“Our research program is global,” said ALS Association Chief Scientist Lucie Bruijn, Ph.D., M.B.A., in a recent webinar in which she provided an up-to-date overview of The Association’s multi-faceted research program.

The program funds projects in six key areas, all with an ultimate goal of translating findings to new treatments for ALS. “We fund partnerships between academia and industry, and we support and encourage large consortia of research centers, to create teams for speeding new discoveries.”

Dr. Bruijn outlined recent advances in each key area:

1. Genetics
Five to 10 percent of ALS is familial, likely indicating a genetic origin, and many cases of sporadic disease may also be due to genes. Genetic models of ALS are crucial for understanding disease mechanisms and testing new treatments as well. “We have seen an incredible increase in the number of genes in the last five years,” Dr. Bruijn said, most significantly the C9orf72 gene. However, she noted, most ALS geneticists agree that there is likely another gene of that magnitude waiting to be discovered. But even less common genes contribute to understanding disease pathways. “Once we have a pathway, we have a target for therapy.”

Two new discoveries illustrate that point: Matrin-3, a rare cause of ALS, encodes a protein that binds to RNA and DNA. This further strengthens that case, that RNA handling is an important cause of ALS, as suggested by both the TDP-43 and C9orf72 genes. TREM2 is a risk factor gene, increasing the likelihood of developing ALS. It is involved in activating immune cells of the brain, called microglia, highlighting the importance of so-called neuroinflammation in accelerating ALS.

There is also much more to learn about known ALS genes. An unanswered question for the C9orf72 gene is whether repeat length is related to disease severity or progression. If so, the repeat length could be used to help understand disease prognosis.

2. Modeling and Mechanisms
“Modeling ALS in simple systems helps us identify risk factors and disease mechanisms,” Dr. Bruijn said. Models include rodents, fruit flies, nematode worms, and cells. “The challenge for
all diseases, not just ALS, is that models are imperfect. That’s why we need to combine results from each,” and use caution in interpreting therapeutic results. The newest model is a canine. Certain dogs bear a mutation in the SOD1 gene, similar to that in humans, which causes an age-related motor neuron disease. The larger size and greater complexity of the nervous system means that results of an experimental therapy in the dog model are likely to be a better predictor of results in humans.

3. Therapy Development
The Association continues to provide critical support for development of new therapies. Dr. Bruijn noted that delivery of antisense therapy to the central nervous system, first tried in people with ALS, has been successfully tested in another motor neuron disease, spinal muscular atrophy. Antisense is now also being actively developed against the C9orf72 gene. The biotechnology company Isis, who developed the antisense molecules used in these trials, is now partnering with Biogen, a much larger company with the resources to push this therapy quickly forward. “Within the next year or so, we hope to see a clinical trial,” Dr. Bruijn said.

There is also a renewed interest in gene therapy, delivering therapeutic genes directly to ailing cells. While older gene delivery systems relied on viruses that proved potentially harmful, newer approaches use a benign vector called adeno-associated virus. Specific types of AAV can efficiently reach cells throughout the central nervous system, suggesting a promising method for delivering a therapeutic gene, such as a growth factor.

Work is also going forward on other treatment strategies, including boosting a cell protein handling process called autophagy, to prevent build-up of potentially toxic proteins such as TDP-43 and SOD1.

4. Stem Cells
Stem cells as therapy are being tried in two different ways. Injection of neural stem cells was shown to be safe in the recently completed Neuralstem trial. A follow-up trial in more people with ALS, looking for evidence of effect on progression, is now underway at three centers in Atlanta, Georgia; Boston, Massachusetts and Ann Arbor, Michigan. Enrollment is limited to those closest to the centers.

A new trial of stem cells genetically modified to carry a growth factor is being developed at Cedars-Sinai Medical Center in Los Angeles. The trial is likely to start early in 2015.

Stem cells are also critically important in research, since they can be developed from individual people with ALS, and studied for differences and similarities between individuals. They also provide an unlimited supply of cells that can be turned into motor neurons to understand better why they die in the disease.

5 and 6. Biomarkers and Clinical Studies
The ALS Association has supported the TREAT ALS/NEALS clinical trial network since 2008. The network is a highly trained group of ALS clinical researchers, whose aim is to quickly conduct
trials of the highest quality. The network offers people with ALS personal guidance regarding eligibility and access to trials, or any other questions regarding clinical trials. For information, contact them at alstrials@partners.org or 877-458-0631.

“There is an urgent need for biomarkers,” Dr. Bruijn stressed, to facilitate clinical trials in multiple ways. These objective measures are of several types. A diagnostic biomarker would reduce the time from first symptoms to definitive diagnosis, often a long and difficult process for people with ALS and their families. Biomarkers for different types of ALS, especially slow versus fast progression, would aid in stratifying clinical trials, allowing a treatment’s therapeutic “signal” to emerge more readily from the “noise” of monthly fluctuations in function so common in people with ALS. And pharmacodynamic markers are vital to tell researchers whether a drug has reached the intended target within the nervous system and within the target cell.

Recent progress on each of these types of biomarkers has been encouraging. The ratio of certain proteins, called neurofilaments and complement C3, is elevated in ALS. Tests for this ratio are currently being developed and standardized to use in clinical trials, and eventually perhaps for diagnosis. Changes in immune cells in the blood related to disease progression show promise as a marker of immune system involvement, which may relate to progression. Several neuroimaging markers are being developed to track disease progression and response to therapy. An exciting avenue is the search for a neuroimaging marker, ligand, that will bind to the TDP-43 protein. This protein accumulates in most people with ALS, and may contribute to the disease. By imaging it over time, it may be possible to understand better how the disease spreads, and whether it declines in response to therapy.

To view the webinar, follow this link: https://alsa.webex.com/alsa/ldr.php?RCID=d89175dc4db09a00b0386b8f283c42fd