Since its discovery as an ALS gene in 2009, TDP-43 has become the focus of intense research into the causes of ALS. Mutations in the TDP-43 gene cause the TDP-43 protein to mislocalize in motor neurons, away from the nucleus where it is normally found, and into the cytoplasm (the material surrounding the nucleus), where it aggregates into clumps that can be seen under the microscope.

There is much that is still unknown about TDP-43, beginning with a full understanding of its normal function and including: why it aggregates, whether the aggregates are intrinsically toxic, and whether targeting the aggregated protein may be therapeutic in ALS.

The search for answers to these questions is what drives Leonard Petrucelli, Ph.D., and colleagues in his lab at the Mayo Clinic in Jacksonville, Florida, where he is Chair of Neuroscience. Dr. Petrucelli described his work in a recent webinar sponsored by The ALS Association and hosted by ALS Association Chief Scientist Lucie Bruijn, Ph.D.

TDP-43’s importance to understanding ALS goes far beyond the relatively few ALS cases caused by the mutations. This is because aggregates principally composed of TDP-43 protein occur in most forms of ALS, including sporadic forms, which have no known genetic cause. Whatever is causing the aggregation in these cases may be the clue to unraveling what causes the disease.

“We are trying to determine if TDP-43 mutation causes a toxic gain of function, or a loss of function, or both,” he said. The answer matters greatly, because it will help determine the kinds of therapy that would best counteract the effects. If the protein has taken on a new, toxic, function, then blocking that function may reduce its effect. On the other hand, if the motor neurons are suffering because of a loss of the normal function, then therapies that replace or make up for that lost function may be helpful.

One aspect of TDP-43 that Dr. Petrucelli is exploring is that the mutant form of the protein is chemically altered after it is made, gaining multiple phosphate groups, and being cleaved into fragments.

“We believe the accumulation of these TDP43 fragments inside the cell is not a good thing, and perhaps trying to prevent this might be a therapeutic approach for the disease,” he said.

These fragments can be studied using antibodies, which bind to the fragments and can be visualized using a fluorescent tag that glows under the microscope. The amount of fluorescence serves as a marker for TDP-43 based toxicity. “We believe the best way to understand the disease is with a biomarker,” which may help diagnose the disease and monitor the response to potential new treatments.
A key step in understanding the role of the mislocalization and aggregation of TDP-43 is to develop cell and animal models of the disease, Dr. Petrucelli said. His lab has been instrumental in creating these models, which contain TDP-43 mutations.

Among the models Dr. Petrucelli has developed is a mouse carrying TDP-43 mutations, which he deposited in the ALS disease model library at Jackson Laboratory, so that other researchers can use it. Another model is a roundworm, about the size of a pinhead, whose own genome carries a gene similar to TDP-43. “This increases our confidence that this is a good model to use,” he said.

“Generating such models allow us to screen chemical libraries for compounds that will prevent those clumps of protein from occurring.” That screening process has begun, initially using 58,000 chemical compounds, to determine their effect on aggregation. But Dr. Petrucelli cautioned that while screening is a fairly rapid process, the entire drug development process, ending with a drug that can be tested in the clinic, can take many years.

“The ALS Association has been absolutely instrumental in supporting our research,” he said.

Dr. Bruijn noted that Dr. Petrucelli’s lab, which she recently visited, “is a tremendous cross-section of talent, with some of the top people in pathology and clinical research.” She also noted that his lab, and others in the ALS field, are doing screening at a very high level, meaning that replication of results—a critical step in the early development of potential drugs—can come faster.

To see the webinar, visit: https://alsa.webex.com/alsa/ldr.php?AT=pb&SP=MC&rID=64825307&rKey=640cc14701b0752e