Mutations in the protein SOD1 were the first-discovered genetic cause of ALS, and account for about 20 percent of familial cases. Melvin Reichman, Ph.D., of the Lankenau Institute for Medical Research in Wynnewood, PA, has developed a novel strategy for finding compounds that might mitigate the effects of mutation on the protein. Dr. Reichman, whose work is supported by The ALS Association’s TREAT ALS™ research program, outlined his approach in a recent webinar, sponsored by The Association.

“There are over 150 mutations known in the SOD1 gene, and all of the ones that have been studied have increased the propensity of the protein to aggregate,” he said. Aggregation occurs when the protein misfolds, leading multiple protein molecules to clump together. Exactly how aggregation is linked to disease is still unclear, he noted, but the most common hypothesis is that aggregation increases multiple kinds of oxidative stress within neurons. “SOD1 is one of the most abundant proteins in neurons, and that may be one of the reason that, if it aggregates, it has an effect,” Dr. Reichman said.

Normal SOD1 exists as a dimer, in which two molecules bind together to form an active enzyme. A key step in aggregation is dissociation of this dimer into monomers, or single protein molecules. While this prevents the enzyme from functioning, this loss of enzymatic activity does not seem to be involved in ALS. Instead, dissociation is followed by formation of mismatched dimers (joined in a non-native way), or linking of several monomers together to make oligomers. Both forms then proceed to aggregate into larger clumps.

“If we could find a dimer-stabilizing drug, we might be able to prevent SOD1 from falling apart,” Dr. Reichman said, and thus prevent the entire chain of events that ultimately leads to neuronal cell death. To that end, he has developed a lab assay that measures the dissociation of normal dimers.

The assay uses an enzyme from fireflies, called luciferase, which emits light under the right conditions. In Dr. Reichman’s work, the enzyme is split into two parts, one located on each half of the SOD1 dimer. When the normal dimer is intact, the enzyme works and emits light. When it dissociates, the enzyme comes apart as well, and produces no light. “We are looking for drugs that stabilize the dimer,” and thus allow the production of light in the assay, he said. He has also modified the assay to find drugs that prevent the formation of mismatched dimers.

His early results have turned up such a compound, called 110711, that seems to fit the bill, although much remains to be studied about it, including exactly how it works, and how to improve it to make a better drug candidate. Dr. Reichman noted that a key collaborator in his studies has been Association-funded scientist Dave Borchelt, Ph.D., of the University of Florida.
The second aim of his work is to test combinations of already-approved drugs, “to see if maybe two small molecules can do the trick where one cannot,” Dr. Reichman said. He is currently working through a library of FDA-approved compounds in the split luciferase assay. If such a combination can be found, and if they work at the doses each is already approved for, “we could go from bench right to bedside.”

Whether SOD1 aggregation is also involved in sporadic forms of ALS is controversial, Dr. Reichman said, but if it is, this work could also have therapeutic implications there as well. And aggregation of the protein TDP-43 is common to virtually all ALS, so that compounds that inhibit aggregation generally may have even wider application.

“We are excited to be supporting Dr. Reichman’s research through the TREAT ALS™ program,” commented webinar host Lucie Bruijn, Ph.D., MBA, Chief Scientist for The ALS Association. “This is a very exciting approach to finding therapies, including combination therapies, which may have great promise.”

Further information about Dr. Reichman’s work can be found here:
www.LIMRcgc.org