What can the tiny fruit fly, also known as Drosophila melanogaster, tell us about Alzheimer’s disease and Down’s syndrome? It turns out, a lot! Nearly 75% of a group of readily identified genes that are mutated, amplified, or deleted in a diverse set of human diseases have a counterpart in Drosophila. Indeed, these little creatures have been used as a model organism for genetic investigations for over a century.

Drosophila have many characteristics that allow researchers to explore animal development and behavior, neurobiology, and human genetic diseases and conditions. Because of their short life cycle, well-established genetics and behavioral analyses, and evolutionarily conserved genes and signaling pathways, scientists can rapidly delineate the gene-to-function-to-behavior relationships across a relatively short time period.

Karen T. Chang PhD, an Associate Professor of Physiology & Neuroscience whose lab is in the Zilkha Neurogenetic Institute, uses Drosophila as a simple model organism for her research. By combining genetics, molecular/cellular techniques, imaging, electrophysiology, and behavioral assays, her lab is taking a multidisciplinary approach to understand mechanisms important for normal neuronal functions and underlying neurological disorders.

The Chang lab is systematically investigating the functions of key candidate Down syndrome genes in the nervous system using Drosophila. Down syndrome is a genetic disorder caused by full or partial triplication of chromosome 21. Individuals with Down syndrome have learning disabilities and a significantly increased risk of developing Alzheimer’s disease. Therefore, an understanding of key candidate genes and signaling pathways perturbed in Down syndrome can shed light on fundamental mechanisms important for learning and memory, as well as on cellular changes that contribute to dementia seen in Alzheimer’s disease.

While working on a project to dissect molecular pathways that influence memory, Dr Chang and her colleagues showed that a protein upregulated in Down syndrome called DSCR1 is crucial for normal learning and memory. They also found that surprisingly, DSCR1 functionally interacts with the Amyloid Precursor Protein (APP) to differentially affect neurodegeneration and memory as a function of age. This work has implications for understanding Alzheimer’s disease in Down syndrome, as APP and DSCR1 have been shown to be perturbed in both conditions. By understanding the detailed mechanisms of DSCR1-APP functional interaction during aging, combined with future work using mammalian systems to validate her findings, Dr. Chang hopes to better understand and eventually devise strategies to combat neurodegeneration and memory impairments during aging.

Down syndrome individuals have increased risk of developing Alzheimer’s disease when they get older. It is thought that an extra copy of the amyloid precursor protein (APP) may lead to a buildup of protein clumps in the brain called beta-amyloid plaques, which is one hallmark of Alzheimer’s disease.

Karen T. Chang PhD
Associate Professor,
Physiology & Neuroscience

Karen T. Chang PhD

The fly neuromuscular juncture (NMJ) is a glutamatergic synapse and an excellent model for studying genes and mechanisms regulating synaptic development and function. In this image, red marks presynaptic neuronal membranes and green identifies postsynaptic glutamate receptors.
Another question Dr Chang is working to address is how neurons communicate with high fidelity to govern complex brain functions such as learning and memory. This work focuses on understanding mechanisms regulating synaptic vesicle recycling, which is critical for maintaining communication between neurons during periods of high neuronal activity, like processing or forming memories.

Neurons relay information from one neuron to another through a specialized structure called the synapse. Chemical synapses release neurotransmitters from small, round, seemingly identical organelles called synaptic vesicles. Neurons can fire at very rapid rates. Synapses also need to release synaptic vesicles at high rates in order to ensure reliable communication. Because the synapses are located far away from the neuronal cell body where most protein synthesis occurs, it is believed that one mechanism to enable the synapses to function properly without depleting their supply of synaptic vesicles is to rapidly retrieve and recycle the vesicle components following their release.

Dr Chang and her group discovered that the Minibrain/Dyrk1A kinase — a strong candidate gene for Down syndrome and autism spectrum disorder — is present at neuronal terminals and important for synaptic vesicle recycling. Dr Chang also found that Synaptojanin, a gene perturbed in Down syndrome and mutated in Parkinson’s disease, is a substrate of Minibrain kinase in vivo. Synaptic activity acutely triggers phosphorylation of Synaptojanin by Minibrain, thereby enhancing synaptojanin’s enzymatic activity to influence synaptic vesicle recycling.

These findings provide mechanistic insights into how a neuron fine tunes its function in order to meet the demand of the synapse, and further suggest that neurological disorders such as Down syndrome, Autism, and Parkinson’s disease may share common disturbances in synaptic vesicle recycling.

Dr Karen Chang joined the faculty at USC in September of 2009, and was promoted to Associate Professor in Spring 2017. She obtained her PhD in Neurobiology from the University of California, San Diego, in the lab of Darwin Berg PhD. She then went on to conduct her postdoctoral research with Kyung-Tai Min PhD at the National Institutes of Health in Bethesda, Maryland, later moving with Dr Min when his lab was relocated to Indiana University at Bloomington. It was in Dr Min’s lab where Dr Chang first utilized the powerful genetics of Drosophila to investigate genes important for learning and memory.

Protein phosphorylation is the major molecular mechanism through which protein function is regulated in response to extracellular stimuli both inside and outside the nervous system.

A former recipient of the NIH Pathway to Independence award (K99/R00), Dr Chang currently holds an R01 from the National Institute of Neurological Disorders and Stroke and an R21 from the National Cancer Institute (both NIH). She has received grants from the Jerome Lejeune Foundation, Alzheimer’s Association and Global Down Syndrome Foundation and the Zilkha Neurogenetic Institute. If you are interested in supporting or learning more about Dr Chang’s research, please contact zni@usc.edu.

Support for ZNI

We wish to express our profound gratitude to the following individuals who have made generous donations to the Zilkha Neurogenetic Institute over the past year, allowing our research programs to stay world-class:

- Anonymous
- Wallis Annenberg
- Helene Galen
- Eva & Marc Stern
- Selim Zilkha & Mary Hayley

An Optimistic View of Curing Alzheimer Disease

The JAMA Network — which includes blogs from the Journal of American Medicine — produced a 36-minute conversation with Rudolph Tanzi PhD of Harvard University and Berislav Zlokovic MD PhD of the Keck School of Medicine of USC. The podcast can be accessed at http://jamanetwork.com/learning/audio-player/14072698. Despite disappointing results of some clinical trials over the past year, both researchers say new approaches are beginning to make advances in clinical treatments for Alzheimer’s disease. The Journal of the American Medical Association (JAMA) is the premier outlet for scientific research across the world.
Zlokovic installed as Mary Hayley and Selim Zilkha Chair in Alzheimer’s Disease Research

Saying it was “an incredible honor” and one of the great moments in his professional career, Berislav V Zlokovic MD PhD was installed as the inaugural holder of the Mary Hayley and Selim Zilkha Chair in Alzheimer’s Disease Research at a ceremony held 4 May 2017 at the Zilkha Neurogenetic Institute (ZNI). Dr Zlokovic’s research focuses on the links between the health of blood vessels in the brain and degenerative brain diseases. His accomplishments have earned him worldwide acclaim. As director of the ZNI, Dr Zlokovic acknowledged the great work of the faculty. Calling his colleagues “talented scientists,” he remarked how despite the odds, the researchers at ZNI are securing more grants each year, publishing in the best journals and importantly, training the next generation of scientists. Dr Zlokovic also thanked President C L Max Nikias, Provost Michael Quick for their support of the institute. He reserved his warmest thanks for Mary Hayley and Selim Zilkha, thanking them for their seemingly endless drive and energy that inspires the researchers at ZNI to do the very best science while building a world-class research institute.

Leducq Transatlantic Network Meeting Held at ZNI

The Zilkha Neurogenetic Institute (ZNI) hosted in October 2017 the second meeting of the Leducq Transatlantic Network, welcoming distinguished scientists whose research focuses on dementia and small vessel disease of the brain, a condition that affects more than 50% of the elderly population. The first meeting was held in Spring 2017 in Copenhagen, Denmark. The ZNI-hosted program focused on presenting progress made by the network in this first year of funding and included presentations from junior and senior investigators. Joanna Wardlaw MD (University of Edinburgh) and Berislav Zlokovic MD PhD are the European and North American Coordinators respectively for the newly-funded Leducq Transatlantic Network “Understanding the Role of Perivascular Space in Cerebral Small Vessel Disease,” which is composed of an international group of investigators at nine different institutions, and funded by the Fondation Leducq. The Network includes Maiken Nedergaard MD DMSc (University of Copenhagen), Sandra Black MD (Sunnybrook Health Sciences Centre, Toronto), Ken Smith PhD (University College London), Serge Charpak MD DPhil (Université Paris Descartes), and Hélène Benveniste MD PhD (Yale University).

Arthur Toga PhD, Director of the USC Mark & Mary Stevens Neuroimaging and Informatics Institute gave the keynote address. Other speakers included Anne Joutel MD PhD (Université Paris Diderot), Martin Dichgans MD (Institute for Stroke and Dementia Research, Munich), Danny Wang PhD (INI/USC), Donna Wilcock PhD (University of Kentucky), Roderick Corriveau PhD (National Institute of Neurological Disorders and Stroke, NIH), and Rashid Deane PhD (University of Rochester NY). The event also featured a “data blitz” session of short presentations by 13 Leducq Fellows. The meeting was underwritten in part by The Helene & Louis Galen Family Foundation.
From Investigation to Integration: 4th Annual AD Symposium Held at ZNI

In April 2017, the Zilkha Neurogenetic Institute (ZNI) hosted the 4th Annual Zilkha International Symposium on Alzheimer Disease and Related Disorders, “From Investigation to Integration: New Basic, Translational & Clinical Efforts in Alzheimer’s Disease & Related Disorders.” Co-organized by Berislav Zlokovic MD PhD (USC), Rudolph Tanzi PhD (Harvard Univ) and David Holtzman MD (Wash U at St Louis), the event once more attracted prominent researchers in the field. A dozen speakers presented unpublished work, including Virginia Lee PhD and John Trojanowski MD PhD (U Penn), Ronald Petersen MD PhD and Len Petrucelli PhD (Mayo Clinic), with discussions led by seven moderators and chairs, including Roger Nitsch MD (Univ Zurich), Robert Vassar PhD, (Northwestern) and Maria Carrillo PhD (Alzheimer’s Association). The annual event is supported by a generous donation from Eva and Marc Stern. Next year’s symposium “Searching for Solutions” is scheduled for April 2018.

Speakers gather on the lawn outside of the 4th Annual Zilkha Symposium on Alzheimer Disease and Related Disorders, April 2017

Neurosurgery-ZNI Incubator Lab Expands

The Zilkha Neurogenetic Institute (ZNI) is pleased to welcome to the neurosurgery-ZNI research program, Frank J Attenello MD MS and Brian Lee MD, Assistant Professors of Clinical Neurosurgery at the Keck School of Medicine of USC, both of whom established their laboratories in early 2017.

Dr Attenello is dedicated to advancing the understanding of gliomas, a type of tumor that arises from glial cells, in the brain or spine. Through his research, he is working to characterize tumor-pericyte interactions with glioblastoma grafts in transgenic mouse models. He is further leveraging his experience with CRISPR technologies to alter tumor expression levels in studies.

Dr Lee is investigating how a brain-machine interface (BMI) — which is a unit implanted into the brain of a paralyzed or injured patient to control an external assistive device, such as a cursor on a computer screen, a motorized wheelchair, or a robotic limb — might be expanded to generate the percept of sensation. Current BMI are guided by visual feedback but Dr Lee’s group would like to engineer artificial sensation via subdural ECoG electrodes, which would be interpreted by subjects as “touch.”

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