Virginia Lee, Ph.D., has been at the center of several critical discoveries in the pathogenesis of neurodegenerative diseases, including ALS. 2006, they found that aggregates in both ALS and frontotemporal dementia (FTD) contained a protein called TDP-43.

“Dr. Lee’s contributions to understanding neurodegenerative diseases have been immense,” according to ALS Association Chief Scientist Lucie Bruijn, Ph.D., who hosted a recent webinar featuring Dr. Lee. Dr. Bruijn noted that Dr. Lee’s work is funded in part by the Jim Koller family and the Greater Philadelphia Chapter of the ALS Association. Dr. Lee is Professor in Alzheimer’s Research at the Perelman School of Medicine at the University of Pittsburgh, in Pennsylvania.

Throughout her career, Dr. Lee said, human tissue samples have been critical to making discoveries about disease. After the proteins involved in aggregates are identified, it is possible to make an animal model based on the gene that makes the protein. But the initial discovery of those proteins requires using tissues from patients, including ALS patients. She expressed her gratitude for the patients and families whose donations of tissue have made these discoveries possible.

Her method for finding an unknown protein begins with isolating the aggregates from brain or spinal cord. “These are insoluble and cannot be degraded, so we use harsh detergents, and get rid of everything but the most insoluble materials,” she said. These are further enriched and purified, and then the isolated protein is injected into a mouse, whose immune system will make antibodies to this foreign protein. These antibodies can be isolated from the mouse, and used as probes in human tissue to label the original protein. This allows her to see the pattern of distribution of the protein.

Other techniques are used to identify the unknown protein, and then if the protein has been described before, she can use that information to begin to understand how it may cause disease. That was the case for TDP-43. “This was new to us,” she said. “We didn't know anything about this protein. We found in the literature that it was an RNA binding protein, and that it seemed to have very broad functions,” including regulating how genes are read in the nucleus, and how that information is translated into proteins. This understanding is the basis for determining how the mutation in the TDP-43 gene causes ALS, work that is ongoing.

The fact that the same protein formed inclusions in both ALS and FTD was highly suggestive that the two diseases were linked in the degenerative process, she said. That link was made even stronger recently with the discovery of the C9ORF72 gene, which causes both diseases.
Using the antibodies to TDP-43, Dr. Lee has shown that aggregates form in spinal cord in ALS patients, and in both brain and spinal cord in ALS and FTD. “The distribution of the pathology correlates with symptoms,” she said. In ALS, they are most concentrated in the motor neurons, while in FTD, they are found especially in the frontal cortex, a part of the brain involved in personality and behavior.

For reasons still unknown, TDP-43 aggregates occur in most cases of ALS, but not those due to SOD1 or FUS mutations. “Why is this so important? If you don't have TDP 43 pathology it is very likely that the mechanism of pathogenesis will be different,” she said. Both mechanisms affect the neuron, but the mechanism itself may be quite different. By determining the mechanism, it may be possible to design a therapy to interrupt the pathogenic process.

“There is a lot to do,” Dr. Lee concluded. “Most importantly, we need to develop mouse and cell models of the disease,” a process that is proceeding now. “We can then test different ways to treat the mouse models with different kinds of therapy.”

“Dr. Lee’s work, and her many successes, really highlights the importance and value of human tissue,” Dr. Bruijn said. “We are very grateful to the families who have provided it.”

You can view the presentation in its entirety at https://alsa.webex.com/alsa/lrd.php?AT=pb&SP=MC&rID=65081547&rKey=ebe86e3be9cf54ce