Research Update Webinar Highlights Progress, New Directions and Unmet Needs

Research Webinar: July 23, 2013
Speaker: ALS Association Chief Scientist Lucie Bruijn, Ph.D.

The ALS Association continues to catalyze vital research into the causes of and cure for ALS, as evidenced by its latest round of grants supporting new projects, new treatment trials and promising young researchers. The state of ALS research was the topic of a webinar featuring Lucie Bruijn, Ph.D., Chief Scientist for the Association. Dr. Bruijn outlined recent progress, new directions and major unmet needs in the quest for new treatments for ALS.

Genes and Models

The discovery of genes for ALS has skyrocketed recently, Dr. Bruijn noted. Almost a decade passed between the discovery of the SOD1 gene in 1993 and the discovery of the next ALS gene. In contrast, in the past decade more than a dozen new genes have been found, including C9orf72, the most common genetic cause of ALS. The new gene discoveries have also brought new researchers into the field, and new genetic models are leading to new fundamental discoveries about ALS. “None of these models are a complete picture of the human disease, but we need them for research,” Dr. Bruijn said. “We also need human tissues and clinical trials. There is a synergy between them.”

“We have learned a lot about ALS in SOD1 mice, despite that SOD1 mutations account for only 2 percent of all ALS. For instance, the SOD1 mouse taught us the importance of the cells that surround and support neurons, called astrocytes.” Drugs tested in animal models of ALS have not been successful in humans, but Dr. Bruijn noted that this may be due more to the low bar used to judge success in the models, rather than a disconnect between animal and human susceptibility to a truly beneficial drug. “We may have overinterpreted effects in mouse models, but it is incorrect to conclude that the mouse model is useless,” she continued.

Partners in Drug Development

The ALS Association has been instrumental in forging partnerships among academic researchers, who often discover new mechanisms of disease; biotech companies, who are among the first to develop new therapies; and larger pharmaceutical companies with the resources to conduct large clinical trials. The recent development of antisense oligonucleotides (ASOs) against SOD1 mutations is a good example. The Association heavily funded “a novel and risky study” by Don Cleveland, Ph.D., to test whether ASOs could bind to the messenger from the mutant gene before it could make protein. Success in an animal model led to the first clinical trial of ASO therapy for any neurologic disease. That trial showed that anti-SOD1 therapy was safe when delivered into the space surrounding the spinal cord. Isis Pharmaceuticals, the biotech company that developed the treatment, is now modifying the ASOs to improve availability.

"We are confident that in the next year or so, there will be a new clinical trial in SOD1 ALS," Dr. Bruijn said. The same approach has potential to treat the mutation in C9orf72 patients, she noted, and preclinical work on that is currently being funded by The Association. Early results indicate that the treatment is safe in rodents, and can lower the amount of the toxic messenger RNA from the mutant gene. "RNA toxicity is a whole new biology that is coming into view in ALS," she said.

Cell therapies are also being developed. The recent announcement of positive results in NeuralStem's safety trial indicates that transplanting neural stem cells into the spinal cord is safe in ALS patients. That trial is now progressing to look for signs of efficacy. At the same time, Clive Svendsen, Ph.D., is developing cells that have been engineered to release a growth factor called GDNF, which nourishes motor neurons. Work is underway to scale up cell production, and his group plans to file an application with the Food and Drug Administration for permission to begin a clinical trial, possibly as early as next year. "It's very important to have multiple approaches going on," Dr. Bruijn said, "because each is so new and unproven. We are looking forward to further results from all these trials."

The Association's new grants will also continue support for the TREAT ALS/NEALS clinical trials network, a partnership between The Association and the Northeast ALS Consortium of clinical researchers. The network has expanded greatly in recent years and is now seen as a model for a similar trials network in Europe. ALS Association funding will support ongoing projects to strengthen trials in multiple ways and new projects to create a database for safely sharing trial data among researchers to catalyze new understanding of patient response to treatment. Funding will also support the Clinical Research Learning Institute for ALS patients and the Clinical Trial Expert Line, which makes available a full-time staff member to answer questions and help people navigate through clinical trials information. Help is available by telephone at 877-458-0631 during regular business hours, Eastern Standard Time, or by email at alstrials@partners.org .

More information on ongoing and new trials can be found at www.clinicaltrials.gov , and on this website at http://www.alsa.org/research/about-als-research/clinical-trials.html

The Need for Biomarkers

Trials will be aided by biomarkers, measurable indicators of disease progression or response to therapy. "This is an urgent, largely unmet need in ALS," Dr. Bruijn said. "A biomarker tells us if the drug is getting to where it is supposed to go and is it having the effect we want." Several important research meetings were held this year, co-sponsored by The ALS Association, in which biomarkers emerged as a unanimous priority among scientists, industry representatives, and funding agencies. The Association is funding a wide range of research in the hunt for biomarkers, including work to develop neuroimaging biomarkers, markers in the blood and cerebrospinal fluid, and others. "Donating tissue to these studies is highly important," Dr. Bruijn noted. The search for biomarkers also will be conducted in iPS cells (induced pluripotent stem cells) derived from ALS patients. iPS cells are becoming a key model for studying ALS, since they are genetically identical to the person with ALS who donated them.

In response to a question at the end of the webinar, Dr. Bruijn noted that progress in developing disease-altering treatments in most neurologic diseases has been slow. An important exception is multiple sclerosis, which has seen an explosion of new treatments over the past decade. This is, in part, attributable to the development of biomarkers, since they have allowed researchers to quickly evaluate the effect of a potential treatment in human patients.

To listen to the entire webinar given by Dr. Bruijn, visit alsa.webex.com.