ALS Research Update

Research Webinar: February 24, 2014
Presented by: ALS Association Chief Scientist Lucie Bruijn, Ph.D.

ALS Research: The Year in Review

By Richard Robinson

“\[quote\]I am very encouraged by the progress in understanding ALS,\[quote\] said Lucie Bruijn, Ph.D., Association Chief Scientist, in a recent webinar that provided an overview of the many advances in ALS research in the past year. “Although we don’t yet have the treatments we want, we are very well positioned to develop them in the near future.”

Among the most promising developments, she said, were findings based on the discovery several years ago of the C9ORF72 gene, the most common gene for ALS. This discovery was the highlight of two solid decades of finding new genes, beginning with the SOD1 gene in 1993.

“That was a game changer for understanding ALS,” she said. The pace of discovery increased dramatically as a result, because it allowed an explosion of experiments in animal models. And every new gene provides another piece of the puzzle and another potential target for therapy development. “Genetics has been invaluable in modeling the disease, especially at its very earliest stages.” Recently, ALS has been modeled in flies, worms, and fish, each offering unique insights.

Dr. Bruijn continued, “Our challenge, of course, is to understand the human disease, and specifically, the sequence of events and the molecules involved in damaging motor neurons. Those targets are what drive drug discovery.”

Drug discovery and development are expensive, with an average of $1.8 billion dollars spent to bring a successful drug to market. Because most drugs fail before they reach the market, those costs put a high premium on learning from every clinical trial, even those with negative results. That means that a trial of a new drug should include a “biomarker,” or molecular signature, to indicate whether the drug reached the intended target and had the desired effect at the molecular level. Development of such biomarkers has been a focus of research funded by The Association.

Biomarkers for diagnosis and disease progression are also needed in ALS, and important progress has been made in developing them. Elevation of a protein called neurofilament heavy chain appears to be associated with the presence of ALS and a more rapid disease course. Work is ongoing to verify and extend these results. Electrical activity of the muscle is also being developed as a clinical biomarker that could accelerate clinical trials.
The Association has also taken the lead in facilitating partnerships among academic labs, biotechnology companies, and large pharmaceutical companies through its TREAT-ALS program. “This is where The ALS Association has been able to play a pivotal role,” Dr. Bruijn said. “Studies that used to be done only in academia are now often done in partnership with larger companies, to accelerate translation of new developments into new treatments.” The Association has also been instrumental in funding clinical trial development, through its partnership with the NEALS clinical trial consortium. “And we also have a community of people with ALS who are very eager to be a part of clinical studies, and that also accelerates discovery.”

Among the successes of the TREAT-ALS program has been the development of antisense oligonucleotide (ASO) therapy, beginning with the most basic research in mice and moving through the first clinical trial of ASOs in any neurologic disease. ASOs bind to the messenger RNA made from a mutant gene, preventing that messenger from making mutant protein. Recently, ASOs combating the mutant SOD1 gene were shown to be safe in people with ALS when delivered to the space around the spinal cord. The approach is also being developed for ALS due to the C9ORF72 gene. This approach has the potential to treat many genetic diseases besides ALS, heightening the interest in it across the neurologic community.

Induced pluripotent stem cells (iPS cells) have become a major focus of ALS research, given their potential to model the disease in a new and powerful way. Skin cells from a person with ALS can be transformed into iPS cells, which can be further transformed into motor neurons to study the disease process in human cells in unprecedented detail.

Stem cells are also being tested as therapy, first in the ongoing NeuralStem trial, whose results will be forthcoming in the near future, and soon in another trial, which will test the therapeutic potential of cells engineered to make growth factors. The hope is that, implanted into the spinal cord, these cells can provide support for remaining motor neurons to keep them alive.

“The many different avenues being pursued for therapy are a testament to the commitment of the scientific community to finding a cure for ALS,” Dr. Bruijn noted. The interest in the entire community, from basic scientists to large pharmaceutical companies, is intense, and The ALS Association is providing vital leadership to fund that research and to coordinate and accelerate those efforts.

In response to questions from webinar participants, Dr. Bruijn said:

--The negative results seen in the Phase 3 dexprimipexole study, following the positive results in the Phase 2 trial, were unfortunate but not surprising in the context of drug development. It is not uncommon to see a small effect in Phase 2 but not in phase 3, because in smaller trials, positive results can happen by chance, rather than due to a true drug effect. This occurs in trials in many diseases and is one of the challenges of testing new drugs.
--There are no good data suggesting that vitamins either harm or help in ALS. Taking a vitamin supplement is reasonable for general health, but no studies support an effect on the disease process.

--Smoking is a risk factor for ALS, but it is not known whether quitting after the disease begins affects the course of the disease. Stopping smoking is nonetheless encouraged for its other health benefits, including on lung performance and blood pressure.

To see the entire presentation visit: https://alsa.webex.com/alsa/ldr.php?RCID=81b247d25788227872935e3605296002.