing on meningioma research. Additional collaborations at USC have been established with the Farnham laboratory.

Academic and community-based activities that our laboratory has been involved with include the USC Pituitary Symposium and Chordoma Foundation Community Conference, both hosted here at The USC Norris Comprehensive Cancer Center.

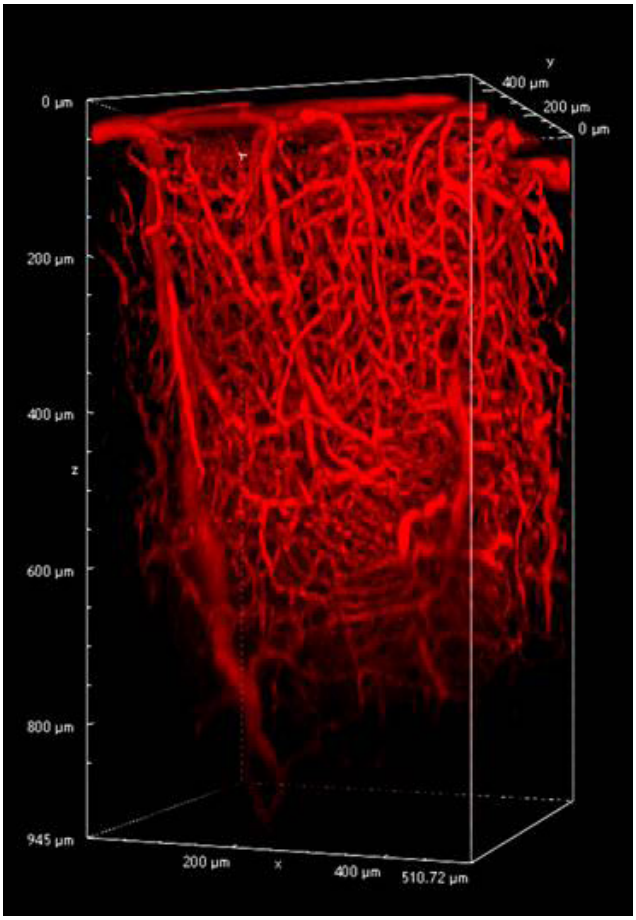
Li Zhang

The Zhang Lab continued their multiple-aspect investigation of the neural circuits at different auditory processing stages along the central auditory pathway. By integrating a series of cutting-edge techniques, they were able to reveal some new computational mechanisms exploited by the auditory circuits to process acoustic information. In particular, they have recently explored the neural circuitry underlying an auditory-motor behavior, and revealed that sensory cortex can directly drive innate defense behavior through corticofugal projections, a previously unrecognized neural pathway mediated by the inferior colliculus.

Berislav V. Zlokovic

We have developed an advanced dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) technique to evaluate subtle changes in the cerebrovascular integrity and blood-brain barrier (BBB) permeability in the living human brain that have not been possible to study before (Montagne et al., Neuron 2015). This technique has now been used in several clinical centers in North America to evaluate cerebrovascular integrity in individuals with no cognitive impairment but at genetic risk for Alzheimer's disease, i.e., in APOE4 carriers for sporadic AD, and PSEN1 mutation carriers for early onset familial AD. This neuroimaging biomarker allows for early diagnostics of vascular changes (BBB breakdown) preceding and/or contributing to dementia and AD, and possibly other neurodegenerative disorders. Next, we developed new molecular biomarkers in cerebrospinal fluid and blood for early detection of vascular changes in the brain of individuals at genetic risk for AD or with vascular risk factors such as hypertension and diabetes. These molecular biomarkers have been studied now in several centers in North America and Europe. Finally, we developed a new combination therapy for brain repair after stroke with 3K3A-APC and human neural stem cells. We were able to show that 3K3A-APC, a medicine developed for stroke by our group in collaboration with Scripps (Griffin) and ZZ Biotech and currently studied as a neuroprotective agent in stroke patients - Phase 2 studies funded by NINDS, is able to promote neuronal differentiation from transplanted human embryonic neural stem cells supporting both structural and functional integration of grafted stem-cell-derived neurons into brain circuits of the host (mice) (Wang, Zhao et al., Nature Medicine, 2016).

Photo credit: Zlokovic/Zhao



3D reconstruction of a mouse brain angiogram using two-photon in vivo imaging.

Alexandre Bonnin
Dr. Bonnin taught in the USC Neuroscience Graduate Program, as well as Pharmacology to 1st year USC medical students. Additionally, Dr. Bonnin was an invited speaker and session co-chair at national and international symposia (including those held in Paris, France and Milan, Italy). He was an invited speaker at the International Neuroplacentology Meeting (Washington), International Society for Serotonin Research (Seattle), Molecular Toxicology IDP (Los Angeles), and Zika Virus Awareness Symposium (Los Angeles). He is also a member of the USC Institutional Biosafety Committee.

Daniel Campbell
Dr. Campbell's contributions to the understanding of the role of noncoding RNAs in psychiatric disorders was recognized by an invitation to give a lectures at Harvard University and appointments to the editorial boards of Developmental Neuroscience and Behavioral and Psychiatric Genetics. He was also the co-Chair for Genetics on the Program Committee for the International Meeting For Autism Research.

Jeannie Chen
Dr. Chen served on the Scientific Advisory Board of the Karl Kirchgessner Foundation.

Robert H. Chow
Dr. Chow served as a mentor for the following programs: CIRM summer internship, CIRM Bridges internship, and Bridging the Gaps: Bench to Bedside Summer Research Program.

Hong-Wei Dong
Dr. Dong was invited to give several domestic and international talks, including a talk entitled "Assembling global neural networks of the mouse brain" at the Gordon Research Conference, Molecular and Cellular Neurobiology, in Hong Kong and a talk at the Institute of Neuroscience in Shanghai, at the Chinese Science of Academy. He also served as a sub-group co-chair at theNIH-organized Brain Initiative Cell Census Consortium (BICCC), BRAIN Initiative Investigator meeting in Bethesda, NIH, entitled: "Mouse Connectome Project: From Terabytes Of Pixels To Intuitive Brain Networks." The major mission of this consortium is to promote collaborations among BRAIN Investigators and provide strategic recommendations for characterizing neuronal cell types in the brain.

Rick A. Friedman
Dr. Friedman volunteered for College Bound, a non-profit organization facilitating Shure High School students college preparation. He also served as a Healthy Hearing Physician volunteer for the Special Olympic World games.

Radha Kalluri
Dr. Kalluri served on the Editorial Board of 'Otology and Neurotology' and the Executive Committee of the Neuroscience Graduate Program. She is also a founding member of the a networking group for Early Career Investigators in Auditory Neuroscience.

Ralf Langen
Dr. Langen was one of the organizers for the 2016 Protein Society Meeting, a large international meeting for scientists working on proteins. He gave numerous invited lectures at international meetings, including a FASEB meeting, 2016 CHDI conference and an NINDS workshop. At USC, he has been serving on the curriculum committee, the seminar series committee and the admissions committee. He also serves as a permanent member of an NIH study section (BPNS).

William Mack
Dr. Mack was elected to the Society of Neurointerventional Surgeons Board of Directors and was an Associate Editor for Journal of Neurointerventional Surgery and on the editorial board of World Neurosurgery as the Book Review Section Editor. Dr. Mack was also awarded a 2014 Keck School of Medicine Outstanding Research Scholarly Project Mentor Award at Keck.

Janos Peti-Peterdi
Dr. Peti-Peterdi served as the director of the USC Multiphoton Microscopy Core. He also serves on the Keck School of Medicine Faculty Research Council, and the Faculty Appointments, Promotion, and Tenure Committee. He is elected member of the European Academy of Sciences and Arts, and the American Society for Clinical Investigation. He received the 2015 Young Investigator Award of the American Society of Nephrology. He became the first honorary international member of the Japanese Society of Nephrology in 2016.

Ansgar Siemer
Dr. Siemer continued to serve on USC's PIBBS (Programs in Biomedical and Biological Sciences) admission committee. He co-organized the retreat of the Department of Biochemistry and Molecular Biology in Spring 2016. Furthermore, Dr. Siemer started organizing a new PhD program in Structure and Biophysics in Medicine together with Dr. Langen.

Huizhong (Whit) Tao
Dr. Tao served as the co-director of the Neuroscience Graduate Program core course. She also served as director of a graduate level advanced seminar course "Optogenetics and Circuit Mapping".

Tobias S. Ulmer
Dr. Ulmer was invited to give a lecture at the University of Turku, Finland, Turku Centre for Biotechnology. His talk, "Mechanism of Integrin Transmembrane Signaling," was given on February 9, 2016.

Kai Wang

Dr. Wang reviewed grant applications for a number of agencies, including American Cancer Society - Institutional Research Grant (ACS-IRG) and Wellcome Trust. He also participated in the Program Committee for 2nd International Conference on Algorithms for Computational Biology held in Mexico City, Mexico from August 4-6, 2016. He was also invited to give lectures, including "Bigdata techniques for genome analysis" for the Emerging Information and Technology Association, at the Massachusetts Institute of Technology, Boston, MA, on 08/07/2015; " Bioinformatics Approaches for Functional Interpretation of Genome Variation" for the Department of Bioinformatics and Genomics, at the University of North Carolina, Charlotte, NC, on 11/20/2015; "Workshop on ANNOVAR and wANNOVAR " for the Centre for Healthcare Innovation, at the University of Manitoba, Winnipeg, Canada, on 01/25/2016; "Bioinformatics Approaches for Functional Interpretation of Genome Variation" for the Edge of Science & Medicine Lecture, at the Winnipeg Regional Health Authority, Winnipeg, Canada, on 01/26/2016.

Li Zhang

Dr. Zhang was invited to speak at the several conferences and workshops, including giving a talk entitled "Cortical Circuits on Action" at the COSYNE workshop; a seminar at the University of Illinois at Urbana-Champaign; a workshop entitled, "Understanding Neural Excitation/Inhibition" at the University of Sheffield, UK; a talk at the Eleventh International Workshop on Auditory Processing, Rimrock Dude Ranch, in Cody, Wyoming, 2015; a talk entitled "How Inhibition Shape Sensory Cortex Information" at The University of Texas at San Antonio; a talk entitled "Inhibitory Mechanism for Auditory Cortical Processing", at the UCL, UK; serving as a session chair at a symposium at the University of Virginia, 2015; giving a seminar entitled "Neural Circuits for Auditory Processing and Behavior" at the Georgia Regents University, Department of Neuroscience & Regenerative Medicine, Augusta, GA; and talk at the Winter Conference on Brain Research (WCBR), in Breckenridge, CO.

Berislav V. Zlokovic

Dr. Zlokovic presented the prestigious Bishop lecture at the Washington University St Louis. He was also elected in 2015 into the European Academy of Sciences – Life Sciences section.

In April 2016, he organized the 3rd Annual Zilkha Symposium on Alzheimer Disease and Related Disorders entitled "Breaking through Barriers: From Bench to Bedside". This day-long event featured an international group, including the 10 out of the top 20 neuroscientists in the world, presenting mostly unpublished preclinical and clinical data, and approaching AD from multiple disciplines. Dr. Zlokovic was invited speaker at the following workshop/conferences:

Neurovascular pathways to cognitive dysfunction and neurodegeneration, Speaker, ISCBFM 2015, Vancouver, Jun 2015; The Intersection of Metabolic and Neurocognitive Dysfunction Workshop, Speaker, NIDDK, Bethesda, 2015, Jul 2015; The Blood Brain Barrier in Alzheimer's Disease, AAIC 2015, Speaker, Wash DC, Jul 2015; 6th Intl Symposium on Schizophrenia, Grass – Autoimmunity and Mental Disease, Max Plank, Speaker, Germany, Sep 2015; The 25th Adler Symposium, "Vascular Biology and BBB", La Jolla, CA, February 2016; Cure Alzheimer's Fund 2016 Research Consortium, La Jolla, CA, February 2016; Association for Research in Otolaryngology 39th Annual MidWinter Meeting, "Blood-brain barrier (BBB) and Neurodegeneration: How the BBB informs inner ear research", San Diego, CA, February 2016; Global Alzheimer's Leadership Series, "Biological Underpinnings of Vascular Contributions to Dementia", Paris, February 2016; The National Heart, Lung and Blood Institute 2016 Working Group on Lipid and Lipoprotein Metabolism and Alzheimer's disease and Related Dementias, Speaker, Bethesda, June 6-7, 2016; The National Heart, Lung and Blood Institute 2016 Blood Brain Interface Workshop, Chair and Speaker, Bethesda, June 7-8, 2016; The Cambridge Healthtech Institute Blood-Brain Barrier Conference, "BBB Breakdown in neurodegenerative diseases: contributions to disease pathogenesis and implications for drug delivery", Boston, June 15-16, 2016.

collaborations

Alexandre Bonnin

- Irina Burd of Johns Hopkins University; collaborating on fetal brain imaging studies following maternal exposure to stress and antidepressant drugs.
- Anne Andrews of UCLA; collaborating on fast microdialysis studies to measure offspring neurochemical activity following prenatal exposure to stress and antidepressant drugs.
- Gerard Karsenty of Columbia University, NY; collaborating on a study related to the role of a bone-derived molecule in fetal brain development.
- George Anderson of Yale University; collaborating on fetal, placental and maternal measures of biogenic amines.
- Robert Schwarcz of University of Maryland; collaborating on fetal, placental, and maternal measures of specific biogenic amines.
- Brett Lund of USC Neurology; investigating the effect of maternal infection on fetal cytokine levels.
- Skyla Herod of Azusa Pacific College; studying placental and fetal brain development in serotonin transporter knockout mouse model.
- Jae Jung, USC; collaboration on the study of Zika virus maternal-fetal transmission during pregnancy.

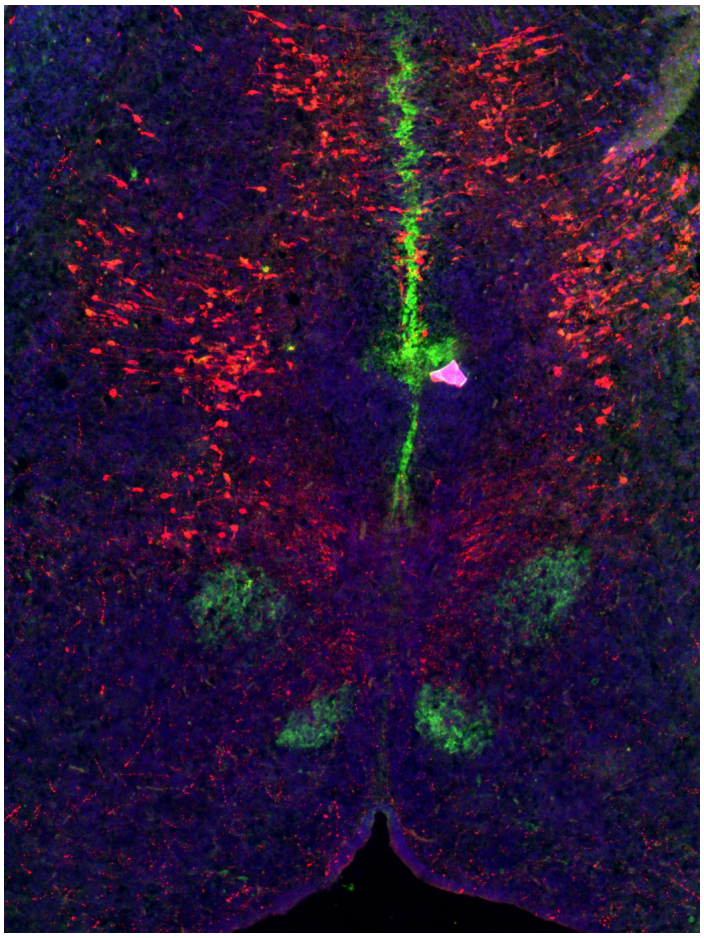
Daniel Campbell

- Wange Lu, USC Broad Institute; studying the impact of autism-related genetic variants on neuronal differentiation
- James Knowles of ZNI; studying gene expression changes caused by non-coding RNAs.
- Heather Volk of Johns Hopkins University; investigating gene-environment interactions in autism.
- Kevin V. Morris of Scripps Research Institute; studying the molecular mechanisms of non-coding RNAs.
- Judy Van de Water of UC Davis; studying the genetic basis of altered immune sensitivities in autism
- Lisa Croen of Kaiser Permanente; studying the genetic basis of altered immune sensitivities in autism.

Karen Chang

- Tai Min of UNIST, Korea; investigating common molecular pathways altered in Down syndrome and Fragile X syndrome, two of the most common genetic causes of mental retardation.
- Dion Dickman of USC, Dept. of Neurobiology; studying the role of a novel synaptic kinase in regulating synaptic growth and function.
- Ralf Langen, Zilkha Neurogenetic Institute, USC; examining the effects of post-translational modification on membrane protein functions.
- Sergey Nuzhdin of USC: mechanisms regulating learning and memory.

Photo credit: Bonnin



Serotonin (red) and S100a10 protein (green) in the mouse fetal hindbrain.

Jeannie Chen

- Alapakkam Sampath of UCLA; investigating the signal transfer from the photoreceptor sensory neurons to bipolar cells during retinal degeneration and during recovery from degeneration.
- Greg Field of Duke University; investigating how changes in retinal ganglion cell receptive fields during retinal degeneration and during recovery from degeneration.
- Amy Lee of USC, Department of Biochemistry and Molecular Biology; investigating the role of endoplasmic reticulum stress in certain genetic mutations leading to blindness.
- Ralf Langen of ZNI; investigating amyloid structures in eyes affected with macular degeneration and exploring therapeutic agents to dissolve these structures.
- M. Carter Cornwall of Boston University; collaborating on the molecular mechanisms that regulate recovery of light sensitivity following bright light exposure.
- King-Wai Yau of Johns Hopkins University School of Medicine; collaborating on the role of calcium-feedback to the olfactory sensory neurons in sensitivity adjustment during odorant adaptation.
- Vsevolod Gurevich of Vanderbilt University; studying function of visual arrestins in the physiology of the photoreceptor cell.
- Gordon Fain of UCLA; collaborating on mechanisms that regulate phototransduction in rod and cone photoreceptors.
- Vladimir Kefalov of Washington University; investigating proteins that regulate calcium concentration in rod and cone photoreceptors.

Robert H. Chow

- James Knowles of ZNI; We are collaborating to correlate physiology and transcriptomics of single adult and fetal brain neurons.
- Sivaraj Sivaramakrishnan of University of Minnesota. We have developed a novel genetically encoded ratiometric calcium indicator.
- Oleg Evgrafov of USC. We have developed a novel 3D culture of differentiated nasal neuroepithelial biopsy cells, in order to test hypothesis that such cells will form synapses, and, if derived from schizophrenic patients, the synapses will be abnormal.
- Cheng-Ming Chuong of USC. We have tested the role of electrical and calcium signaling in development of chick feather bud morphology.
- Ralf Langen of ZNI; investigating the potentiating effect of free fatty acids and monophthalates (plasticisers) in potentiating amyloid peptide cytotoxicity, in the setting of obesity in type 2 diabetes and Alzheimer's.

Robert Chow (cont.)

- Jeannie Chen of ZNI; We are applying our new genetically encoded ratiometric calcium indicator to study cytoplasmic calcium of photoreceptors in vivo and in vitro in mouse models of photoreceptor degeneration.
- Mark Humayun and James Weiland of USC, Department of Ophthalmology. We are collaborating on two projects: 1) improving performance of the Argus II retinal prosthesis, and 2) development of a novel photovoltaic nanoswitch for remote optical control of neuron activity.
- Koping Kirk Shung of USC, Viterbi School of Engineering; collaborating on a project to distinguish highly invasive breast cancer cells from less invasive cancer cells, using high-frequency ultrasound stimulation of cytoplasmic calcium elevation.
- I-Chueh Huang of USC: studying the cellular tropism of Zika virus in fetal brain tissue, and mechanisms to prevent Zika virus replication
- Michael Bonaguidi, Jonathan Russin, Charles Liu, William Mack and others (all at USC). We have created an interdisciplinary team to study the mechanism of epilepsy.

Marcelo Coba

- Guoping Feng, Stanley Center for Psychiatric Research, Broad Institute, Boston; studying of SHANK3 mutations in psychiatric disorders, and their role in postsynaptic signaling.
- Justin Ichida, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC; collaborating on hiPSC cells for the study of neurodevelopmental processes in psychiatric disease.
- James Knowles of ZNI; studying the role of synaptic signaling complexes in Obsessive compulsive disorder and Schizophrenia.
- Ted Abel of University of Pennsylvania; studying the role of Shank3, Fmr1 and AKAP signaling mechanisms associated to neurological disease.
- Marco Bortolato of Kansas University; collaborating on the role of NMDAR signaling in the pathophysiological processes underlying impulsive aggression and related neurodevelopmental disorders (autism-spectrum disorder, ADHD, Tourette syndrome).
- Thomas O'Dell of UCLA; collaborating on the role of TNiK and Dlgap1 signaling in synaptic plasticity, learning and memory.
- Chao Zhang of USC; investigating the chemical genomics approaches to the study of protein kinase signaling.
- Fengzhu Sun, Department of Computational Biology and Bioinformatics at USC; analyzing of protein domains and their role in synaptic signaling complexes associated to Schizophrenia.
- Pat Levitt of USC-CHLA; working to determine of the Autism Risk factor MET interactome and its role in the developing synapse
- Sivaraj Sivaramakrishnan, Department of Genetics, Cell Biology & Development
- College of Biological Sciences, University of Minnesota. Using fluorescent nano-probes for the functional regulation of protein kinase activity
- Fowzan S Alkuraya, MD, Head, Developmental Genetics Unit, King Faisal Specialist Hospital and Research Center. Saudi Arabia. Studying the role of mutations in the protein kinase TNIK, found in patients with intellectual disability and their function in neuronal development.

David V. Conti

- Sylvia Richardson and Paul Newcombe of MRC Biostatistics Unit, Cambridge, UK; developing of Bayesian model selection for functional integration in genetic association studies.
- Chris Haiman of USC, Department of Preventative Medicine; investigating the role of genetic variants in prostate cancer.

David V. Conti (cont.)

- Marc Tischkowitz of University of Cambridge, Dept. of Medical Genetics, Jonine Bernstein of Dept. of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center; collaborating on WECARE Study (Women's Environmental, Cancer, and Radiation Epidemiology) which examines genetic susceptibility and radiation exposure in breast cancer.
- Frank Gilliland and Jim Gauderman of USC, Department of Preventative Medicine; examining the role of genetic variation and pollution in asthma and lung function development in over 10,000 children followed for over 10 years in Los Angeles.
- James Knowles and Carlos Pato of ZNI; examining genetic sequence data to identify variants involved in schizophrenia.
- Wendy Cozen of USC, Department of Preventative Medicine; through genetic association studies, they are investigating the role genes play in multiple myeloma and Hodgkin's lymphoma.
- Duncan Thomas of USC, Department of Preventative Medicine; developing new statistical approaches to the analysis of genes and environmental factors that interact via biological pathways.
- Kiros Berhane of USC, Department of Preventative Medicine; developing new statistical methods that incorporate both age and sex related changes in the dynamic relationship between weight, height and obesity as well as the complex multi-level relationships of determinants of obesity.
- Lilyana Amescua of USC, Department of Neurology; investigating the impact of genetics in Multiple Sclerosis using a Hispanic population sampled in Los Angeles and novel statistical methods.
- Danieli Salinas of USC, Department of Pediatrics; estimating clinical outcomes and classifying CFTR variants of unknown significance in children with a positive newborn screening for Cystic Fibrosis.
- Duncan Thomas, Jim Gauderman, Juan Pablo Lewinger, Paul Marjoram, Kim Sigmund, Paul Thomas, Josh Millstein, Haiyu Mi of USC, Department of Preventive Medicine; Program Project to develop statistical methods for intergrative genomics in cancer.
- Jim Gauderman of USC and Riki Peters of the Fred Hutch Cancer Center: Using functional Genomics to Inform Gene Environment Interactions for Colorectal Cancer.

Hong-Wei Dong

- Jean Shih, Department of Pharmacology, USC. We collaborate on characterizing disruption of cortico-striatal pathways in the mouse models of Autism.
- X William Yang, Department of Neuropsychiatry, UCLA. We collaborate on characterizing connectopathies in the mouse models of Huntington's disease.
- Peyman Golshani, Department of Neurology, UCLA. Collaborative project: Optogenetic treatment of social behavior in autism.

Rick A. Friedman

- Jake Lusis of UCLA; analyzing of transcriptome data and GWAS for hearing traits.
- Eleazar Eskin of UCLA; using of the Efficient Mixed Model Analysis of our GWAS data.
- Hooman Allayee of USC; analyzing GWAS for hearing and balance traits.
- Takahiro Ohyama of ZNI; developing of constructs for transgenics, knockouts, and organ culture for Fhod3 experiments.
- Justin Ichida and Neil Segil of Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research BCC at USC; looking at genetic phenotypes in culture

Radha Kalluri

- Ruth Anne Eatock of University of Chicago; working on a computational model for defining information transfer in the vestibular sensory periphery (ongoing).
- Neil Segil, Takahiro Ohyama, Justin Ichida of Departments of Otolaryngology and Broad at USC; studying the molecular basis of neuronal differentiation in directly differentiated neurons (ongoing).
- Carolina Abdala of Department of Otolaryngology at USC; using otoacoustic emissions to non-invasively probe the status of mechanical transduction in hearing impaired humans (ongoing).
- Christopher Shera of Department of Otolaryngology at USC; collaborating on understanding the mechanical basis of low-frequency hearing (ongoing).
- Jason Zevin of Department of Psychology at USC; collaborating on understanding individual variability in speech perception ability (ongoing).
- Raymond Goldsworthy Department of Otolaryngology of USC; linking behavioral and physiological measures of frequency resolution in humans (ongoing).

James A. Knowles

- Oleg Evgrafov, Robert Chow, Derek Sieburth, Kai Wang, Li Zhang, Marcelo Coba, David Conti, Dan Campbell, Chris Haiman, William Mack of ZNI. ONGOING. Various projects with ZNI investigators on studies of genetic expression and genetic variation in health and disease (e.g., autism, schizophrenia)
- Ewa Deelman, Jonathan Buckley, Graham Casey, Colin Dias, Mike Kahn, Carl Kesselman, Jerold Shinbane, Justin Ichida, Arthur Toga, Paul Thompson, Yonggang Shi, Gerry Coetzee, Peggy Farnham and Brad Peterson of USC; collaborating on various projects including the identification of susceptibility genes for complex diseases. ONGOING
- Dan Stein of University of Capetown, Gerry Nestadt and Jack Samuels of Johns Hopkins University, Abby Fyer of Columbia University, Ben Greenberg and Steve Rasmussen of Brown University, James McCracken and John Piacentini of UCLA, David Pauls, Scott Rauch and Dan Geller of Harvard University, Dennis Murphy and Yin Shugart of NIH, Carol Matthews of UCSF, and Stephanie Dulawa of University of Chicago, Russel Jacobs of CalTech; studying Obsessive compulsive disorder (OCD). ONGOING
- Mohammad Ayub of Queens University, Kingston, ONT; Jim Fallon, Fabio Macciardi and Biff Bunney of UC Irvine; Barbara Lipska of the NIMH Intermural Program; working on Early-onset major depression. ONGOING
- Steven McCarroll of Harvard University/Broad Institute, Mike Boehnke and Goncalo Abecasis of the University of Michigan; Ayman Fanous of the Veterans Administration, Washington DC; Mohammad Ayub of Queens University, Kingston, ONT; studying Schizophrenia. ONGOING
- Ned Kalin, Pat Rosebloom, Jonathan Oler, and Drew Fox of the University of Wisconsin, Madison; genetic studies of anxiety in primates. ONGOING.

Ralf Langen

- Harvey McMahon of Laboratory of Molecular Biology in Cambridge; investigating mechanisms of membrane curvature induction by proteins.
- Alasdair Steven of the NIH; using a cryo electron microscopy to look at mechanisms of membrane curvature and protein misfolding in neurodegenerative diseases.
- Tobias Ulmer of ZNI; combining NMR and EPR-based approaches to determine structures of amyloidogenic proteins involved in neurodegeneration.
- Ansgar Siemer of ZNI; combining solid state and NMR and EPR-based approaches to determine structures of amyloidogenic proteins involved in neurodegeneration.

Ralf Langen (cont.)

- Martin Kast of USC, Department of Molecular Microbiology & Immunology; investigating membrane-bound annexin A2 complexes as receptors for HPV entry.
- Oliver Daumke of University of Berlin; investigating control of membrane curvature by EHD-2.
- Ian Hawaorth of USC, Department of Pharmacy; combining EPR and computational methods for determining protein structures.
- Robert Chow of ZNI; investigating membrane-mediated toxicity of amyloidogenic proteins in Alzheimer's disease and type-2 diabetes.
- Songi Han of UC Santa Barbara; using novel EPR and NMR-based methods to monitor water exposure and its application to protein misfolding and membrane interaction.
- Julio Camarero of USC, Department of Pharmacy; engineering cyclotides in order to make them misfolding inhibitors that could be used as drugs against Alzheimer's disease, Parkinson's disease and type-2 diabetes
- Pinchas Cohen of USC, School of Gerontology; investigating the misfolding inhibition of mitochondrially derived peptide.
- Ali Koshnan, Caltech; huntingtin antibody interactions.
- Rohit Pappu, Washington University; interaction of huntingtin with profilin, a potential misfolding inhibitor.

William Mack

- Caleb Finch of USC Gerentology and Constantinos Sioutas of USC Environmental Engineering; collaborating on studies of the effects of particulate matter exposure from vehicular exhaust on the progression of stroke and cerebral hypoperfusion
- Kai Wang of ZNI; collaborating on studies characterizing genetic and epigenetic signatures of Meningiomas.
- James Knowles of ZNI; working on a large study designed to evaluate cellular heterogeneity of temporal and cerebellar cells using patchclamp and RNA-Seq of single cells.
- Robert Chow of ZNI; collaborating on a large study designed to evaluate cellular hetereogeneity of temporal and cerebellar cells using patchclamp and RNA-Seq of single

Takahiro Ohyama

- Neil Segil and Justin Ichida of Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC; researching factors that directly transform somatic cells into auditory sensory cells.
- Pinchas Cohen of USC Davis School of Gerontology; testing protective effects of mitochondria-derived peptides on drug-induced hair cell damage.
- Rick Friedman of ZNI; testing molecular functions of genes identified through genetic screening of mouse hearing disease model.

Janos Peti-Peterdi

- Michael Caplan of Yale University and Jennifer Pluznick of Johns Hopkins; collaborating on the role of olfactory receptors in the kidney.
- Andrew McMahon of USC; analysis of the macula densa cell molecular fingerprint.
- Genevieve Nguyen of College de France, Paris; studying the role of the prorenin receptor in macula densa cells.
- Dominique Eladari and Regine Cambrey of INSERM, France; working novel electrolyte transport mechanisms in the distal nephron.
- Paola Romagnani of University of Florence; studying Intrarenal stem cells.

Janos Peti-Peterdi (cont.)

- Andrew Salmon of University of Bristol; studying the role of the glomerular glycocalyx.
- Thomas Benzing of University of Cologne; researching calcium imaging of podocytes in vivo.
- Akira Nishiyama of Kagawa University; studying glomerular filtration of renin and prorenin.
- Peter Deen of University of Nijmegen; investigating the role of GPR91 in distal nephron ion transport.
- Attila Szabo and Agnes Prokai of Semmelweis; studying multiphoton imaging of the effects of calcineurin inhibitors in the kidney
- Laura Perin of Children's Hospital Los Angeles; studying the role of amniotic fluid-derived stem cells in kidney repair.
- Valter Longo of USC; studying the mechanism of liver regeneration.
- Alicia McDonough of USC, Dept. of Neurobiology; studying the role of the intra-renal renin-angiotenisn system
- Rudy Ortiz of UC Merced; studying the role of mitochondrial factors in cell and tissue metabolism.
- Stuart Shankland of University of Washington, Seattle; studying the mechanisms of glomerular dysfunction and repair.
- Katalin Susztak of University of Pennsylvania; studying podocyte function in health and disease.
- Giuseppe Remuzzi of University of Bergamo; collaborating on a clinical study of a new therapeutic approach to kidney regeneration.
- Jochen Reiser (Rush University) and Sanja Sever (Harvard University); studying the effects of suPAR on the glomerular filter
- Inderbir Gill (USC KSOM Urology); human translational studies on the macula densa renal tissue repair mechanism
- Chaim Jacob (USC KSOM); studying the role of glomerular immune cells in lupus nephritis

Derek Sieburth

- James Knowles of ZNI; sequencing entire genomes of the nematode C. elegans to identify mutations that cause defects in synaptic transmission and profiling changes in gene expression patters in the nematode C. elegans in response to oxidative stress.
- Robert Chow of ZNI; examining how calcium regulates the release of neurotransmitters in real time from living tissue (using Total Internal Reflection Fluorescence Microscopy).

Ansgar Siemer

- Ralf Langen of ZNI; studying the structure and dynamic of toxic huntingtin fibril
- Kausik Si of Stowers Institute for Medical Research; studying the structure of the functional amyloid Orb2 responsible for long-term memory
- Ralf Langen of ZNI; studying the structure and dynamic of toxic huntingtin fibril
- Kausik Si of Stowers Institute for Medical Research; studying the structure of the functional amyloid Orb2 responsible for long-term memory

Huizhong (Whit) Tao

- Jonah Chan of University of California at San Francisco; studying how retinal activity through vision changes the maturation status of myelin wrapping on optic nerve fibers.
- Josh Z. Huang of Cold Spring Harbor; researching on the functional properties of cortical inhibitory neurons.
- Li Zhang of Zilkha Neurogenetic Institute; studying common inhibitory mechanisms underlying visual and auditory cortical processing.
- Xiaohui Zhang of State Key Laboratory of Cognitive Neuroscience & Learning and IDG/McGovern Institute for Brain Research, Beijing Normal University, China; studying mechanisms underlying critical period dependent cortical plasticity.

Terrence Town

- John Breitner, MD, MPH and Judes Poirier, PhD (McGill University, Canada) We are working as a group to determine safety and efficacy of non-steroidal anti-inflammatory drugs for the prevention of Alzheimer's disease.
- Tarek Fahmy, PhD (Yale University Department of Biomaterials) Collaboration to evaluate a next-generation nanoparticle drug delivery system for prevention and treatment of Alzheimer's disease and pediatric brain cancer.
- Li-Huei Tsai, PhD (Harvard University HHMI Investigator) Collaboration to investigate aberrant cyclin-dependent kinase activation in our novel transgenic Alzheimer rat model.
- Erol Fikrig, MD (Yale University HHMI Investigator) Collaboration to interrogate neuro-immune mechanisms of West Nile encephalitis
- Richard A. Flavell, PhD (Yale University HHMI Investigator and National Academy member), Collaboration on developing mouse models with human immune systems as a critical tool to examine stem cell graft tolerance vs. rejection.
- Pasko Rakic, MD (Yale University National Academy member and winner of the 'new Nobel' Kavli Prize in Neuroscience), whose wide-reaching expertise in neurobiology has been invaluable for understanding cellular biological aspects of our rodent models of neurodegenerative disease.
- Eliezer Masliah, MD (UCSD; ranked as one of the top 10 AD researchers) Collaboration on developing and characterizing rodent models of Alzheimer's disease.
- Caleb 'Tuck' Finch, PhD (University of Southern California) has made major contributions to our understanding of aging biology and we are working together to understand the role of pollution on brain inflammation and Alzheimer's disease pathology in pre-clinical animal models.
- Helena Choi, MD (University of Southern California) is an internationally recognized neuropathologist who plays a key role in the USC ADRC, and we are validating observations that my group has made in mouse models using human Alzheimer patient samples.
- Betza Zlokovic, PhD (Director, ZNI, University of Southern California) has made fundamental contributions to our understanding of pericyte biology in the central nervous system and in Alzheimer's disease. We are actively collaborating to extend his findings with the blood-brain-barrier into our novel Alzheimer transgenic rat model.

Tobias S. Ulmer

- Mark Ginsberg of UC San Diego; collaborating on the integrin receptor cell biology
- Woojin An of USC; collaborating on histone protein structure and interactions
- Ralf Langen of ZNI; collaborating on the role of huntingtin in Huntington's disease

Kai Wang

- James Knowles of ZNI; evaluating biological and technical noises of single-neuron RNA-Seq data and benchmarking different bioinformatics algorithms on these data.
- Peter Robinson of Charité - Universitätsmedizin Berlin; developing variant annotation and prioritization software tools that incorporate phenotype information and model organism information.
- Jiang Zhong of USC Dental School; evaluating variant calling from RNA-Seq data

Li Zhang

- Hongwei Dong and Jean Shih; studying corticostriatal projection and movement control
- Huizhong Whit Tao of ZNI; investigating imaging processing in the visual cortex.
- Berislav V. Zlokovic of ZNI; investigating the impact of brain vascular defects on the functional cortical circuitry
- Qilong Ying; Broad Institute, generating transgenic rats
- Pin Wang, BCE, engineering new AAV virus for circuit tracing

Berislav V. Zlokovic

- Arthur Toga of USC, Institute of Neuroimaging and Informatics; imaging living human brain cerebrovascular system and BBB
- Paul Thompson, USC, Depts. of Neurology, Psychiatry & Behavioral Sciences and Engineering; imaging in animal models of human diseases with vascular deficits
- Helena Chui of USC, Dept. of Neurology: collaboration within USC Alzheimer's Research Disease Center;
- Lon C. Schneider of USC; collaboration within Alzheimer's Research Disease Center;
- Terrence Town of ZNI; collaboration on BBB functions in the rat model of AD
- Hong-Wei Dong of ZNI; collaboration on effects of pericytes on mouse brain circuits
- Roberta Brinton of USC, Depts. of Pharmacology & Pharmaceutical Science, Biomedical Engineering, and Neurology;
- Russell Jacobs of ZNI; collaboration on BBB and blood flow studies in models of neurological disorders;
- David M. Holtzman of Washington University in St. Louis; working on amyloid-beta metabolism and clearance in brain via LDLR receptors and role of apoE in amyloid-beta clearance.
- John Griffin of Scripps Institute; working on new APC variants for stroke.
- William Mack of ZNI; collaborating on hypoperfusion injury to white matter.
- Meng Law of USC, Dept. of Neuroradiology and Helena Chui of USC, Dept. of Neurology; working on MRI imaging of blood-brain barrier permeability in neurologically normal and MS patients and patients at risk for Alzheimer's disease.
- Collins Liu of USC, Dept. of Neurology and Helena Chui of USC, Dept. of Neurology; studying cerebrospinal fluid and plasma biomarkers of the blood-brain barrier damage in individuals at risk for Alzheimer's disease.
- Scott Fraser of USC, Depts. of Biological Sciences and Biomedical Engineering and Andy McMahon of USC, Broad CIRM Center; working on serial two-photon tomography, cutting-edge technique that allows for fully automated brain imaging.

Berislav V. Zlokovic (cont.)

- Justin Ichida of USC, Broad CIRM Center; working on iPSC and fibroblasts from Alzheimer's patients conversion into neurons and in vitro trials with 3K3A-APC in human ALS models as well as nee PICALM mutations in AD.
- Washington University Alzheimer's Disease Research Center; collaborating on CSF biomarkers of blood-brain barrier damage in individuals at risk for Alzheimer's as well as individuals with mild cognitive impairment and Alzheimer's with apoE4 allele vs. non-apoE4, as well as on postmortem brain tissue analysis and effects of apoE4 on blood-brain barrier integrity.
- Nunzio Pomara of New York Medical Center; examining CSF biomarkers of blood-brain barrier injury in cognitively normal individuals at risk for Alzheimer's.
- Antonio Damasio of USC, Brain Creativity Institute; studying the molecular basis of feelings.
- Pat Lyden of Cedars Sinai; working on Phase 2 clinical trial for stroke with 3K2A-APC.
- Caleb Finch of USC; examining the blood-brain barrier permeability in 5FAD mice on different apoE genotype.
- Jae Jung of USC; working on brain-specific TRIpartite Motif protein 9 and Ziuka virus and BBB
- Michael Harrington of Huntington Hospital and USC; collaborating on imaging blood-brain barrier integrity in apoE4 individuals and CSF biomarkers.
- Daniel Nation of USC; working on CSF and imaging biomarkers in individuals at high risk for hypertension.
- John Morris of Washington University in St. Louis; collaborating on imaging and CSF biomarkers and apoE genotype
- Anne Fagan of Washington University in St. Louis; collaborating on CSF biomarkers and apoE genotype.
- Tammie Benzinger of Washington University in St. Louis; working on imaging vascular biomarkers in mild cognitive impairment.
- John McArdle of USC; working on longitudinal data and dynamic analysis methods, statistical analysis.
- Judy Pa of USC; working on structural and functional connectivity, neuroimaging, AD and MCI.
- John Ringman of USC; collaborating on AD, PSEN1, ADAD, imaging and biomarkers.
- Eric Reiman of Banner Alzheimer's Institute, AZ; collaborating on neuroimaging, genomics, biomarkes, APOE, PSEN1.
- Richard Caselli of Mayo Clinic, AZ; collaborating on neuroimaging, genomics and biomarkers.

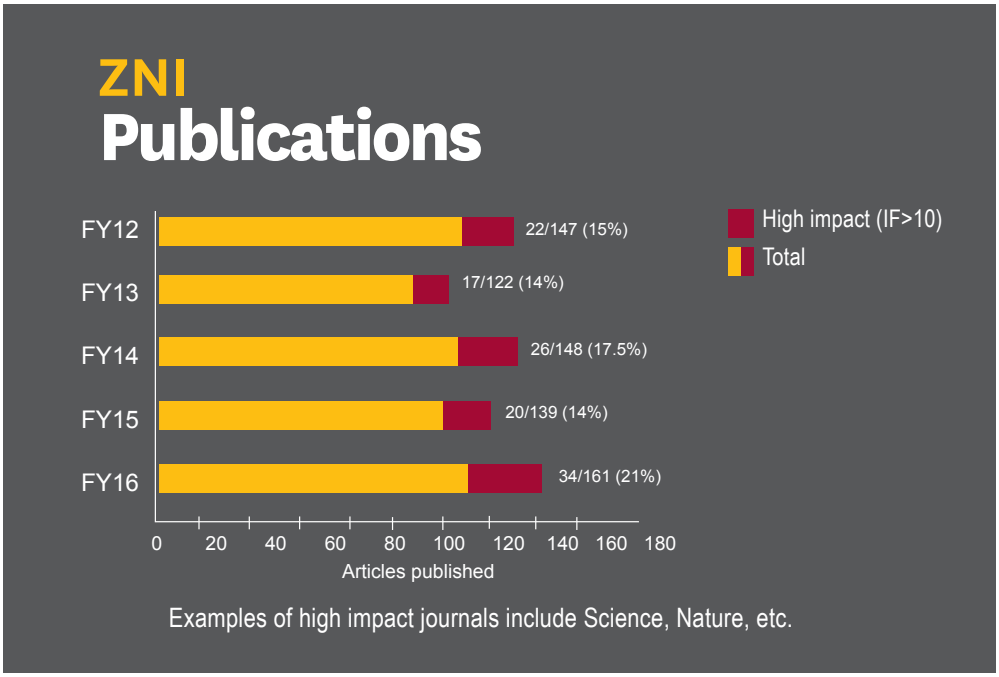
fy16 faculty publications

The primary method for communicating scientific advancements is to document one's research by writing a paper outlining the methods and resources applied to an experimental problem, reporting the findings and submitting this work to a journal whose audience is comprised of other researchers working in the same or similar field.

A typical scholarly, scientific journal article is peer-reviewed by a group of researchers who examine thoroughly the approach and techniques deployed, validate the data and ensure the conclusions are empirically sound. Most papers contain citations of previous work, upon which the current paper is based, building upon sometimes generations of scientists who have led the field to our current state of knowledge.

A journal's impact factor is a measure of the frequency with which the average article in a journal has been cited in a particular year. The impact factor is calculated by dividing the number of citations in the current year to articles published in the two previous years by the total number of articles published in the two previous years. While the expectation is that all peer-reviewed publications move science forward, in some areas of study coverage is not as widespread and thus the impact factor of a journal in a highly specialized field will not necessarily have the same impact factor as the broader journals like Science and Nature. The number of papers an institution publishes in high-impact journals is one of several measures of productivity.

In 2015, ZNI faculty published 139 papers, and 14% of these were in high impact journals. During the reporting period of 2016, ZNI researchers published 161 papers, with 21% in high impact journals. ZNI scientists continue to raise the bar with these publications.



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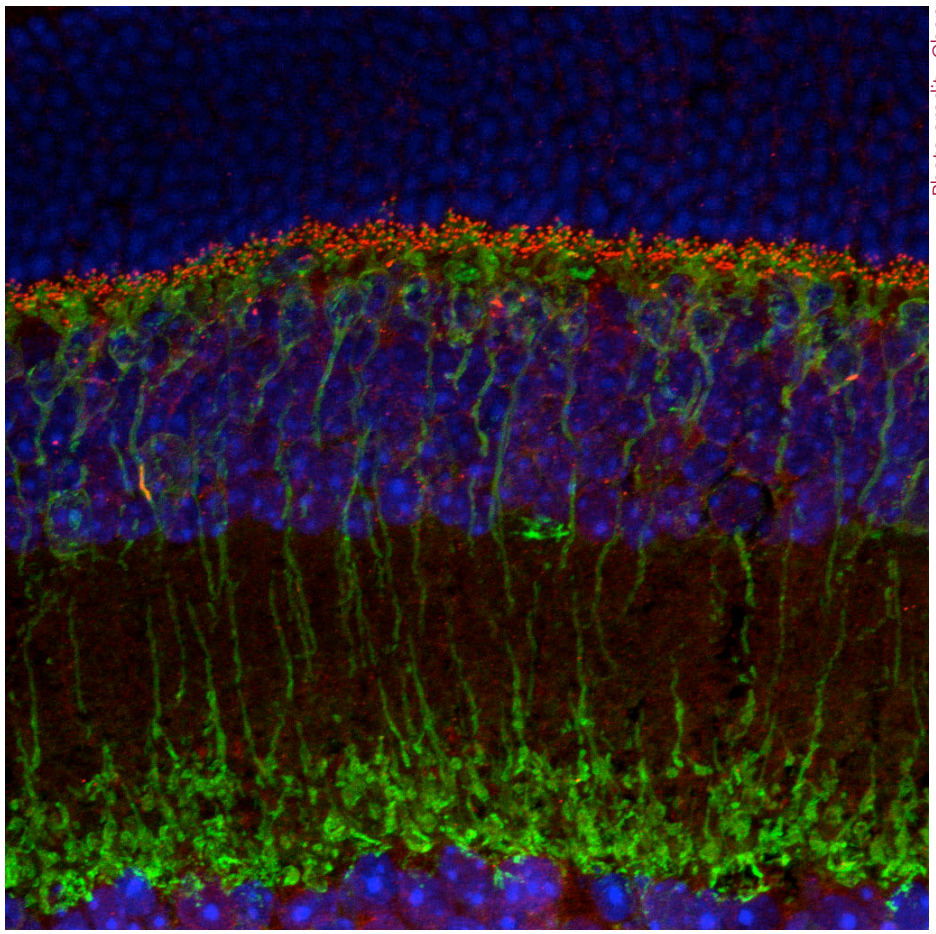

Photo credit: Chen

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postdoctoral trainees

A postdoctoral researcher is a person professionally conducting research after the completion of their doctoral studies, typically after obtaining a PhD. The ultimate goal of a postdoctoral researcher, or fellow, is to pursue additional research, training, or teaching in order to have better skills to pursue a career in academia, research or industry. Generally, postdocs work independently but under the supervision of an established principal investigator with a complementary funded research program. Listed below are ZNI's postdoctoral trainees, (their mentors), and the titles of their research projects.

Jennifer King (Alexandre Bonnin) "Investigation of the role of a new adaptor protein in fetal brain development"

Yen Chang (Alexandre Bonnin) "Maternal stress and antidepressants effects on fetal brain development"

Ligia Gallindo (Alexandre Bonnin) "Effects of Maternal Depression and Antidepressant Treatments on Fetal Neurodevelopment"

Patrick Hecht (Daniel Campbell) "Identification and Functional Characterization of Non-Coding RNAs in Autism Spectrum Disorder"

Inmaculada Ballesteros Yanez (Daniel Campbell) "Non-Coding RNAs in the Transcriptional Landscape of Human Neural Progenitor Cell Differentiation"

Junhua Geng (Karen Chang) "Mechanisms regulating bulk vesicle retrieval."

Tian Wang (Jeannie Chen) "Phototransreduction in Dark Adaptation and Retinal Degeneration"

Rahul Kumar (Jeannie Chen)

Ming Yi (Sonia) Lim (Robert Chow) "Single-Cell Analysis" and "Photovoltaic Nanoswitches for Remote Optical Control of Neurons"

Reymundo Dominguez (Robert Chow) "Single-Cell Analysis"

Houri Hintiryan (Hong-Wei Dong) "Identify Neuroendocrine genes that are vulnerable to chronic psychological stress" and "The Mouse Connectome Project."

Photo credit: Tao

R to L: Leena Ibrahim Marosh, Dr. Huizhong (Whit) Tao, Lingyun Li, and Young Joo Kim.

Nicholas Foster (Hong-Wei Dong) "Mouse brain connectome mapping of cortical and striatal long-distance axon projection deficits in Huntington's Disease mouse models"

Michael Bienkowski (Hong-Wei Dong) "The Mouse Connectome Project"

Pezhman Salehi Dermanaki (Hong-Wei Dong) "Novel genes involved in age-related and noise-induced hearing loss in mice"

Nitin Pandey (Ralf Langen) "Huntingtin folding and misfolding"

Jose Bravo Arrendondo (Ralf Langen) "Protein dynamics in amyloid diseases"

Dorinne Desposito (Janos Peti-Peterdi) "Novel regulatory mechanisms of the glomerular endothelium"

Anne Riquier-Brison (Janos Peti-Peterdi) "The role of macula densa cells in chronic kidney disease"

Ju-Young Moon (Janos Peti-Peterdi) "Novel tissue remodeling mechanism in the diabetic kidney"

Kengo Kidokoro (Janos Peti-Peterdi) "Tracking podocyte fate in nephrotic syndrome"

Hiroyuki Kadoya (Janos Peti-Peterdi) "The role of glomerular glycocalyx and T cells in lupus nephritis"

Ina Schiessl (Janos Peti-Peterdi) "Intravital imaging of cell death dynamics in the kidney"

Toshiki Doi (Janos Peti-Peterdi) “Macula densa-mediated tissue remodeling in renovascular hypertension”

Urvi Shroff (Janos Peti-Peterdi) “Development of a macula densa cell line”

Sunjin Kim (Derek Sieburth) “Regulation of synaptic function by stress signaling”

Mingxi Hu (Derek Sieburth) “Control of rhythmic behaviors by neuropeptide signaling”

Marie-Victoire Guillot-Sestier (Terrence Town) “T-cell TGF-beta signaling control of the immune response to cerebral Abeta” and “Amyloid-beta clearance by central vs. peripheral IL10R deficient mononuclear phagocytes”

Tara M. Weitz (Terrence Town) “Pharmacological Blockade of TGF-beta Signaling in Peripheral Macrophages in the TgF344-AD Rat Model of Alzheimer’s Disease”

Kevin Doty (Terrence Town) “Modulating Microglial Activation in Alzheimer’s Disease by Deleting Innate Immune STAT3 Signaling”

Leandro Lima (Kai Wang) "Development of copy number variation calling tools"

Qian Liu (Kai Wang) "Long-read sequencing for diagnosing trinucleotide repeat expansion syndrome"

Atlas Khan (Kai Wang) "neural network for analysis of genetic variants"

Feixue Liang (Li Zhang)

Gil Carvalho (Berislav Zlokovic) “Cellular Basis of Feelings and Sentience”

Kassandra Kisler Elliott (Berislav Zlokovic) “Pericyte Regulation of Neurovascular Coupling and Local Brain Oxygen Supply”

Axel Montagne (Berislav Zlokovic) “Quantitative Dynamic Contrast-Enhanced Magnetic Resonance Imaging to Evaluate Blood-Brain Barrier Integrity in Alzheimer’s Disease and Related Disorders”

Amy Nelson (Berislav Zlokovic) “The Role of Pericytes in Hippocampal Function”

graduate students

For an institute our size, ZNI has a relatively large graduate student population of 52 individuals who are pursuing advanced degrees from a variety of USC programs and departments: Neuroscience, Preventive Medicine, Biostatistics and Physiology & Biophysics, and PIBBS (Programs in Biomedical and Biological Sciences), which includes degrees in Cancer Biology & Genomics; Development, Stem Cells & Regenerative Medicine; Medical Biology; and Molecular Structure & Signaling). Each graduate student works with a ZNI faculty mentor for up to 5 years before defending their thesis and being awarded a Ms or PhD, depending upon the program. Below is the list of students working at ZNI, (their mentors), and their projects.

Nick Goeden (Alexandre Bonnin) "Placental Tryptophan Metabolic Dysfunction: A Potential Pathway for the Developmental Programming of Mental Disorders"

Juan Velasquez (Alexandre Bonnin) "Effects of Maternal Depression and Antidepressant Treatments on Fetal Neurodevelopment"

Jessica DeWitt (Daniel Campbell) "Neurobiological Impact of Non-Coding RNAs with Genome-wide Significant Association with Autism"

Joo Yeun Lee (Karen Chang) "A Novel DnaJ Domain Protein Regulates Synaptic Development and Maintains Stem Cell Niche in Drosophilia"

Liping Wang (Karen Chang) " Regulation of synaptic vesicle endocytosis by the minibrain kinase"

Jung-Hwa Cho (Robert Chow) "Calcium Sensitivity of Large-dense Core Vesicle Exocytosis in Complexin 2 Knock-out Mouse Chromaffin Cells"

Jason Lou (Robert Chow) "Improving Performance of Argus II Retinal Prosthesis"

Brent Wilkinson (Marcelo Coba) “Synaptic Signaling Networks”
Zhao Yang (David Conti) “Integrated analysis of germline, omic and disease data”

Lilit Chemenyan (David Conti) “Bayesian model selection for functional integration in genetic association studies”

Kan Wang (David Conti) “Multiethnic fine-mapping in genetic association studies”

Muye Zhong (Hong-Wei Dong) “The Mouse Connectome Project”

Monica Song (Hong-Wei Dong) “The Mouse Connectome Project”

Nora Benavidez (Hong-Wei Dong) “The Mouse Connectome Project”

Christopher Ventura (Radha Kalluri) “The role of hyperpolarization-activated inward currents in shaping neuronal function in the vestibular nerve”

Alex Markowitz (Radha Kalluri) “The biophysical development of spiral ganglion neurons”

JaeMun (Hugo) Kim (James A. Knowles) “Single Cell RNA Sequencing”

Edder Lopez (James A. Knowles) “Differentiation of Neural Progenitors to cortical neurons in 2D and 3D Cultures”

Chris Armoskus (James A. Knowles and Kai Wang) “Statistical Analysis of Genetic Variation Predisposing to Schizophrenia” / “Comprehensive detection of expression QTLs in CNON cells”

Emily Chen (James Knowles) “Investigating Major Depressive Disorder by Next-Generation Sequencing and Differential Gene Expression in Brains of Suicide Completers”

Photo credit: Dong

Hong-Wei Dong lab

Alan Okada (Ralf Langen) “Understanding and Preventing Misfolding in Neurodegeneration and Diabetes”

Natalie Kegulian (Ralf Langen) “Identifying toxic conformations in huntingtin”

Meixin Tao (Ralf Langen) Protein Membrane interaction

Hank Chang (William Mack) Particulate matter exposure/ Cerebral Hypoperfusion

Reymundo Dominguez (William Mack) Estradiaol/ Cerebral Hypoperfusion

Jackey Qi (Derek Sieburth) “ Regulation of oxidative stress response by neuroendocrine signaling”

Ukjin Choi (Derek Sieburth) “An Innexin family member negatively regulates neuronal excitability”

Silvia Cervantes Cortes (Ralf Langen and Ansgar Siemer) “Structural investigation of huntingtin fibrils with solid-state NMR and EPR”

Alexander (Sandy) Falk (Ansgar Siemer) “Interaction of Orb2 isoforms A and B”

Maria Conrad (Ansgar Siemer) “Oligomer formation and membrane interaction of Orb2A”

Brian Zingg (Huizhong Tao and Li Zhang) “Using viral tools and optogenetics to dissect functional neural circuits for defensive Behaviors”

Xiaolin Chou (Huizhong Tao) “Fear conditioning induced cortical synaptic plasticity”

Lingyun Li (Huizhong Tao) “How Inhibitory Circuits Mediate Lateral Refinement of Auditory Cortical Processing

Leena Ibrahim Marosh (Huizhong Tao) “Cross-Modality Sharpening of Visual Cortical Processing through a Top-Down Circuit”

Wen Zhong (Huizhong Tao)

Haifu Li (Huizhong Tao)

Kwok (Chris) Im (Terrence Town) “T cell TGF-beta Signaling as a Therapeutic Target for Pediatric Brain Tumors”

David Gate (Terrence Town)

Brian P. Leung (Terrence Town) “C1q Signals through TREM2 to Control Aβ Phagocytosis in Alzheimer’s Disease”

Alicia Quihuis (Terrence Town)

Diana Schall (Tobias S. Ulmer) “Structural basis of brain carnitine palmitoyltransferase 1 function”

Benjamin Frey (Tobias S. Ulmer) “Application of nanodiscs to membrane protein reconstitution”

ChengLiang Dong (Kai Wang) “iCAGES: genome-guided precision medicine for cancer treatment”

Yunfei Guo (Kai Wang) “SeqMule: An Automated Pipeline for Whole Genome/Exome Analysis on Mendelian Diseases”

Hui Yang (Kai Wang) “Phenotype-based detection of causal SNPs and CNVs from next-generation sequencing data”

Young Joo Kim (Li Zhang) “Molecular Mechanisms for the Development of Auditory Cochlear Innervation Pattern”

Lukas Mesik (Li Zhang) “Functional Characterization of Inhibitory Interneurons During Development”
Qi Fang (Li Zhang) “visual cortical processing in awake mice”

Zhenggang Zhang (Li Zhang)

Pan Kong (Berislav Zlokovic) “Glut1 and Picalm”

Anita Ramanathan (Berislav Zlokovic) “The Cell-specific Influence of PICALM in AD Pathogenesis”

Sanket Rege (Berislav Zlokovic) “Enhanced Transport of Amyloid-beta into the Brain with Overexpression of Human RAGE in the Endothelium”

Melanie Sweeney (Berislav Zlokovic) “APOE ε4 Allele Modulates Risk for CSF Biomarkers of Neurovascular Injury in Alzheimer’s Disease”

Divna Lazic (Berislav Zlokovic) “Understanding the role of Mfsd2a Transporter in the Blood-Brain Barrier Dysfunction in Alzheimer’s Disease”

Zach Hall Travel Award Winners

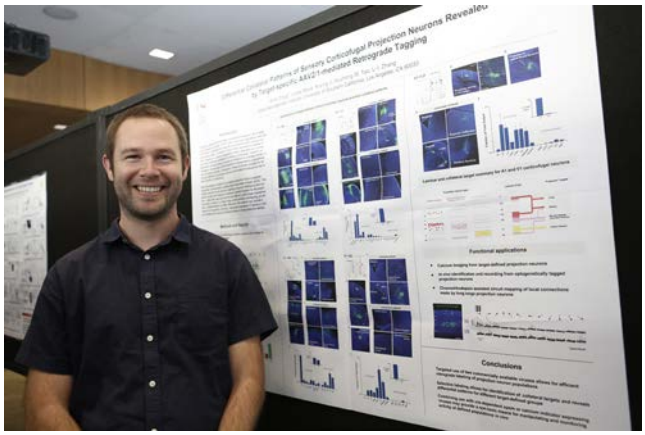
In the formative years of ZNI, Dr Zach Hall served as Senior Associate Dean for Academic Development at the Keck School of Medicine of USC and was a contributing founder of the Zilkha Neurogenetic Institute Named in his honor and funded in part with a donation by Dr Hall and his wife Julie Giacobassi, ZNI is pleased to offer each year, travel awards to qualified graduate students working with ZNI Investigators. The grants are meant to allow a student to attend a scientific meeting, collaborative trip or research training opportunity that they otherwise might not afford, thereby making a positive difference in their training. The competitive application process requires students to submit a mini-grant proposal, including a description of their research project, CV and letter of nomination from their mentor.

In 2015, an unprecedented number of students received funds to attend two distinct meetings, presenting posters to an international crowd of researchers in their respective fields. While ZNI usually limits awards to four per year, the submissions were particularly strong in FY16 and we expanded the number of grants from four to seven.

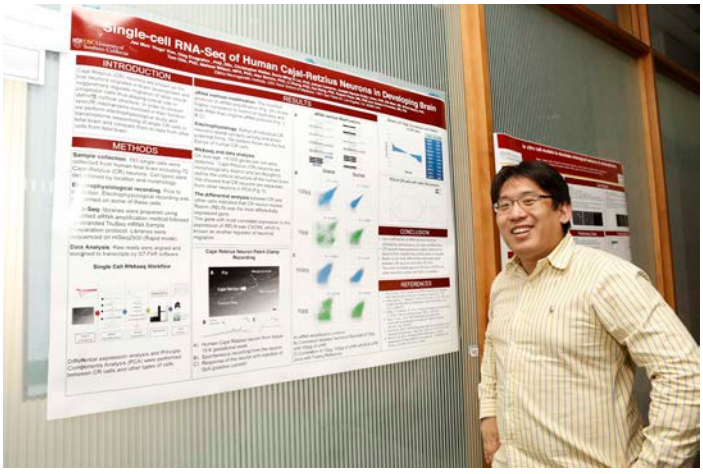
Five of the awardees used their award to present individual posters of their work at the Society of Neuroscience annual meeting in Chicago, IL: **Brent Wilkinson** (laboratory of Dr Marcelo Coba), **Leena Ibrahim** (laboratory of Dr Huizhong Tao), **Brian Zingg** (laboratory of Dr Li Zhang), **Kwok (Chris) Im** (laboratory of Dr Terrence Town), **Joo-yeun Lee** (laboratory of Dr Karen Chang)

Two awardees shared their work at the American Society of Human Genetics meeting held in Baltimore, MD: **Jae Mun (Hugo) Kim** (laboratory of Dr James Knowles) and **Chris Armoskus** (laboratory of Dr Kai Wang)

After returning from their travels, each graduate student also participates in the poster session held in association with the annual Zach Hall lecture, sharing their work with colleagues in and around USC. In addition, all recipients attend a celebratory lunch with Dr Zach Hall on the day of the event. ZNI is proud to contribute to the growth of all the awardees.



Top: 2015 Zach Hall Travel Award Winner Brian Zingg presents his poster from the Society for Neuroscience meeting.



Right: 2015 Zach Hall Travel Award Winner Jae Mun (Hugo) Kim shares his poster from the American Society of Human Genetics meeting.

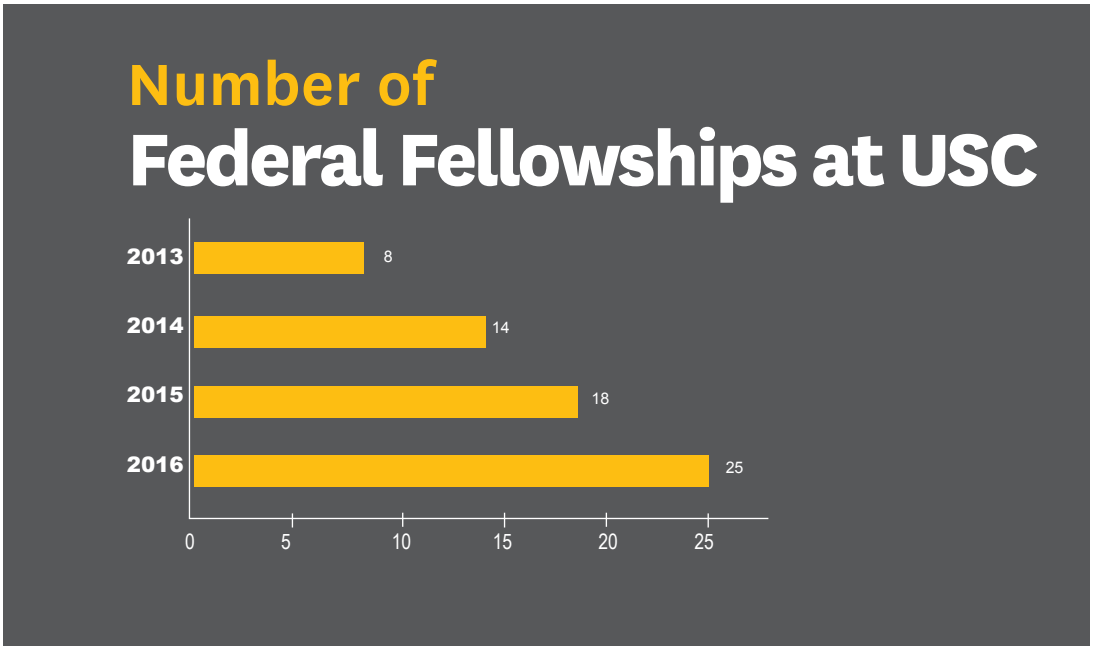
Photo credit: Steve Cohn

NRSA Grant Training

Partnering with the USC Graduate Program in Neuroscience, ZNI again in FY16 hosted workshops for graduate students who could benefit from applying for and receiving a fellowship under the National Institute of Health (NIH)'s Ruth L. Kirchstein National Research Service Awards (NRSA) program. The NRSAs are a family of grants provided by the NIH for training researchers in the behavioral sciences and health sciences. They are highly selective and a very prestigious source of funding for doctoral and postdoctoral trainees, as the grants are notably difficult to obtain. Only applications with very good impact scores are funded, based on budget cutoffs determined by each individual NIH institute.

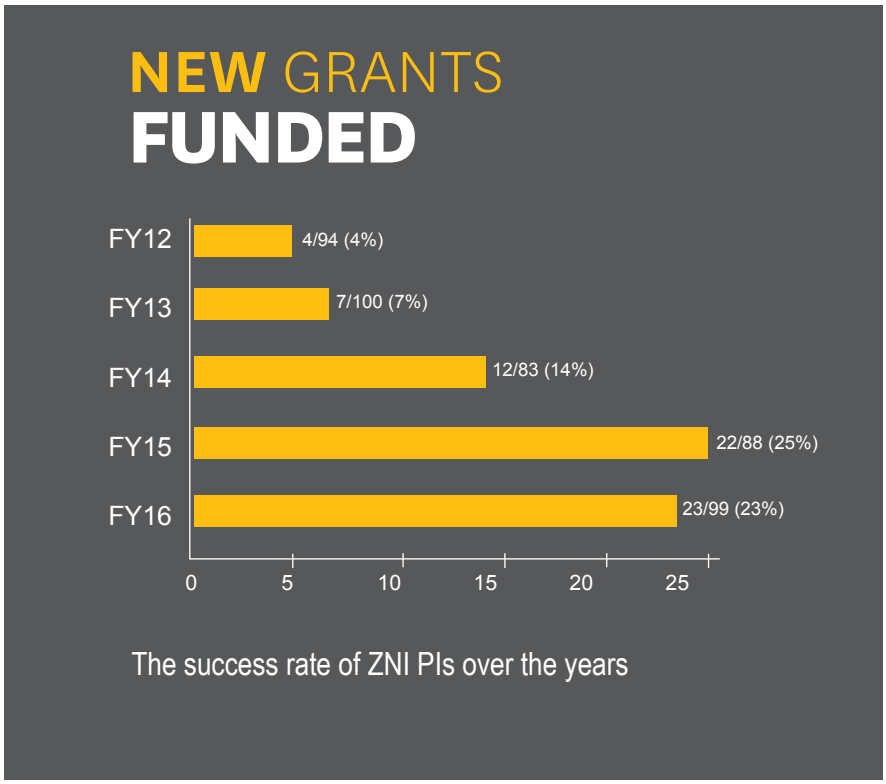
The two-day workshops are team taught at ZNI by **M. Carter Cornwall, MD, PhD**, Professor of Physiology & Biophysics at the University of Utah; **Jeannie Chen, PhD**, ZNI member and Professor of Cell & Neurobiology; and **Kathie Eagleson PhD**, Associate Professor of Research in Pediatrics, USC/Childrens Hospital of Los Angeles. The workshops are built around the idea of having students submit their draft applications for an in-depth and critical review. The instructors share sample successful applications, provide writing critiques but also cover tips and tricks from a reviewer's point of view. Individuals who avail themselves to this opportunity dramatically increase their success rate when submitting final NRSA grant applications.

With the advent of these workshops, USC has seen dramatic increases to the number of NRSAs awarded, from 8 in 2013 to 25 in 2016!



grants and contracts

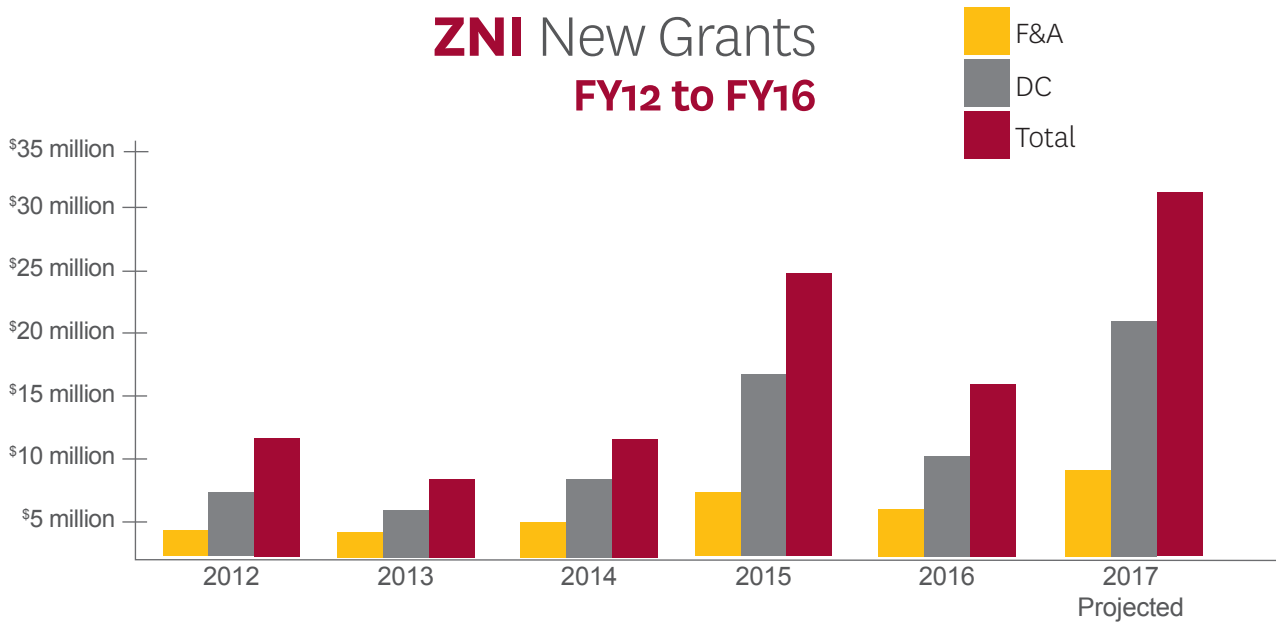
When it comes to submitting and securing grants, PIs at ZNI are very active and successful. We received 23 awards out of 99 proposals submitted, roughly 24% average or 2 out of every 8 grants per month. ZNI PIs held 82 sponsored projects during FY16, with the majority from 12 different NIH institutes. While the amount of dollars received stayed nearly flat from the prior year, the number of PIs receiving more than one R01 jumped from one in 2014 to seven ZNI faculty in 2016.



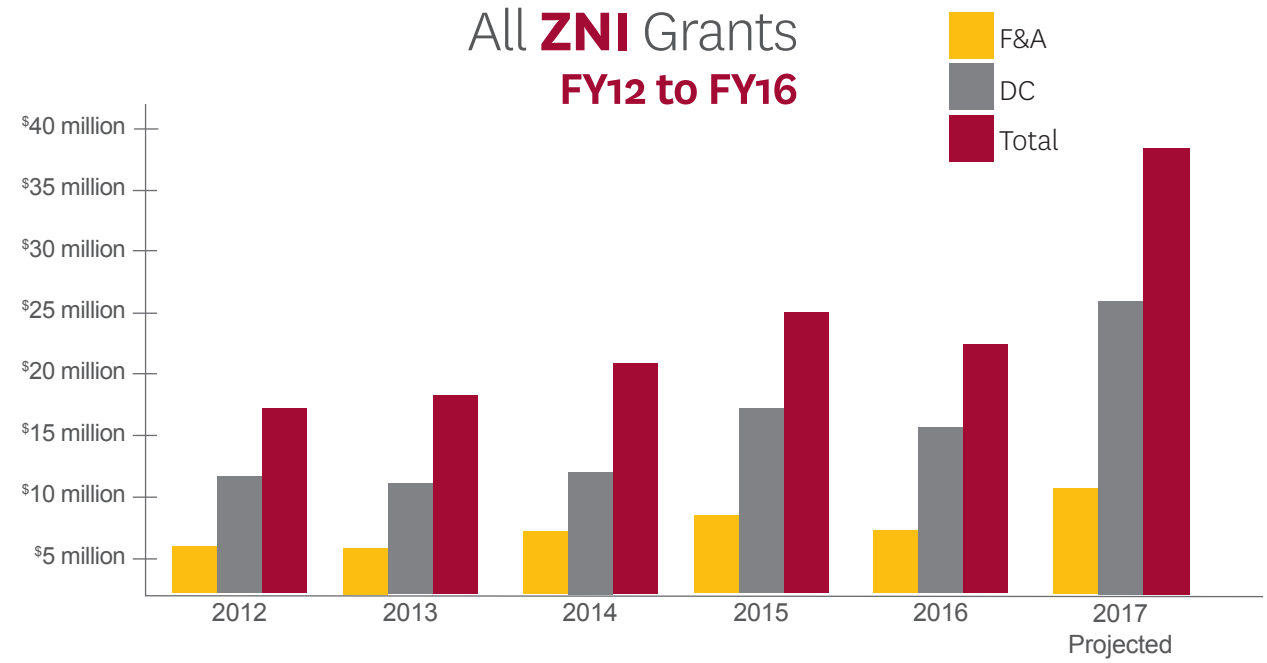
The success rate of ZNI PIs over the years

7

Total number of faculty members now holding more than one RO1 awards

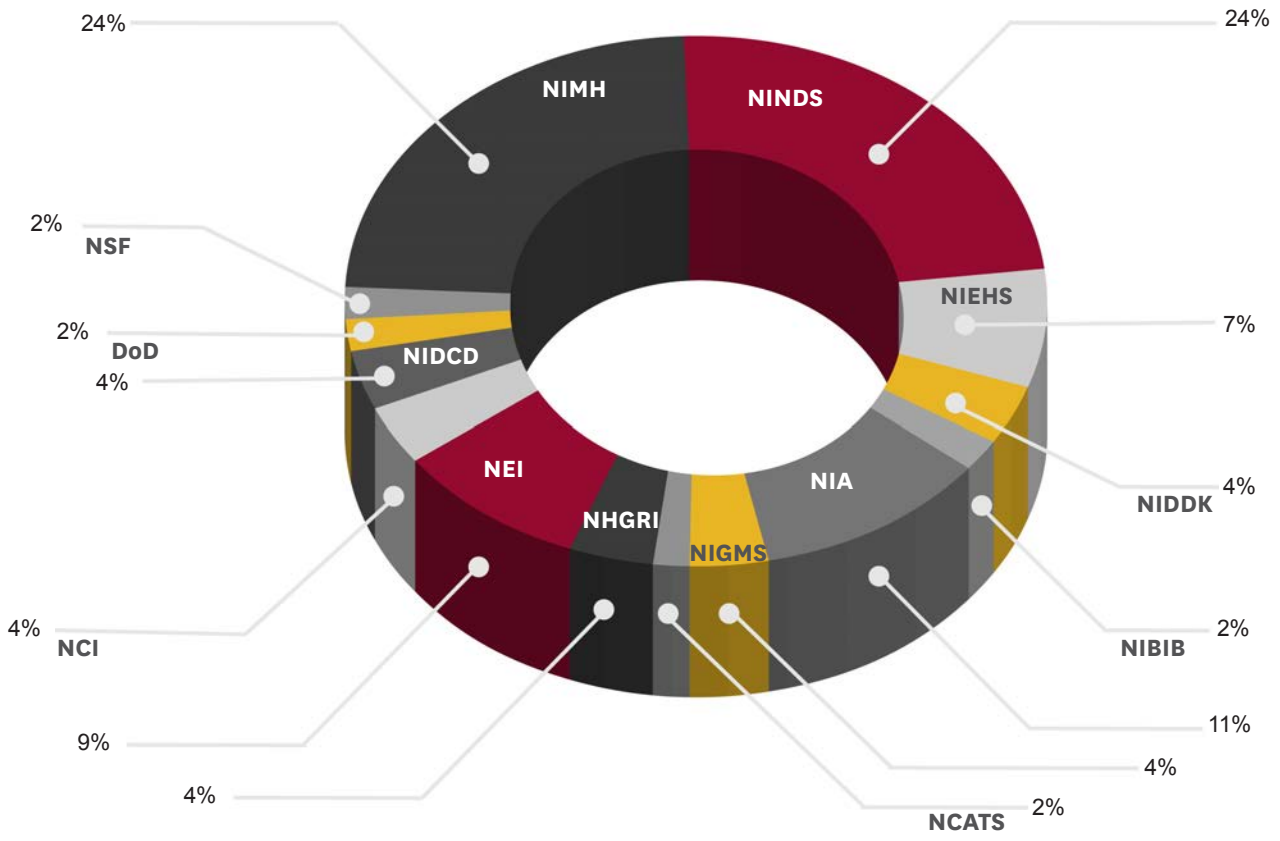


Across the years, total dollar amoungs of new grants at ZNI has been increasing.



Multi-PI, multi-center projects at ZNI are helping grow our grants portfolio.

2016 ZNI SPONSORED Projects by Federal Agency



NIDCD - National Institute on Deafness and Other Communication Disorders
NCI - National Cancer Institute
NEI - National Eye Institute
NHGRI - National Human Genome Research Institute
NCATS - National Center for Advancing Translational Sciences
NIGMS - National Institute of General Medical Sciences
NIA - National Institute on Aging
NIBIB - National Institute of Biomedical Imaging & Bioengineering
NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS - National Institute of Environmental Health Sciences
NINDS - National Institute of Neurological Disorders and Stroke
NIMH - National Institute of Mental Health
NSF - National Science Foundation
DoD - Department of Defense

ZNI Active Awards - Fiscal Year 2016

ZNI Investigator	Funding Agency	Direct Costs	F&A Costs	Total Costs	Project Title
Bonnin, Alex	Autism Science Foundation Fellowship (Goeden)	$25,000	-	$25,000	The impact of maternal inflammation during pregnancy on placental tryptophan metabolism, and downstream
Bonnin, Alex	Childrens Hospital of Los Angeles SubK (National Institute of Mental Health R01)	$15,303	$9,947	$25,250	Enduring Effects of Early-Life Serotonin Signaling
Bonnin, Alex	Department of Defense	$400,000	$135,699	$535,699	Altered Placental Tryptophan Metabolism: A Crucial Molecular Pathway for the Fetal Programming of Neurodevelopmental Disorders
Bonnin, Alex	University of Maryland SubK (National Institute of Mental Health R01)	$30,418	$19,582	$50,000	Kynurenic Acid and Cognitive Abnormalities
Bonnin, Alex	National Institute of Mental Health R01	$236,907	$129,537	$366,444	Prenatal stress and antidepressants effects on offspring brain development
Campbell, Daniel	National Institute of Mental Health R01	$252,636	$164,214	$416,850	Biology of Non-Coding RNAs Associated with Psychiatric Disorders
Campbell, Daniel	Johns Hopkins University (National Institue of Environmental Health Science R01)	$16,234	$21,104	$37,338	Prospective Evaluation of Air Pollution, Cognition, and Autism from Birth Onward
Chang, Karen	Lejeune Foundation	$47,974	$4,796	$52,770	Systematic analysis of genes contributing to synaptic defects in Down Syndrome
Chang, Karen	Alzheimer's Association	$272,730	$27,270	$300,000	Functional Protein Interactions in Alzheimer's Disease and Down Syndrome
Chang, Karen	National Institute of Neurological Disorders & Stroke R01	$218,750	$142,188	$360,938	Role of DYRK1A/MNB in Synaptic growth and function

ZNI Investigator	Funding Agency	Direct Costs	F&A Costs	Total Costs	Project Title
Chen, Jeannie	National Eye Institute R01	$376,557	$242,566	$619,123	Phototransduction in dark adaptation and retinal degeneration
Chen, Jeannie	National Eye Institute R01 (renewal)	$401,813	$240,273	$642,086	Phototransduction in dark adaptation and retinal degeneration
Chow, Bob	National Eye Institute R01 (Ophthalmology Satellite)	$130,465	$84,802	$215,267	Experimental and Clinical Investigations of Retinal Stimulation
Chow, Bob	National Science Foundation (Ophthalmology Satellite)	$135,308	$87,517	$222,825	Retinal Nanophotoswitch
Chow, Bob	National Institute of Mental Health U01	$187,267	$121,723	$308,990	Evaluation of Cellular Heterogeneity Using Patchclamp and RNA-Seq of Single Cells
Chow, Bob	National Institute of Biomedical Imaging and Bioengineering (BMES Satellite)	$24,030	$15,380	$39,410	A Resource on Medical Ultrasonic Transducer Technology
Chow, Bob	National Center for Advancing Translational Sciences (CTSI Pilot)	$28,500	-	$28,500	Photovoltaic Nanoswitches for Next-Generation Artificial Retina
Coba, Marcelo	University of Utah SubK (National Institute of Mental Health R01)	$120,202	$78,131	$198,333	Deciphering gene-environment interactions in pathologica reasctive agression
Conti, David	National Cancer Institute R01	$136,543	$88,753	$225,296	Incorporating intermediate biomarkers of folate with colorectal cancer
Evgrafov, Oleg	National Institute of Mental Health R01	$404,134	$244,983	$649,117	Transcriptome Sequencing of Neuronal Cell Lines from Patients with Schizophrenia
Evgrafov, Oleg	Brain & Behavior Research Foundation	$92,592	$7,408	$100,000	In Vitro Modeling of Altered Brain Development in Schizophrenia
Knowles, James	National Institute of Environmental Health Sciences R01	$396,000	$245,520	$641,520	Discovery of genetic variation influencing schizophrenia using next generation DNA sequencing

ZNI Investigator	Funding Agency	Direct Costs	F&A Costs	Total Costs	Project Title
Knowles, James	National Human Genome Research Institute R01 (Satellite from Biomedical Engineering)	$39,374	$25,363	$64,737	Robust and Portable Workflow-based tolls for MRNA and Genome re-sequencing
Knowles, James	National Institute of Mental Health U01	$995,905	$632,713	$1,628,618	Evaluation of Cellular Heterogeneity Using Patchclamp and RNA-Seq of Single Cells
Knowles, James	International OCD Foundation	$43,629	-	$43,629	Replication of Genome-Wide Association Findings
Knowles, James	University of Wisconsin SubK (National Institute of Mental Health R01)	$12,680	$8,242	$20,922	Brain Mechanisms Mediating Genetic Risk for Anxiety and Depression
Knowles, James	National Institute of Mental Health U01	$477,505	$310,378	$787,883	The USC PsychENCODE Project
Knowles, James	National Institute of Mental Health (Administrative Supplement)	$97,000	$63,050	$160,050	The USC PsychENCODE Project - supplement
Knowles, James	State University of New York SubK (National Institute of Mental Health R01)	$248,918	$161,797	$410,715	African Ancestry Genomic Psychiatry Cohort
Knowles, James / Pato, Michele	National Institute of Mental Health R01	$449,805	$292,373	$742,178	Addition of OCD to the Genomic Psychiatry Cohort
Langen, Ralf	CHDI Foundation	$412,864	$61,930	$474,794	How structure and dynamics of monomeric huntington are modulated by post-translational modifications and polyQ length
Langen, Ralf	National Institute of Neurological Disorders & Stroke R01	$245,750	$159,431	$405,181	Molecular mechanisms of huntingtin misfolding
Langen, Ralf	National Institute of General Medical Sciences R01	$197,500	$128,375	$325,875	Membrane remodeling by alpha-synuclein: implications for function and disease

ZNI Investigator	Funding Agency	Direct Costs	F&A Costs	Total Costs	Project Title
Langen, Ralf	Washington University (National Institute of Neurological Disorders & Stroke R01)	$108,591	$70,584	$179,175	Mechanism of modulation of huntington exon 1 aggregation by profilin
Mack, William	Brain Aneurysm Foundation	$25,000	-	$25,000	MRI Perfusion Permeability and Matrix Metalloproteinase 9 Levels associated with cerebral vasospasm following aneurysmal
Mack, William	National Institute of Environmental Health Sciences R01 (ONES Award)	$297,127	$178,963	$476,090	Neurotoxicity of Airborne Particles: Role of Chronic Cerebral Hypoperfusion
Peti-Peterdi, Janos	French Diabetes Society Fellowship (Desposito)	$31,587	-	$31,587	New mechanisms of tissue remodeling in diabetic nephropathy
Peti-Peterdi, Janos	National Institute of Diabetes and Digestive and Kidney Diseases R01	$900,000	$585,000	$1,485,000	Novel imaging approach to study podocyte function in vivo
Peti-Peterdi, Janos	Amgen	$137,931	$62,069	$200,000	Validation of Prodocyte TRPC6 as a Target in Glomerular Pathology
Peti-Peterdi, Janos	American Heart Association	$127,272	$12,728	$140,000	The role of macula densa cells in renovascular disease
Peti-Peterdi, Janos	American Diabetes Association	$100,000	$15,000	$115,000	Novel tissue remodeling mechanisms in diabetic kidney disease
Peti-Peterdi, Janos	National Institute of Diabetes and Digestive and Kidney Diseases R01	$269,015	$174,860	$443,875	Multiphoton imaging of the juxtaglomerular apparatus
Peti-Peterdi, Janos	Amgen	$110,319	$71,707	$182,026	Validation of GPR91 as a target in diabetic nepropathy
Peti-Peterdi, Janos	Lilly	$253,269	$164,625	$417,894	Multiphoton imaging of the renal hemodynamic effects of Compound X

ZNI Investigator	Funding Agency	Direct Costs	F&A Costs	Total Costs	Project Title
Sieburth, Derek	National Institute of Neurological Disorders & Stroke R01	$218,750	$135,625	$354,375	Stress Regulation of synaptic transmission
Sieburth, Derek	National Institute of Neurological Disorders & Stroke R01 (Gerontology Satellite)	$6,822	$4,434	$11,256	Oxygen Radical Toxicity and Protein Degradation
Sieburth, Derek	National Institute of Neurological Disorders & Stroke R56	$250,000	$162,500	$412,500	Stress Regulation of Synaptic Transmission
Sieburth, Derek	National Institute of Environmental Health Sciences (EHR Pilot Project Grants P30)	$40,000	$26,000	$66,000	Environmental Exposures, Host Factors and Human Disease
Siemer, Ansgar	Whitehall Foundation	$200,143	$24,857	$225,000	The Function of Amyloid Proteins in Long-Term Memory
Siemer, Ansgar / Langen, Ralf	National Institute of Neurological Disorders & Stroke R01	$41,466	$26,953	$68,419	Molecular mechanisms of huntingtin misfolding
Siemer, Ansgar / Langen, Ralf	National Institute of Neurological Disorders & Stroke R01 Diversity Supplement	$32,201	$20,931	$53,132	Molecular mechanism of huntingtin misfolding - diversity supplement
Siemer, Ansgar	National Institute of General Medical Sciences R01	$211,018	$131,107	$342,125	Orb2 a functional amyloid in long-term memory: Its structure and how it forms
Tao, Huizhong	National Eye Institute R01	$288,948	$184,926	$473,874	Inhibitory Synaptic Mechanisms underlying visual cortical processing
Tao, Huizhong	Kirchgessner (Karl) Foundation	$50,000	-	$50,000	The Karl Kirchgessner Foundation Vision Research Grant
Tao, Huizhong	National Eye Institute R01	$250,000	$162,500	$412,500	Synaptic circuitry mechanisms underlying functional development of visual cortex

ZNI Investigator	Funding Agency	Direct Costs	F&A Costs	Total Costs	Project Title
Town, Terrence	National Institute of Neurological Disorders & Stroke F31 Fellowship (Gate)	$36,276	-	$36,276	Targeting Abeta phagocytosis by blocking IRAK-M innate immunity in Alzheimer mice
Town, Terrence	National Institute of Neurological Disorders & Stroke R01	$218,750	$142,188	$360,938	Peripheral TGF-beta Pathway Inhibitor Therapy in Alzheimer's Rats
Town, Terrence	National Cancer Institute R21	$130,500	$84,825	$215,325	T cell TGF-beta signaling as a terapeutic target for pediatric brain tumors
Town, Terrence	Bright Focus Foundation Fellowship (Guillot-Sestier)	$99,646	-	$99,646	AB clearance by Central vs. Peripheral IL-10R-/- monocytes
Town, Terrence	Cure Alzheimer's Fund	$150,000	-	$150,000	Targeting Beneficial Innate Immunity in Alzheimer's by IRAK-M deletion
Town, Terrence	National Institute of Neurological Disorders & Stroke R01 (Administrative Supplement)	$30,303	$19,697	$50,000	Peripheral TGF-beta pathway inhibitor therapy in Alzheimers's rats
Town, Terrence	Douglas Hospital Research Centre	$200,000	-	$200,000	Readying cerebrospinal fluid and plasma measurements by MSD assay
Ulmer, Tobias	American Heart Association	$127,272	$12,728	$140,000	Ectodomain-Transmembrane Domain Coupling in Integrin Receptor Signaling
Ulmer, Tobias	Spastic Paraplegia	$150,000	-	$150,000	Structural basis of brain carnitine palmitoyltransferase 1 function
Wang, Kai	National Human Genome Research Institute R01	$220,000	$143,000	$363,000	Integrated variation detection annotation and analysis for high-throughout sequencing
Wang, Kai	National Institute of Mental Health R01	$250,000	$146,250	$396,250	Understanding the functional impacts of genetic variants in mental disorders

ZNI Investigator	Funding Agency	Direct Costs	F&A Costs	Total Costs	Project Title
Zhang, Li	National Institute on Deafness & Other Communication Disorders R01	$247,534	$160,897	$408,431	Inhibitor circultry mechanism for auditory cortical processing
Zhang, Li	Packard Foundation	$157,516	$17,484	$175,000	Structure of Synaptic Circuitry Underlying Cortical Function
Zhang, Li	National Institute on Deafness and Other Communication Disorder F31 Fellowship (Zingg)	$43,120	-	$43,120	Functional Properties of Subclasses of Layer 5 Projection Neurons in Auditory
Zhao, Zhen	Alzheimer's Association	$90,888	$9,088	$99,976	PICALM mediated autophagic Aß clearance and toxicity mitigation in pericyte
Zhao, Zhen	National Institute of Aging P50 (Satellite Neurology Memory and Aging)	$19,333	$12,566	$31,899	Alzheimer Disease Research Center - Pilot 32.2 Zhao
Zlokovic, Berislav	National Institute for Aging R01	$51,604	$6,305	$57,909	Caloric Restriction and Alzheimers ABeta Clearance Pathway
Zlokovic, Berislav	National Institute of Neurological Disorders & Stroke R01	$412,491	$186,251	$598,742	Alzheimer's Abeta. Apoliproteins and Blood-Brain Barrier
Zlokovic, Berislav	National Institute for Aging R01	$198,850	$129,252	$328,102	The Role of Pericytes in the Adult and the Aging Brain
Zlokovic, Berislav	National Institute of Neurological Disorders & Stroke R01	$465,004	$171,074	$636,078	Activated protein C system in Stroke Models
Zlokovic, Berislav	Cedars Sinai Medical Center SubK (National Institute of Neurological Disorders & Stroke U01)	$6,008	$3,905	$9,913	ZZ-3K3A-201: Safety evaluation of 3K3A-APC in Ischemic Stroke
Zlokovic, Berislav	Cure Alzheimer's Fund	$250,000	-	$250,000	The Role of PICALM in Vascular Clearance of Amyloid-beta

ZNI Investigator	Funding Agency	Direct Costs	F&A Costs	Total Costs	Project Title
Zlokovic, Berislav	National Institute for Aging R01	$395,012	$197,928	$592,940	Cerebrovascular beta-Amyloidosis: A-beta CNS Transport Pathways
Zlokovic, Berislav	Alzheimer's Disease Research Center (National Institute for Aging)	$30,105	$19,569	$49,674	Project 1 Zlokovic
Zlokovic, Berislav	Alzheimer's Disease Research Center (National Institute for Aging)	$93,384	$60,699	$154,083	Project 1 Zlokovic
Zlokovic, Berislav	Cure Alzheimer's Fund	$375,170	-	$375,170	PICALM gene therapy and drug screening for Abeta Clearance
Zlokovic, Berislav	Cure Alzheimer's Fund	$200,000	-	$200,000	The Role of PICALM Mutations in Alzheimer's Disease
Total		**$15,539,785**	**$7,545,444**	**$23,085,229**	

Total number of **Active Grants FY16**

Federal Grants (includes 1 DOD, 1 NSF)	53	$ 18,783,341
Federal Fellowships	2	$ 79,396
Foundation/Private Grants	19	$ 3,266,339
Non-Federal Fellowships	3	$ 156,223
Industry	3	$ 799,930
Total	**80**	**$23,085,229**

znl events

ZNI hosts an extensive number of academic activities throughout the year, ranging from our regular seminar series to more interactive workshops and meetings as well as chalk talks and journal clubs. We pride ourselves in inviting some of the best minds in the field to come and share their expertise and latest findings through our seminar series. Some of the offerings from FY 16 are below.

ZNI Seminar Series

7/13/2015
"Alzheimer's Association Research Update"
Maria Carrillo, PhD, Chief Science Officer, Alzheimer's Association

8/9/2015
"The Transthyretin Amyloidoses: From Delineating the Molecular Mechanism of Aggregation Linked to Pathology to a Regulatory Agency Approved Drug"
Jeffrey Kelly, PhD, Lia Annenberg Hazen Professor of Chemistry, Chair, Department of Molecular and Experimental Medicine, Scripps Research Institute

10/28/2015
"Membrane Protein Assembly and Folding: Biology Meets Thermodynamics"
Stephen H. White, PhD, Professor, Department of Physiology and Biophysics, Univeristy of California, Irvine

11/4/2015
"Quantitative Microscopic Imagining and Genetics for Investigation of Neurodegeneration and Mental Disease"
Anna Devor, PhD, Associate Professor, Department of Neurosciences and Radiology, University of California, San Diego

11/11/2015
"Aggregating Genetic Variants and Mutations Using Network Models of Cell Biology"
Trey Ideker, PhD, Professor, Departments of Medicine and Bioengineering, University of California, San Diego

11/18/2015
"Cannabinoids, Memory, and Depression"
Xia Zhang, PhD, Director, Translational Neuroscience Laboratory, University of Ottawa, Institute of Mental Health Research at the Royal Ottowa

12/9/2015
"Flexible Sensory Representations in Auditory Cortex"
Jeff Isaacson, PhD, Professor, Department of Neuroscience, University of California, San Diego

12/16/2015
"Genetic Dissection of Cortical Circuit Organization and Assembly-- Chandeliers Light Up Pyramids"
Z. Josh Huang, PhD, Charles and Marie Robertson Professor in Neuroscience, Cold Spring Harbor Laboratory

1/29/2016
"What Does the Olfactory Bulb Contribute to Order Perception: Comparing Input and Output"
Lawrence Cohen,PhD, Professor of Cellular & Molecular Physiology, Yale University; Principal Scientist, Korea Institute of Science and Technology

2/3/2016
"Genetic Approaches to Brain Circuit Mapping and Cell Type Characterization"
Hongkui Zeng, PhD, Investigator, Cell & Circuit Genetics, Allen Institute for Brain Science

2/10/2016
"Molecular Structures of Amyloid-B Fibrils, In Vitro and In Vivo: Insights From Solid State NMR"
Robert Tycko, PhD, Senior Investigator, Laboraty of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health

2/16/2016
"Can We Prevent Stroke and Dementia Together?"
Vladimir Hachinski, MD, DSc, Distinguished University Professor, Department of Clinical Neurological Sciences, University of Western Ontario

3/2/2016
"Role of Neurogranin in Learning and Plasticity"
Weifeng Xu,PhD, Principal Investigator; Assistant Professor of Neuroscience, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology

3/16/2016
"Regulation of Glutamatergic Synaptic Transmission by Wnt Signaling"
Andres Barria, PhD, Associate Professor, Department of Physiology & Biophysics, University of Washington

3/23/2016
" 'Pictures at an Exhibition' – 'Confetti' Vignettes and Some Insights into Ren-Expressing Cell Lineage During Development, Neoplasia and Injury"
Kenneth Gross, PhD, Chair, Department of Molecular and Cellular Biology, Roswell Park Cancer Institute

3/30/2016
"Ultra-Short Synaptic Delays and Fast Endocytosis at Mature CNS Synapses"
Henrique von Gersdorff, PhD, Senior Scientist, The Vollum Institute, Oregon Health and Science University

Zach Hall Lecture

Photo credit: Steve Cohn

From R to L: Keynote speaker Roger Nicoll, ZNI director Berislav Zlokovic, Speaker Ansgar Siemer, Speaker Judy Pa

The Zilkha Neurogenetic Institute hosted the 6th Annual Zach Hall Lecture on 1 December 2015 in the Herklotz Seminar Room at ZNI. The lecture—named in honor of ZNI's inaugural director Zach W. Hall, PhD—is a day-long event, featuring scientific reports, seminars, a poster session showcasing the work of over 25 labs, as well as opportunities for graduate students and postdoctoral fellows to have direct contact and conversations with established scientists and senior faculty in formal and informal ways.

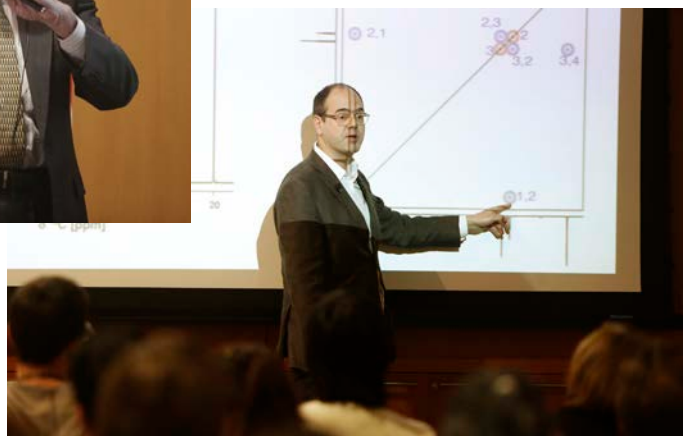
The afternoon began with a presentation by **Judy Pa, PhD**, Assistant Professor in the Department of Neurology and a member of the USC Mark & Mary Stevens Neuroimaging and Informatics Institute. Her talk was entitled "Attention and Memory Systems in Aging and Dementia." Dr Pa was followed by **Ansgar Siemer, PhD**, Assistant Professor of Biochemistry & Molecular Biology and faculty at ZNI, who presented his work exploring "Amyloid Fibrils in Long-Term Memory and Neurodegenerative Disease". Both talks preceded the keynote lecture "Long-term Potentiation: A Cellular Model for Learning" delivered by **Roger Nicoll, MD**, who is Professor of Cellular and Molecular Pharmacology at the University of California, San Francisco.

Dr. Nicoll is a world leader in elucidating the basic mechanisms underlying synaptic transmission and synaptic plasticity in the mammalian brain. His numerous contributions over the last 40 years have laid the foundation for much of our understanding of how neurons communicate and the adaptations in synaptic communication that underlie normal and pathological behavior. In experiments of unusual clarity and rigor, he has revealed the subtlety and complexity of this signaling. Perhaps his most important contribution has been in elucidating a number of the key cellular and molecular steps by which the brain stores information, one of the most important and enigmatic functions of the brain.

Dr. Nicoll has received several awards including the Borden Award for the best research completed during medical school, a Javits Award, the Alden Spencer Award, the Luigi Galvani Award, 2 NIH Career Development Awards, 3 NIH MERIT Awards, election to the National Academy of Sciences in 1994, election to the American Academy of Arts and Sciences in 1999, and selected for the Morris Herzstein endowed Chair in 1999. In 2006 he was awarded the Perl/UNC Neuroscience Award for his contributions to the field of neuroscience and the Peter Gruber Foundation Prize for outstanding achievements in neuroscience. In 2008 he received the J. Allyn Taylor International Prize in Medicine. More recent awards include: The National Academy of Science Award in Neuroscience, the 23rd Annual Pasarow Award, The Kuffler Lectures at UCSD, The Axelrod Prize from the SfN, the Scolnick Prize (MIT), The Grass Lecture (SfN), the Gerard Prize (SfN) and the Warren Alpert Foundation Prize (Harvard).

The seminars were followed by a scientific poster session featuring over 40 separate presentations from researchers representing the various disciplines studied in laboratories. The range of work speaks to the depth and breadth of the types of research conducted at ZNI. The poster session always affords time for spontaneous yet valuable discussions among the students and researchers at ZNI and USC as well as other members of the broader scientific community.

ZNI is proud to continue the tradition of presenting the annual Zach Hall lecture which has attracted some of the biggest names in science to USC.



Top: Judy Pa describes her work during the annual Zach Hall Lecture.

Middle: Roger Nicoll giving the keynote lecture.

Bottom: Ansgar Siemer showing a graph of his findings.

Photo credit: Steve Cohn

Zilkha Symposium on ADRD

Photo credit: Steve Cohn

The 3rd Annual Zilkha Symposium on Alzheimer Disease & Related Disorders (ADRD), **"Bench to Bedside and Beyond: Relating Discovery Research to Translational Developments and Clinical Efforts"** was held on 15 April 2016, with national and international leaders in the field convening at USC to share their work: **Christer Betsholtz, MD, PhD**, Uppsala Univ (Sweden); **David Brody, MD, PhD**, Wash U Medical School; **Jeffrey Cummings, MD**, Cleveland Clinic Lou Ruvo Center for Brain Health; **David M Holtzman, MD**, Wash U Medical School; **Costantino Iadecola MD**, Weill Cornell Medical College; **John Ringman, MD**, USC Neurology; **M. Elizabeth Ross, MD**, PhD, Weill Cornell Medical College; **Philip Scheltens, MD, PhD**, Vrije Universiteit Medical Center (Amsterdam, Netherlands); **Sangram Sisodia, PhD**, Univ of Chicago; **Rudolph Tanzi, PhD**, Harvard; and B**erislav Zlokovic, MD, PhD**, Zilkha Neurogentic Institute (USC). Session chairs included **Maria Carrillo, PhD**, VP, Medical & Scientific Relations, Alzheimers Association; **Roderick Corriveau, PhD**, Program Director, NINDS (NIH); **Helena Chui, MD** (Chair, USC Neurology). Co-organizers for the symposia with Dr. Zlokovic were David M Holtzman MD (Wash U) and Rudi Tanzi, PhD (Harvard). Opening remarks were given by Dr. Zlokovic and Mr. Selim Zilkha. The day-long event was underwritten by a generous gift from Eva and Marc Stern.

Planning is now underway for an expanded program for the 4th Annual Zilkha Alzheimer Symposium, "From Investigation to Integration: New Basic, Translational and Clinical Efforts in Alzheimer's Disease and Related Disorders," scheduled for 5 May 2017.

Joint ADRC – ZNI Pilot Project Program

FY16 was the inaugural year for the **USC Alzheimer Disease Research Center (ADRC) and Zilkha Neurogenetic Institute (ZNI) Pilot Project Program**, where the ADRC and ZNI combined resources and efforts to support promising research projects requiring seed funding.

The ADRC-ZNI Pilot Project Program invites clinical and basic science investigators to submit letters of intent for 12-month pilot projects. The ADRC focuses on mild cognitive changes related to Alzheimer's, cerebrovascular disease, and their interactions in diverse communities. With the support of the ZNI, there are new opportunities to explore basic, clinical and psychosocial approaches to the pathogenesis, prevention, and treatment of early cognitive impairment in humans and animal models. The program is especially interested in new approaches to intervention and translational research from preclinical to early phase trials. Projects that use data available through the National Alzheimer's Coordinating Center or the USC ADRC are strongly encouraged.

The ADRC-ZNI Pilot Project Program grants are designed for junior faculty level investigators, but are also awarded to senior investigators with experience in areas other than AD research, PIs who want to expand the scope of their work to include the AD research field or who want to explore a new hypothesis, method, or approach that is not an extension of ongoing AD research. Postdoctoral fellows with a faculty sponsor are also eligible. Successful applicants receive direct costs up to $30,000 for one-year pilot projects.

For FY16, three ADRC-ZNI Pilot Awards were given to
Judy Pa, PhD, Assistant Professor of Neurology (USC) "Analyzing amyloid and tau PET data: A tracer-agnostic pipeline"

Michael Harrington, MB, ChB, FRCP, Director of Neurosciences (Huntington Medical Research Institutes) "A mechanism for degeneration of aging neuronal membranes in Alzheimer's disease"

Kevin King, MD, Assistant Professor of Clinical Radiology (USC) "Vascular determinants of blood flow and metabolic rate"

It is expected that four more awards will be given out in FY17. This new collaboration between the ADRC and ZNI enables the support of additional pilot projects, using the same integrated solicitation and review process.

Los Angeles Brain Bee

In late January, nearly 100 high school students from the southern California region were buzzing around the health science campus of USC, as they participated in the **Los Angeles-Irvine Brain Bee**. Sponsored by the Society for Neuroscience, the Brain Bee is designed to engage kids between the ages of 14 and 19 in conversations and hands-on demos to stimulate their interest in the brain sciences, and otherwise encourage them to explore neuroscience as a field of study and perhaps their future vocation.

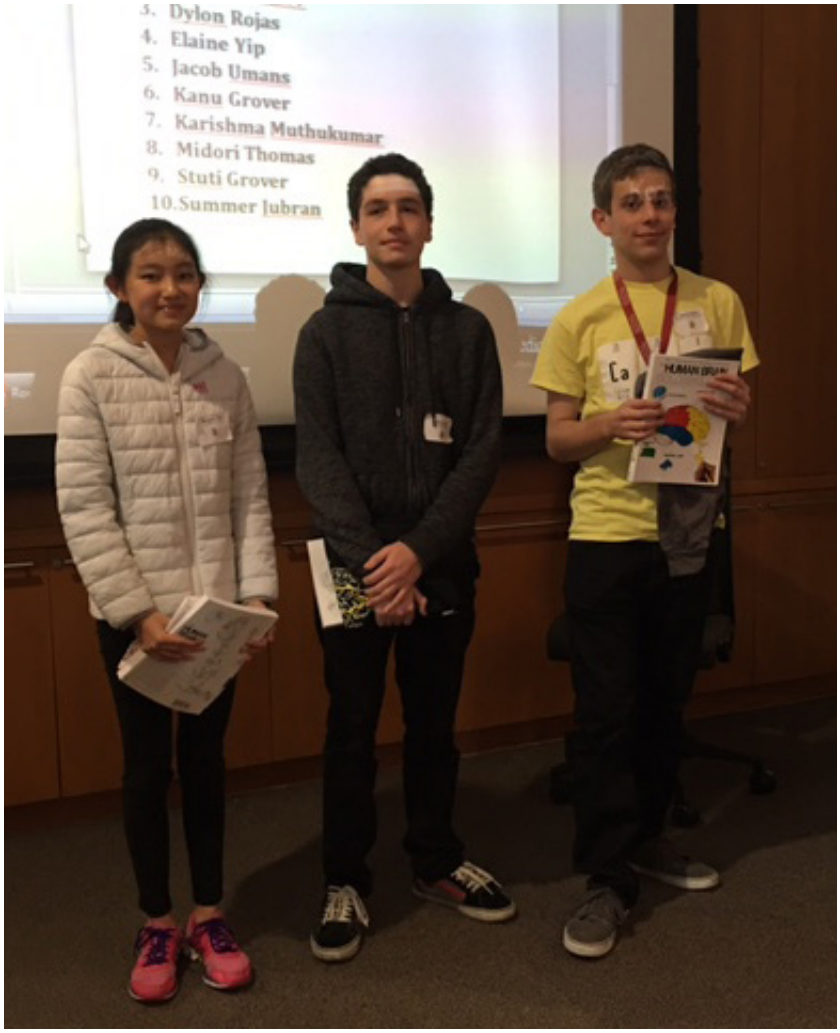
In the months leading up to the event—this year held on Saturday, 30 January 2016 at the Zilkha Neurogenetic Institute—more than 50 graduate students, faculty, postdocs and staff from USC, University of California Los Angeles (UCLA), University of California at Irvine (UCI) and Los Angeles Community College (LACC) attended meetings. Led by **Amy Nelson, PhD** from ZNI, these volunteers shared ideas on how to contact area high schools to recruit students, choose speakers and create publicity materials. The teams including InterAxon groups from all schools reviewed test questions, planned and coordinated with multiple departments and institutions and otherwise pieced together the many details necessary to construct an engaging agenda of multiple overlapping activities for this day-long exploration of the wonders of the brain.

The agenda for the participants included hands-on demonstrations including sheep brain dissections, optical illusions, sensory demonstrations, a rope neuron model, and functional magnetic resonance software to view the brain in 3-D, poster sessions about neurodegenerative diseases, brain computer interfaces, the evolution of the brain, a written exam, as well as a brain anatomy test administered via a timed slide show. From this, 10 finalists received prizes and the top three students played two rounds of a fun, yet challenging, Jeopardy-style game, providing questions to the answers on the screen until a first place winner was announced.

Giveaways were raffled off, items donated by the Brain Research Institute of UCLA, the USC Laboratory of Neuro Imaging (LONI, part of the USC Mark & Mary Stevens Neuroimaging and Informatics Institute), USC Credit Union, Keck Medicine of USC and the Keck School of Medicine. Parking was graciously provided free of charge by USC Transportation and USC Facilities Management covered all of our maintenance needs. Everyone enjoyed a complementary light breakfast, and throughout the day, snacks and fresh fruit donated by Einstein's Bagels and ZNI. Courtesy of LONI and ZNI, a plentiful lunch was served to over 250 people.

Families were escorted on tours around campus and everyone was open to attend a number of professional panels, where experts discussed college and career options. Overflowing crowds listened to a presentation on "Concussion in Youth Sports" given by **David Baron, MD** (Assistant Dean of International Relations at Keck School of Medicine of USC), and a cinematic review of "Hollywood and the Brain" by **Amy Sweetman** (Professor of Psychology at LACC and founder of the LA Brain Bee).

It was a day most will not soon forget, especially Jacob Umans (Capistrano Valley High School) who attended the national Brain Bee in Bethesda, MD in late March. The winner of the nationals goes on to the international Brain Bee in Copenhagen in late 2016.



L to R: 3rd place winner Alexandra So (Harvard Westlake), 2nd place winner Andrew Rodov (South High School Torrance) and 1st place winner Jacob Umans (Capistrano Valley HS)

Music to Remember

Music is a universal language that enables us to express how we feel. For the past several years, ZNI has been examining whether holiday music or patriotic songs might help people with Alzheimer's disease or dementia recover memories.

Music to Remember, a program which began in 2012, sends trained vocalists to sing Christmas carols and other holiday songs at long-term care and assisted living facilities throughout Los Angeles County. ZNI partners with **Alzheimer's Greater Los Angeles** (which also produces Memory Mornings programs) and **LA Opera** as well as the **Alzheimer Disease Research Center** at the Keck School of Medicine of USC.

Holiday music is part of just about everyone's earliest memories, and that may be the key to establishing new connections with people suffering from Alzheimer's. One often remembers things learned when very young, especially if these memories have been reinforced over the years. Holiday music–and for a certain generation, patriotic songs–are auditory experiences that have become ingrained in most of us, due to consistent repetition.

During FY16, a group of LA Opera vocalists sang at more than a dozen hospitals, long-term care or assisted living facilities over five days in December. In addition to singing to people suffering from Alzheimer's disease and dementia, through separate programs LA Opera shares holiday joy with veterans and children in hospitals. Dressed in coats, capped with Santa hats and carrying bells, LA Opera singers stroll through the halls of facilities such as Keiro Nursing Home, the Long Beach Veterans Administration and Huntington Hospital.

The seasonal concerts are part of a general movement toward total patient care. In the course of just 45 minutes of performances by the young singers, one may witness a calm going over someone who is otherwise very disconnected or who may usually be quite agitated. Someone who was only looking down may start to look up with a renewed focus. The music often causes foot tapping and sometimes, tears.

As an added benefit, the young singers from LA Opera went caroling on the Health Science Campus, surprising workers and visitors with an hour of music in the plaza between ZNI and the **Broad Stem Cell Center (BCC)** at the Keck School of Medicine of USC. BCC kindly offered cookies and hot cocoa to those happening by. This is a partnership that provides wonderful memories to all who participate.

administration

The scientists at the Zilkha Neurogenetic Institute are fortunate to have an experienced and long-time administrative staff led by **David Warren**, senior director of operations, finance and administration. The 300+ staff, faculty and students who work at ZNI are supported by facilities manager **Rusty King**, human resources manager **Barbara Lockley**, two full-time contracts & grants coordinators **Gabriela Torres** and **Muoi Thang**, purchasing agent **Leslie Ortiz**, budget/business technician **Marlen Turcios**, program manager **Emily Chu**, executive assistant **Monica Castro** and two lab aides, **Benilda Ramos** and **Manuela Osorio**, who provide glassware and autoclave services. The ZNI administrative staff are dedicated to creating an environment that fully supports faculty so they can best apply their time and energy on doing the very best science.

In addition, the institute acts as a hub for the neuroscience community across campuses, offering a weekly seminar series, hosting neuroscience graduate courses, journal clubs, special lectures, as well as grand rounds for the departments of Psychiatry, Neurology and Neurosurgery. At ZNI, science comes first and everything else is designed to serve the researchers and their scientific pursuits.

FY16 Operating Budget

	Income	Forward From FY15	Expenses	Balance
Program Funds (Endowement)	$2,687,447	$511,152	$2,361,036	$867,563
Departmental Funds (KSOM-Provided)				
Administrative	$637,593	N/A	$640,348	($2,755)
Facilities	$175,000	N/A	$169,081	$5,919
Common Equipment Fund	$151,425	N/A	$145,752	$5,673
Chair's Discretionary	$150,000	N/A	-	$150,000
Deans Development Funds	$670,988	N/A	$678,313	($7,325)
Philanthropy				
Unrestricted Gifts	$63,250	$220,634	$83,670	$200,214
Restricted Gifts	$500,000	-	$77,505	$422,495
Endowed Chair (Principal)	$500,000	$1,036,438	-	$1,536,438

development

The Zilkha Neurogenetic Institute (ZNI) offers numerous high impact funding opportunities for philanthropists who may be interested in supporting an institute that is home to a broad array of basic and clinical research, encompassing all aspects of neuroscience at USC.

Entering our 13th year of collaborative studies, ZNI is poised for continued success under the dynamic leadership of **Dr. Berislav Zlokovic** and his talented team. More than 300 uniquely qualified and highly specialized researchers work together at ZNI every day.

As part of the Keck Medicine Initiative, the Zilkha Neurogenetic Institute fundraising priorities include:

- Support of world-class research faculty and facilities with state-of-the-art equipment and laboratories
- Seed funding to allow ZNI investigators to pursue innovative pilot projects, leading to further external sponsored project support
- Graduate and postdoctoral fellowships to assist in the recruitment of the next generation of clinical and research leaders who share our vision of excellence and innovation

Gifts and grants help us meet our nation's growing demand to improve the quality of life for individuals and society by promoting health, advancing medical research, and developing models and therapeutics for diseases. We hope you will join our efforts to accelerate the discoveries that we hope will improve lives.

To discuss funding opportunities that fit your areas of interest, please contact:

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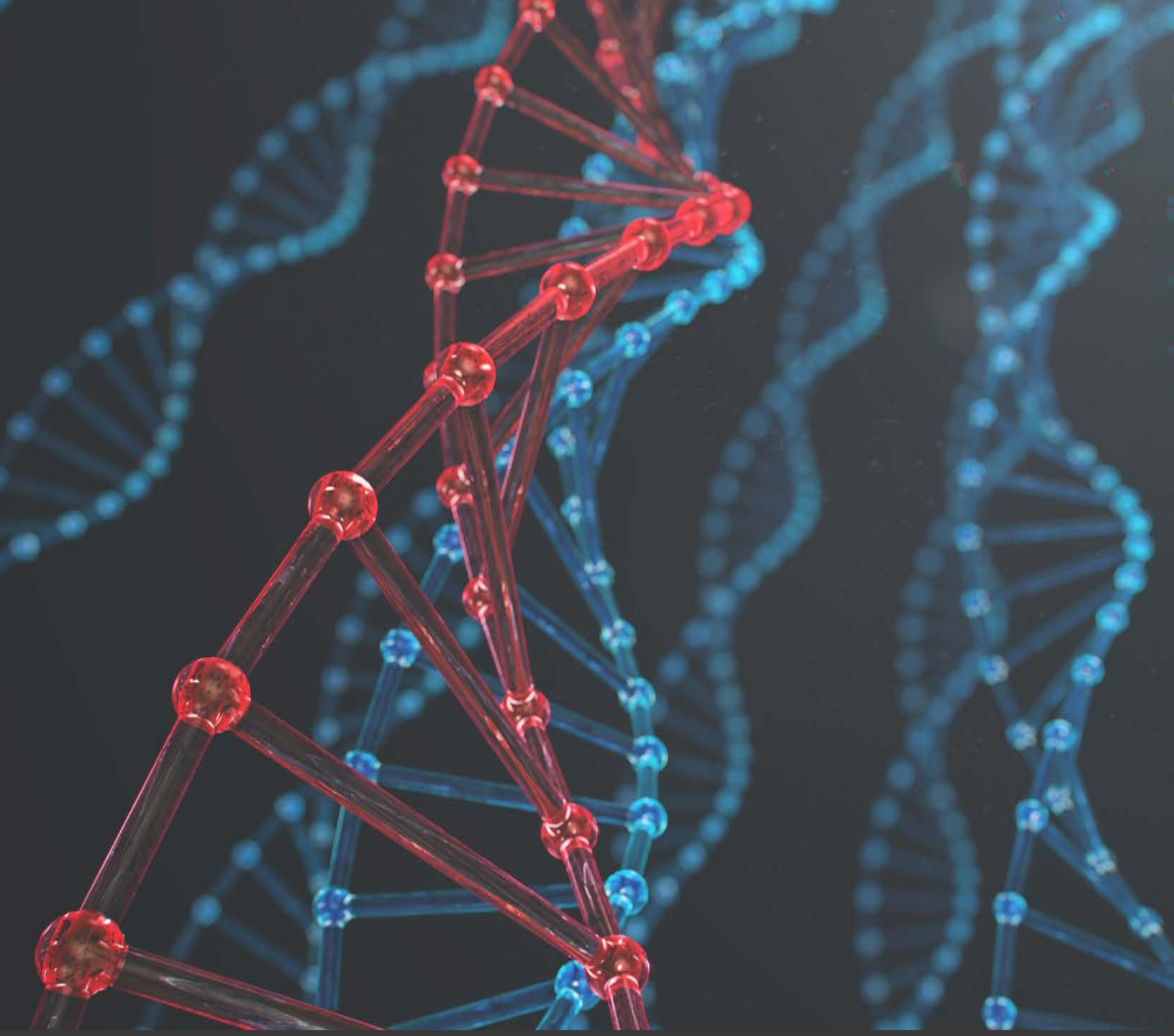
ZNI is dedicated to understanding the complexities of brain and nervous system diseases, disorders and injuries and improving the lives of those suffering from such maladies through scientific discovery and transitional medicine.



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