Yueming Li, PhD

Professor and Director of Graduate Program in Pharmacology
Memorial Sloan-Kettering Cancer Center Institute
Weill Cornell Medical Center

After receiving his doctorate in comparative biochemistry from the University of California, Berkeley, and postdoctoral training from Harvard Medical School, Dr. Li spent many years in the Merck Research Laboratories doing important but clinically focused work on neurodegenerative diseases. "At first, I liked that my work had direct clinical applications," said Dr. Li. "I did a lot of research and made a good contribution to drug development."

However, he decided to return to academia because he missed the freedom of performing research that isn't directly tied to drug development. "The advantage of basic research," Dr. Li says, "is that it can move in directions that you never planned on."

He believes he has found the best of both worlds at Memorial Sloan-Kettering Cancer Center, where he and his team can do both basic research and drug development. "I find this translational element to be essential."

Dr. Li made his mark in Alzheimer's disease research with breakthrough studies of γ-secretase, an enzyme that cleaves the amyloid precursor protein into the fragments that form the deadly plaques characteristic of Alzheimer's. When he first started looking at γ-secretase, research was being done at the cellular level. Dr. Li developed the first process for studying γ-secretase in the test tube, where he could break down the biochemistry of the enzyme.

In 2000, his team's work resulted in the publication of a paper in Nature that opened a new era for the investigation of γ-secretase's role in the pathology of Alzheimer's. Their findings provided the first compelling biochemical evidence that γ-secretase activity is triggered by subunits within the γ-secretase complex called presenilin.

In 2010, his lab made another breakthrough in γ-secretase research. His team has reconstituted γ-secretase using bacteria-expressed recombinant proteins and provided the final proof that presenilin is indeed γ-secretase. And it provided a unique platform for further study of the structure and function of γ-secretase at both the molecular and atomic level, which was previously impossible. This work is considered a landmark in the field.

Dr. Li has since turned his attention to how the processing of the amyloid precursor protein can be changed through modulation of γ-secretase activity. "We're focusing on gamma modulation that is specific to the cleavage of the amyloid precursor protein at the 42 site, Notch receptors and other substrates. We want to

know how we can modulate γ-secretase activity without eliminating it. We want to use modulators to retain physiological role and decrease pathological role."

Dr. Li is drawn to research on neurodegenerative diseases because he is passionate about aging-related diseases. "I believe my expertise in chemical biology provides me with an opportunity to make a significant contribution to a field in critical need of breakthrough discoveries."

The MetLife Foundation Award for Medical Research comes at an opportune time. It will support his team's new effort to discover biomarkers for the disease and to examine how γ-secretase's role and activity change with age – a critical Alzheimer's risk factor. "The award supports basic research," he says, "which is about taking the risks necessary to return life-saving rewards. Right now I have a good team in place, and I'm excited about our prospects for doing some important work."

Dr. Li's other honors include the Top Performance Award-Merck Research Laboratory, a "Hot Paper" by The Scientist, and the Zenith-Fellows Award from the Alzheimer's Association.

Lennart Mucke, MD

Director, Gladstone Institute of Neurological Disease
Joseph B. Martin Distinguished Professor of Neuroscience and Professor of Neurology
University of California, San Francisco

For people familiar with the research of the last 25 years, it may seem to be taking scientists a long time to move from the identification of the genetic risk factors associated with Alzheimer's disease to developing pills to hinder or halt its progression. The reason, according to Dr. Mucke, is that the paths from genetic changes to neurological dysfunction are not well understood. "There is no easy answer to this complex problem," he explains. "You need to attack it from many angles. To date research has been dominated by what can be studied under a microscope. But much of the pathological activity can't be seen in fixed brain sections."

Appreciating the complexity of Alzheimer's, Dr. Mucke has pursued a multidisciplinary, highly collaborative approach to investigating both the structural and the functional aspects of the disease. While the microscope remains a vital tool in his research arsenal, Dr. Mucke has used a variety of approaches—including electrophysiological analyses of brain rhythms and synaptic functions, behavioral assays and newly identified molecular biomarkers—to achieve the most complete picture possible of what is going on. As a result, his team has provided fascinating new insights into the mechanisms underlying the cognitive dysfunction associated with Alzheimer's disease. And they have identified novel therapeutic strategies to block these mechanisms.

For example, Dr. Mucke's team showed that the activities of three proteins associated with Alzheimer's—amyloid-beta, apoE4 and tau—can interfere with the communication among brain cells. These proteins' activities disrupt the delicate balance between the triggering and inhibiting of brain cell activities required to maintain healthy brain functions. Of particular importance is the team's discovery that the interactions of these proteins can begin compromising cell network integrity before the development of the classic amyloid plaques and tau tangles that have become synonymous with Alzheimer's. Of particular interest is that amyloid-beta impairs the activity of critical inhibitory cells, which can be viewed as conductors of the large neuronal orchestras they regulate. "Disrupt the conductor," Dr. Mucke says, "and instead of finely tuned music, what comes out is muddled noise. We want to find a way to protect and strengthen the conductor."

Other researchers have noted that brains afflicted with Alzheimer's exhibit hyperactive neuronal activity. Most hypothesized that this excitation of neurons was compensating for cells that had been compromised or killed by the disease. Dr. Mucke's findings suggest that some of this hyperactivation is not compensatory; it is a primary phenomenon resulting from the buildup of amyloid proteins that can precede full-blown Alzheimer's. "The brains of Alzheimer patients appear to be 'trigger happy,'" he notes, "they have a tendency to go into abnormal rhythms. This disruption probably contributes to cognitive impairments. We're trying to find out how it comes about and how to prevent it."

Dr. Mucke's early results led to experiments designed to address whether blocking abnormal network activity could be useful from a therapeutic perspective. Improving neurotransmission by counteracting the disease-causing activities that amyloid proteins and tau do together and blocking their detrimental effects on network activity have proven to be areas of great promise.

Dr. Mucke is deeply appreciative of the impact the MetLife Foundation Award for Medical Research will have on his work. "The timing couldn't be better. Our lab has two papers under review that focus on the role of a very promising cognition-enhancing factor. The award will help us accelerate and intensify our efforts, so we can turn our latest discoveries into potential therapies for this devastating illness. I also hope that the award will help my Institute attract additional support for these exciting studies."

Dr. Mucke was also a 2002 MetLife Foundation Promising Investigator Award winner. Among Dr. Mucke's other awards are the Khalid Iqbal Lifetime Achievement Award and the Zenith Award from the Alzheimer's Association, as well as the Potamkin Prize from the American Academy of Neurology.