This was a very busy year for ALS research, said ALS Association Chief Scientist Lucie Bruijn, Ph.D., during a webinar surveying the accomplishments of 2013. Building on recently discovered genes, scientists built new disease models to learn more about how these genes cause disease. The first results from those models began to come in, leading to new insights about disease pathways and new ideas for therapy development.

Equally important, advances in the search for ALS biomarkers to monitor disease progression were made this year, offering the hope that clinical researchers will have a powerful tool for rapidly testing response to experimental therapies and accelerating the search for new treatments.

There was disappointing news as well, as the Phase III trial of dexpramipexole was stopped for lack of efficacy. More details of the trial will be emerging later this year. “We were all hopeful,” Dr. Bruijn said. “Although this is disappointing, Biogen [the drug manufacturer] is very committed” to trials in ALS. Both the company and The Association “feel many different approaches at the same time are crucial to find effective treatments.”

**Genes and Model Systems**

Disease-causing genes in ALS offer important insights for two major reasons: they can lead directly to identifying a disease mechanism, and they allow researchers to build a cell or animal model to study the disease further. Together, these may offer clues about sporadic (non-familial) forms of the disease, as well as those caused by the gene under investigation.

“We can build model systems with human cells, mice, yeast, flies, and worms. All of these are incredibly important,” Dr. Bruijn said. The discovery of the C9orf72 gene, which accounts for about 40% of all familial ALS and up to 6% of sporadic ALS, has led multiple groups to begin development of models based on this gene with ALS Association support. “These groups are making significant progress,” she said, with each group beginning to characterize the animals to see how they manifest the effects of the gene mutation.

**Biomarkers**

Several years ago, The ALS Association formed a partnership with leading researchers and biotech companies in the field of biomarker discovery to accelerate the search for markers of ALS. Those efforts have begun to pay off in important ways, Dr. Bruijn reported, with the discovery of a protein in the cerebrospinal fluid (CSF) that is elevated in ALS, called neurofilament heavy chain (NFH). Further work is underway to better characterize this protein and how it changes in ALS, but it is already clear that the level of NFH is higher in ALS patients than in healthy controls; it is also higher in ALS patients than in Alzheimer’s disease patients—
an important indication of sensitivity to the ALS disease process. The goal is to have a biomarker that will change as the disease process changes, so that any effect of a disease-modifying drug can be seen rapidly in a clinical trial.

An important aspect of biomarker development is to make sure samples are taken the same way in each research center. “It was critical to set standards for sample collection,” Dr. Bruijn emphasized, and part of The Association’s funding went to developing and disseminating those standards. “This has formed the basis for many other studies looking for biomarkers.”

The Association has also supported development of a biomarker measured with Positron Emission Tomography (PET) scanning, a type of neuroimaging procedure. The technique measures the level of the glutamate transporter in the brain. Lower levels of this transporter may elevate brain glutamate, a change that may put motor neurons at risk. Ceftriaxone, a drug given to increase the level of the transporter, was tried unsuccessfully in ALS, but without the imaging marker, it was not possible to determine whether the drug actually increased the transporter. “We didn’t know in that trial whether we were hitting the target. Now we can,” Dr. Bruijn said.

Other biomarkers in development include looking at aspects of the immune system and the structure of the spinal cord.

**Stem Cells**

“Stem cells remain a high-priority area,” Dr. Bruijn said. “We are supporting the NeuralStem trial,” which is now expanding to second site. “We know it is safe, and now we hope to increase the numbers of patients to see if has a beneficial effect.” Stem cell therapy continues to be a promising, but unproven treatment for ALS and should remain within carefully monitored clinical trials, Dr. Bruijn stressed.

The Association is also supporting development of induced pluripotent stem cells (iPS cells), which are derived from patient tissue and used especially to study the disease process and screen new treatments.

**Other Initiatives**

Several other important initiatives are ongoing this year:

--Researchers supported by The Association are examining strategies to enhance the connection between motor neurons and muscle.

--Antisense therapies are being developed to target the C9ORF72 gene.

--Novel immunotherapy approaches are being studied, as a result of the improvement seen in one patient during the NeuralStem trial. All patients receiving stem cell transplants are also on an immunosuppression regimen. It was unclear that the improvement that was seen in the one patient after the transplant was due to the stem cells and a possible explanation for the improvement was the immunosuppression regimen.

--The Association is supporting research by the biotech firm PhytoPharm to explore compounds that increase the levels of two nerve growth factors.
Clinicians are studying whether the drug Nuedexta may benefit speech and swallowing, in addition to its approved role in reducing involuntary outbursts of crying or laughing.

The Association is partnering with the Muscular Dystrophy Association to further study diaphragm pacing for improving survival in ALS.

Through The Association’s Clinical Management Program, physicians are expanding opportunities to bring high-quality ALS management to patients in remote areas, through telemedicine.

Dr. Bruijn stressed the value of enrolling in clinical trials for all ALS patients. Details about what trials are available can be found (http://www.alsconsortium.org/browse.php)?

Dr. Bruijn encouraged people with ALS to enroll in the National ALS Registry by visiting: http://www.als.org/als-care/als-registry/registry-enrollment-instructions.html or other national registries, which accept biological samples (such as blood and tissue) and record information on a patient’s clinical and environmental exposure history.

Another useful link addressing some of the questions during the webinar is http://www.alsuntangled.com/completed.html