

November 19, 2019

Mr. Robert Shasha
VIA EMAIL: rshasha@cotswoldgroupinc.com

Dear Robert,

On behalf of the Keck School of Medicine of USC and the Zilkha Neurogenetic Institute, we would like to thank you for your previous support of our programs and share with you some more information regarding our center.

Initiated in 2003 by a generous gift from Selim Zilkha and Mary Hayley as well as an endowment from the WM Keck Foundation, the institute has become internationally recognized for its neuroscience research, and has fostered a scientific community that supports established leaders in their fields while training future innovators in neurological sciences. Our team consists of **over 25 full-time faculty, 40 postdoctoral fellows, 75 graduate students and 100 research staff** studying the neurological processes affecting the brain and nervous system.

At the Zilkha Neurogenetic Institute (ZNI) we promote a bold mission: to find the causes and ultimately the cures for devastating neurological conditions. Our department of physiology and neurobiology was **ranked No. 2 in 2018 by the Blue Ridge Institute for Medical Research**. The University is a 501(c)3 organization, and our taxpayer identification number is 95-1642394. The administrative and facilities operating budget for the institute exceeds \$5 million per year. In the fiscal year ending June 31, 2019, **ZNI researchers held 94 grants with a total of \$39 million in annual direct and indirect costs** — 70% of these awards are federal grants from over a dozen different NIH institutes, 25% are from foundations and the remaining 5% are from industry.

Our faculty have made notable breakthroughs including identifying key biological factors to understand neurodegeneration and developing new techniques to study and analyze disease and identify potential therapies. In addition to conducting research, our faculty are determined to develop interactive and enriching educational programs to train students ranging from undergraduates to medical fellows, helping to ensure a robust pipeline of future leaders. Our students learn from faculty who are making groundbreaking advances in the field of neuroscience and are provided unparalleled research opportunities in an interdisciplinary environment that is internationally recognized to be at the leading-edge of discovery.

Over the past 15 years our team has made significant breakthroughs in the field. Specific research highlights from institute faculty include:

Dr. Berizlav Zlokovic was the first to propose that impaired blood flow and flaws in what's called the blood-brain barrier drive neurodegeneration, which underlies all kinds of cognitive disorders, from Parkinson's to Alzheimer's. His work has shown that declining memory and thinking is only a secondary symptom in people with dementia. The first signal that something is awry occurs in the blood vessels. Additionally, his group identified key cellular and



molecular mechanisms at the blood-brain barrier — work that has the potential to lead to therapies for Alzheimer's. His team's discoveries led to the development of **clinical trials for Alzheimer's disease that are currently being tested in Phase 2 and Phase 3 studies**. Additionally, they have also developed an **pioneering bench-to-bedside therapy for stroke** based on activated protein C treatment as a neuroprotective agent in stroke patients that has successfully completed Phase 2a, and is now in preparation for phase 2b/3 trial.

Dr. Terrence Town is working at the interface between the brain and the immune system to develop a treatment for Alzheimer's disease by enlisting the peripheral innate immune system (specifically, cells called macrophages). Most therapies targeting the disease are impeded by the blood-brain barrier, a natural barrier that protects brain cells from peripheral substances. However, **Dr. Town's group has shown that peripheral macrophages can be instructed to enter the brain from the circulation, where they attack the damaging sticky plaque buildup that is a defining feature of Alzheimer's disease**. His lab has revolutionized the field of Alzheimer's disease by developing **the first rat model of the disease that manifests all of the clinical and biological symptoms of human Alzheimer's**. This serves as an invaluable tool for understanding the causes of Alzheimer's and for pre-clinical testing of cutting-edge treatments. As a testament to the rapid adoption of this model by the field, we have already distributed these AD rats to over 60 academic laboratories spanning 15 nations around the globe.

Dr. Marcelo Coba seeks to bridge the gap between human genetics, synaptic signaling and therapies by determining how disease risk factors are functionally organized in signaling networks and how these networks are altered by mutations associated with complex and degenerative brain disorders. During the past several years her team has utilized technologies such as human induced pluripotent stem cells and genetic editing technologies such as CRISPR-Cas9 to build patient derived neurons and brain organoids to re-create human based disease models. **This new form of discovery will allow for researchers to study the brain in real time and hopefully enhance their understanding of these diseases**.

Dr. Ralf Langen studies the protein misfolding in neurodegenerative diseases. These diseases are caused by proteins that we all make, but they take up toxic structures in disease. **Preventing the formation of these toxic structures is a promising avenue for therapy**. In particular, it is essential to understand what the toxic structures look like, how they can be detected diagnostically, and ultimately how the formation of toxic species can be stopped. Dr. Langen's group has been able to make significant progress in answering these questions and is working to develop better therapies and biomarkers.

On behalf of the team at the Zilkha Neurogenetic Institute, we remain deeply grateful for your previous support and your interest in our programs. I look forward to connecting soon to further outline our vision and host you for a tour of our center the next time you are in town.

With Gratitude,



Elizabeth Stolow