A recent *Nature Communications* article by Berislav Zlokovic, MD, PhD, and members of his laboratory reveals an important correlation between the loss of pericytes and Alzheimer-like neurodegeneration. Pericytes are cells that can be found wrapped around the endothelial cells of capillaries and venules, protecting these blood vessels from harmful elements. These components are crucial players in the body’s vascular system, which is responsible for circulating crucial fluids throughout the body.

One hypothesis about Alzheimer’s disease is that increases in a protein called beta-amyloid lead to nerve cell damage in the brain. Previous studies in mice have shown that increased beta-amyloid levels reproduce some of the problems associated with Alzheimer’s. The animals have memory problems, beta-amyloid plaques in the brain and vascular damage, yet none of the neurofibrillary tangles and neuron loss that are hallmarks of the disease.

The present study used mice genetically engineered to have reduced levels of proteins known to control pericyte growth and survival. The mice displayed accelerated learning and memory problems and also had increased beta-amyloid plaque deposition near brain cells and along brain blood vessels. These findings by the Zlokovic lab suggest that reduced pericyte levels may influence whether increased beta-amyloid leads to tangles and neuron loss, contributing to the neurodegenerative disorder in Alzheimer’s disease. “Pericytes act like the gatekeepers of the blood-brain barrier,” says Zlokovic.

The investigators also confirmed previous findings showing that beta-amyloid accumulation leads to pericyte death. With all of these developments taken together, clearer associations can be drawn between Alzheimer’s disease and other vascular types of dementia. While Alzheimer’s is the leading cause of dementia, vascular dementias are a close second. Additionally, this work paves the way for further avenues of research within the field and may suggest novel targets for possible therapeutic solutions.

Alzheimer’s disease is the sixth leading cause of death in the United States. Currently, more than 5 million Americans are living with the disease, and one in nine people age 65 and older has Alzheimer’s. With such alarming figures, researchers are attempting to understand not only the effects of Alzheimer’s disease but the factors that contribute to the development of full-blown Alzheimer’s disease pathology. More funding for this important work is needed.

The study was co-funded by the National Institute of Neurological Diseases and Stroke (NINDS) and the National Institute on Aging (NIA), parts of the National Institutes of Health. Members of the Zlokovic laboratory who were instrumental in the publication of this article include Abhay Sagare, Zhen Zhao, Qingyi Ma and Anita Ramanathan.

Why is Basic Research Important?

Why do basic biomedical research? Why not just concentrate on treating sick people? How can experiments with animals like mice or rats — so different from people — or experiments with extracts in test tubes possibly have relevance to us?

The answer lies in what we don’t know. With some diseases — especially neurodegenerative disorders like Parkinson’s, Huntington’s or Alzheimer’s disease — we don’t even know enough to begin a treatment that might be successful. We also need to develop models, such as transgenic mice, in which to study certain aspects of diseases before attempting experiments on humans.

By uncovering the cellular or molecular changes involved in diseases, basic research points to approaches for treatment or prevention. Smallpox, polio, pneumonia and many other diseases are no longer the plagues they once were because scientists working in their labs provided the building blocks to understand the genesis, progression and, ultimately, prevention of these conditions.

This is what basic biomedical research is all about. In order to attack major diseases of today like breast cancer, prostate cancer, heart disease, stroke, HIV and Alzheimer’s disease, we need a broader base of knowledge. We need to know more about the specific cellular and molecular changes involved in the development of these conditions. By providing this knowledge, basic biomedical research forms the foundation for advances in the diagnosis, treatment and prevention of such diseases.

Current Facts About Alzheimer’s Disease

• More than 5 MILLION Americans are living with the disease
• ONE IN NINE people age 65 and older has Alzheimer’s disease
• The cost of caring for people with Alzheimer’s and other dementias will rise to $1.2 TRILLION PER YEAR by 2050
• Alzheimer’s disease is the SIXTH leading cause of death in the United States

In the past year, ZNI investigators published more than 120 papers in peer-reviewed journals. Many ZNI scientists have presented their findings in high-impact journals, those publications considered to be highly influential in their fields (Science, Nature, etc.). In 2013, 14% of all publications by ZNI researchers were in high-impact journals.
One major goal of neuroscience is to understand how the mammalian brain functions: how perception and behaviors are generated and controlled, how these functions adapt in response to changes in the dynamic external environment and how specific changes of these functions can result in neurological and psychiatric disorders. To address these types of questions, a fundamental step is to understand the underlying circuitry: how neurons are wired.

Huizhong (Whit) Tao’s research goal is to understand the principles underlying connectivity between neurons in the sensory cortex, which provides a structural basis for the information processing functions these nerve cells perform. The functional and anatomical wiring between neurons has mostly been studied in in vitro (e.g. brain slice) preparations. However the link between the revealed connectivity pattern and actual neuronal function is missing because the synaptic inputs observed in vitro are not necessarily driven by sensory stimuli, meaning that the functional connectivity of the studied neuron in the live animal (in vivo) is still unknown.

To overcome these limitations, Tao’s lab developed several innovative approaches over the years to examine functional synaptic inputs to various types of neurons in an intact brain: synaptic inputs that directly contribute to sensory processing of neurons. Her lab was one of a few to first utilize genetic models of the mouse to address the question of neuronal circuitry. Tao’s contributions to the field to date might be summarized by three major highlights:

First, her lab pioneered a system to dissect sensory-evoked synaptic inputs of opposing forces — excitatory and inhibitory — to the same individual neurons. The results suggest that connections between inhibitory and excitatory neurons are much less selective than among excitatory neurons, which in fact makes excitatory neurons perform better in selecting sensory features. These studies by Tao’s lab may help us understand the mechanism behind age-related decline of cognitive functions.

Second, her lab developed a powerful imaging technique that allows selected recordings from a desired cell type in vivo, which is particularly useful for studying inhibitory neurons that are low in number. Tao’s papers describing this technique and findings on unique functional properties of inhibitory neurons have been well cited. It is important to understand the role of inhibitory neurons in neuronal networks as proper dynamics of the network can be maintained only if the excitatory forces are counteracted by effective inhibitory force.

Third, her lab was the first to apply the first two innovative techniques in the developing cortex. The results have revealed circuitry changes underlying normal maturation of cortical function as well as experience-dependent cortical plasticity at an unprecedentedly fine detail. These findings provide insights into how learning and environmental interactions stimulate changes in neural connections in the developing brain.

In her current studies, Tao is applying these state-of-the-art experimental approaches to awake behaving animals. She and her colleagues seek to reveal the impacts of brain or behavioral states on the functioning and dynamics of cortical synaptic circuits.


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More than a dozen researchers and policymakers from across the globe gathered at the Zilkha Neurogenetic Institute (ZNI) on April 4, 2014, to participate in the 1st Annual Zilkha Symposium on Alzheimer Disease & Related Disorders, entitled “Breaking through the Barriers: Neuronal, Glial and Vascular Contributions.” The international conference was organized by ZNI Director Berislav V. Zlokovic, MD, PhD, who holds the Mary Hayley & Selim Zilkha Chair in Alzheimer’s Disease Research at the Keck School of Medicine of USC, along with Rudolph Tanzi, PhD, Joseph P. & Rose F. Kennedy Professor of Neurology at Harvard University, and David M. Holtzman, MD, Andrew B. & Gretchen P. Jones Professor and Chair of Neurology at Washington University in St. Louis. The all-day symposium featured presentations of mostly unpublished work, experiments still underway that are approaching Alzheimer’s disease (AD) from multiple directions. Investigators shared data about the varied roles of different influences on AD: genetic, vascular, inflammation, astrocytes, neurons and new and innovative methods for mapping changes in the brain, using advanced imaging technology employed by Arthur Toga, Paul Thompson and Hong-Wei Dong at the Keck School of Medicine of USC. USC Executive Vice Provost Michael Quick, PhD, offered introductory remarks for the symposium, followed by ZNI friend and benefactor, Selim Zilkha, who provided a reminder to all attendees of the importance of continued scientific collaboration to “arrest and reverse this terrible disease.” Following Mr Zilkha’s remarks, Maria Carillo, PhD, Vice President of medical & scientific relations at the Alzheimer’s Association, announced that Zilkha and Mary Hayley would be honored in July with the 2014 Jerome H. Stone Philanthropy Award for Alzheimer’s Research, an international award honoring the world’s leading philanthropists and their transformational impact on the global Alzheimer’s research field. The award will be presented at the Alzheimer’s Association International Conference in Copenhagen, Denmark. Carillo chaired several sessions at the Zilkha symposium, along with Roderick Corriveau, PhD, program director of extramural research programs at the National Institute for Neurological Disorders & Stroke, and Helena Chui, MD, McCarron Professor & Chair of Neurology and director of the Alzheimer’s Disease Research Center at USC.

A short video about the symposium is available at http://tinyurl.com/Zilkhasymposium2014

Gabrielle Strobel, MS, executive editor of the alzforum.org website — a scientific community dedicated to furthering the research and understanding of Alzheimer’s disease and related neurodegenerative disorders — attended the Zilkha symposium and summarized the cutting-edge developments presented at the event in a comprehensive four-part series published on the site: Part I, the relationship between hypertension and Alzheimer’s disease and dementia; Part II, the importance of studying the blood-brain barrier (BBB) in Alzheimer research; Part III, the controversial method of research via parabiosis (blood-sharing experiments); and Part IV, the indirect way in which sleep and gene regulation affects neurodegeneration. To view the entire series go to http://www.alzforum.org > News > Conference Coverage.