Antisense therapy for the most common genetic form of ALS is in rapid development, thanks in large part to work spearheaded by Don Cleveland, Ph.D., Professor of Medicine at the University of California at San Diego. Dr. Cleveland discussed the progress in this therapeutic field in a recent webinar.

“Dr. Cleveland is truly a leader in the ALS field,” noted webinar host Lucie Bruijn, Ph.D., M.B.A., Chief Scientist for The ALS Association. “His work has been pivotal in bringing treatment options to the clinic.”

“The last 40 months has been the most exciting time in the history of ALS,” Dr. Cleveland said, with new gene discoveries and very rapid development of new therapies. The outpouring of support for ALS research during the Ice Bucket Challenge was in part a reflection of that excitement. “I want give a big ‘thank you’ to all who were involved in the challenge.”

“One of the key steps in devising therapies was the realization that about 10% of ALS is inherited,” Dr. Cleveland said. While the genetic cause of many familial cases of ALS remains unknown, two genes—SOD1 and C9orf72—cause the majority of familial ALS, and so these have been the first targets for antisense therapy.

Of critical importance was the recognition that the mutation caused disease not because a normal function was lost, but because the protein made by the mutated gene took on a new, toxic function. Dr. Cleveland noted that it was, in fact, Dr. Bruijn who demonstrated this for SOD1 in the mid-1990s.

This feature of the mutation means that silencing the mutant gene should provide effective therapy for the disease. This is the goal of antisense therapy. Dr. Cleveland’s work has been instrumental in showing that in order to be effective, gene silencing must occur not only in motor neurons, the cells that die in ALS, but also in supporting cells called astrocytes and microglia, which drive the neurodegenerative process once it begins. “Targeting these cells can sharply delay disease progression,” he said, based on results in animal models.

Antisense therapy works by targeting the RNA “messenger,” a working copy of the gene that is used to make the corresponding protein. By destroying that messenger, the toxic protein cannot be made. The antisense molecule is a short piece of a DNA-like molecule that matches
the sequence of the RNA messenger. When the two bind together, a cellular enzyme attaches to them, destroying the RNA, while leaving the antisense molecule to seek out and bind to another matching RNA.

Antisense molecules must be delivered directly to the central nervous system. Delivery of antisense molecules against mutant SOD1 was shown in a recent clinical trial to be safe in people with ALS, setting the stage for a larger trial of efficacy.

While that trial was going on, the C9orf72 gene mutation was discovered. This mutation also causes a toxic gain of function, although whether the toxic entity is the messenger RNA itself, or unusual proteins created from it, is not yet clear. Nonetheless, reducing the amount of messenger RNA is likely to be therapeutic in people with ALS, based on promising results from lab experiments.

A clinical trial of antisense therapy against the C9orf72 mutation is expected to get underway by the end of the summer of 2015, Dr. Cleveland said. He noted the extraordinary pace of development of this therapy compared to most drug development. The gene was discovered in 2011, a successful proof-of-principle experiment was conducted within one year, and results from the trial should be available in late 2016.

“We are guardedly optimistic,” he said, recognizing that much still needs to be learned about the safety, tolerability, and efficacy of this experimental therapy.

Dr. Cleveland also noted that another therapeutic approach to antisense delivery is also being developed. In this approach, the gene for the antisense molecule is delivered using a harmless virus, called AAV. Animal experiments show that the gene is spread widely throughout the central nervous system when injected into the lower spinal cord, and it can lower the amount of mutant SOD1 protein. He anticipates clinical trials of this method within three years.

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