New Avenues for Drug Discovery Identify New Pathways and Targets in ALS

Research Webinar March 14, 2012
Host: ALS Association Chief Scientist Lucie Bruijn, Ph.D.
Guest Speaker: Steven Finkbeiner, M.D., Ph.D.

Finding drugs to slow or stop the neurodegeneration in ALS is a hard task, according to Steven Finkbeiner, M.D., Ph.D., but new tools and new insights offer a lot of promise. Dr. Finkbeiner, who is Professor of Neurology at the University of California at San Francisco, and Senior Investigator and Associate Director of the Gladstone Institute of Neurological Disease, spoke about the challenges and new opportunities in a webinar sponsored by The ALS Association and hosted by ALS Association Chief Scientist Lucie Bruijn, Ph.D.

Drug discovery for central nervous system diseases like ALS “appears to be harder than that for other conditions,” such as heart disease or even cancer, he said. “This makes partnerships between drug companies and organizations like The Association even more important.”

“Creating those partnerships among all types of researchers and institutions is a key goal for The ALS Association,” Dr. Bruijn said. “It is through those partnerships, and the exchange of ideas and tools they entail, that we think holds the most hope for advances in ALS.”

One reason drug discovery in general is hard, Dr. Finkbeiner said, is that a drug only works if it fits precisely with its target protein. “Drugs are a little bit like keys that target a door lock,” he explained. The drug molecule binds to a protein and influences its function in some way. Not only must the drug fit its target, but it must also avoid fitting other targets. Side effects often arise from a “key” that opens other “locks” besides the one you are hoping to affect, he said.

Another reason for the difficulty may be that the drug discovery process has depended in large part on testing in mice, which have their weaknesses as models of ALS. While they are mammals like humans are on the protein level—the level at which a drug has its effect—many of a mouse’s proteins are subtly different from the same proteins in humans. “Only a few percent of the proteins found in humans are exactly the same in mice. This has led us to think about whether there are other model systems to look at the effects of drugs that would better predict their effects in humans.”

One alternative to mouse models, pioneered by Dr. Finkbeiner, is a system that takes advantage of induced pluripotent stem cells (iPS cells). These cells are derived from human skin, which have been induced to “roll back up the hill” to be more like stem cells, then reprogrammed to become neurons or other cell types. “All the genes are human, which means that when we test drugs, we can have some confidence that if they work in these cells, they should work in humans,” Dr. Finkbeiner said.

The cells are watched over by a robotic arm microscope, which can precisely track individual cells to watch their response to potential treatments. The microscope robot “can work by itself
for 24 hours a day,” allowing the team to “reconstruct the lifetime of an individual neuron. We can, in effect, perform a physical exam on that cell,” he said. Because so much is known about the individual cells in the dish, many fewer cells are needed to test the effect of a drug. Funding from The ALS Association has helped make this work possible in human motor neurons.

“We are really hopeful that a tool like this is going to be helpful for finding treatments for ALS,” Dr. Finkbeiner said. Despite this progress, there is much to be worked out, “so that for the foreseeable future, we are still going to depend on mouse models,” with iPS cells used to discover new drugs or targets or to confirm leads from animal models.

One pathway Dr. Finkbeiner is especially interested in targeting is called the autophagy (aw-TOFF-a-jee) pathway. It is the principle way the cell recycles worn out or defective proteins, organelles, and other cell components. It is also, he said, “the only known pathway to clear aggregates,” the tangle of proteins found in motor neurons in many ALS patients. His drug screening program has identified a molecule that induces autophagy. A computer search for similar molecules led to a group of 30 related compounds, some already approved by the Food and Drug Administration, with similar or even more potent effects. The most promising are now undergoing testing in disease models. “We have had some early success in our TDP-43 model, reducing the risk of cell death. That’s really exciting, because it gives us hope it may be a promising avenue to pursue for therapy,” Dr. Finkbeiner said.

All this progress requires close collaboration between multiple groups, he stressed, from individual academic researchers to foundations to biotech companies to the big pharmaceutical companies. “There is a critical role for The ALS Association to facilitate these partnerships,” Dr. Finkbeiner said.

The Webinar is available at https://alsa.webex.com/cmp0306ld/webcomponents/docshow/docshow.do?isPluginInstalled=yes&siteurl=alsa&rnd=0.08217981797726148.