Fly Disease Models Provide Rapid Insights into Motor Neuron Diseases
Research Webinar: November 25, 2013
Host: ALS Association Chief Scientist Lucie Bruijn, Ph.D.
Guest Speaker: Brian McCabe, Ph.D.

Increasingly, researchers interested in studying human diseases are turning to fruit flies as their model system of choice. Flies are easy to raise and have very short life cycles, meaning results come in fast. Many impressive genetic tools are available for studying flies: the entire genome sequence is known, many of the fly’s genes are well characterized, and manipulating individual genes is straightforward. Their nervous systems are built along similar lines to ours.

Finally, according Brian McCabe, Ph.D., “Three-quarters of all fly genes have a corresponding gene in the human,” allowing meaningful studies to be done of human genes in this diminutive model organism. Dr. McCabe is Assistant professor at Columbia University in the Center for Motor Neuron Biology and spoke in a recent ALS Association webinar on the insights his lab has gained by studying fly models of two motor neuron diseases: ALS and spinal muscular atrophy (SMA).

Dr. McCabe’s work in SMA has provided some important clues about motor neuron degeneration in that disease, which may have implications for ALS. His lab has shown that while it is motor neurons that degenerate (as they do in ALS), the mutant gene that causes the disease appears to be acting elsewhere. SMA is due to loss of a protein called survival motor neuron (SMN). By knocking out the fly version of SMN, and then replacing it in selected cell types but not in others, he has found that the flies require SMN not in motor neurons, but in other neurons called interneurons and cholinergic neurons. When these neurons were able to make SMN, even when it was absent from motor neurons and muscles, the flies were able to move about normally and had normal lifespans.

The affected flies manifested a change in the electrical firing pattern of their motor neurons, and Dr. McCabe searched for a drug to restore the normal pattern in the same way that adding back the gene did. He found that an approved drug for multiple sclerosis called fampridine partially corrected the firing defect. The same firing defect was found in humans with SMA, and a trial is now in progress to see if fampridine can offer any benefit to adults with a mild form of the disease.

“The fly made a prediction of something that would be present in human disease,” Dr. McCabe noted, one of the most important features of any model.

In ALS, there is not one gene, but many, that can cause the disease. Dr. McCabe’s lab is now looking for links among them, to determine if there is a mechanism common to all of them. He has begun by looking at two (TDP-43 and FUS) that share a common function; each binds to the cellular messenger molecule called RNA. He has knocked out the fly form of the FUS gene,
called cabeza, and has shown that putting the normal human FUS gene into the fly can substitute for it.

But when mutant human FUS is put in instead, the flies develop motor deficits and die early. The same pattern occurs with TDP-43, with rescue by the normal, but not mutant, form of the gene.

Next, Dr. McCabe asked whether the two might be working together within the same pathway; a pathway is a series of reactions within a cell. He found that in flies without FUS, extra TDP-43 provided no benefit. But in flies without TDP-43, extra FUS rescued the flies. This pattern has been observed in many previous cases with other gene pairs, and it indicates that the protein that allows the rescue acts later in the pathway than the other protein. Thus, Dr. McCabe concluded, TDP-43 acts early in whatever pathway the two are involved in (“upstream”), and FUS later on (“downstream”). His most recent work suggests a third ALS gene may also act in the same pathway. The exact function of the pathway remains unknown but is the focus of ongoing research in Dr. McCabe’s lab. Determining how these genes all contribute to one pathway may allow him to identify crucial points in it for therapeutic intervention.

“This research provides a clear example of the importance of having multiple models of disease,” said Association Chief Scientist Lucie Bruijn, Ph.D., who hosted the webinar. “The insights we can get from these model systems are incredible.”

Dr. Bruijn noted that while the drug being tried in SMA is not likely to work in ALS since there is no evidence in ALS of the same electrophysiological change. The repurposing of existing drugs is also a key strategy in ALS therapy development. The most recent example, she added, was of a rheumatoid arthritis drug that is being tested in a clinical trial in ALS, based on evidence suggesting a similar immune system mechanism at work in the two diseases.

To view Dr. McCabe’s entire presentation, visit https://alsa.webex.com/alsa/ldr.php?RCID=fc06ff293f26f4108829db75e0eb3a5c9