Reasons for Hope in ALS Research with the Discovery of NU-9

In a study funded in part by The ALS Association's TREAT ALS program, researchers from Northwestern University have identified the first compound (NU-9) that eliminates the ongoing degeneration of diseased upper motor neurons, a key contributor to ALS. While this news is exciting, this study has only tested the compound in mice and in laboratory neurons and is in the very early stages. Researchers must now determine if this particular compound can be further developed for humans and would need to do additional chemistry to optimize the compound. In addition, assessments are needed to determine whether this compound can get into the brain and spinal cord at appreciable levels, engage with its target and if it is safe and tolerable. Although still early in its development, we are encouraged by the addition of another therapeutic intervention in the ALS drug discovery pipeline and are happy that our funding was able to seed this line of research work.

In a recent Connecting ALS podcast, Dr. Kuldip Dave, vice president of research for The ALS Association, talked about these new findings and the hope they bring to the ALS community and global research collaboration. A portion of that conversation has been edited and condensed below.

ALS research has been making headlines since we turned the calendar into 2021. And one of the more exciting developments is related to a paper published in Clinical and Translational Medicine, describing how researchers at Northwestern reported that they identified a compound that eliminated degeneration of motor neurons that are connected to the development of ALS. What have you heard about this development and what can you tell us about research into the compound known as NU-9?

We're very excited to see these findings published. Let's first talk about the project itself before we talk about NU-9. The ALS association supported Dr. Ozdinler and her team at Northwestern University a few years ago through the funds raised during the Ice Bucket Challenge. And the goal of the project was to find out the protein landscape of healthy and vulnerable, motor neurons in two different stages of the disease. So, what do I mean by that? We know that in ALS we have neurons, which are brain cells that are sick and dying, and we have neurons that are fine and healthy. And we know that those are unhealthy sick neurons, things start to dysfunction. And Dr. Ozdinler wanted to see what proteins are changing in neurons that are sick versus neurons that are fine and healthy.

In other words, can changes in protein landscape lead to neurons being more vulnerable to cell death. And why is this important? Because if we can find those proteins that are specific to unhealthy neurons, then those can serve as markers to tell us something bad is going on, or they can serve to identify new therapeutic targets for us. For example, if we know certain protein is dysfunctional, then we can make drugs against that cookie.

The other reason why Dr. Ozdinler's work that you mentioned, that was published in Clinical and Translational Medicine, why it is so relevant is that it was focusing on upper motor neurons. So, what are upper motor neurons? These neurons take signals from the brain and transmit them to the spinal cord so that movement can happen. So, they're very, very important in ALS.

And we know that these upper motor neurons get sick, degenerate and die in ALS. So this was the rationale for our funding a few years back for this study, and the results of that funding was that her team found that there were certain proteins and protein function that was changed in two very specific cellular structures: the mitochondria, which is the energy producer of our cells; and this other cellular structure called ER

or endoplasmic reticulum. I know that's a big, big word, which is involved in making new proteins and folding them the right way.

So how did they, how did they find this drug? Researchers at Northwestern University screened and tested over 50,000 compounds. And then they did multiple rounds of optimizing the chemistry, and that's how they got this compound, NU-9. Now, remember I told you that they found protein changes in upper motor neurons in two different areas, mitochondria and the ER? They tested this compound, NU-9, in cells and in animals and found that the drug improved the structural integrity of those two structures, the mitochondria and ER. The drug kind of stabilized cell death, and in fact – and this was really significant – reversed some of the pathology, the bad stuff that was going on, essentially making sick neurons healthy again. And in mice, it also improved motor function. So, this is really very, very exciting.

Where are we now in terms of what we know about NU-9? What are the next steps between today and having something that is marketable and available for people with ALS?

Hope is a big thing in ALS. When we see good data, positive results like this, there is certainly going to be a lot of excitement, but there are a couple of things we should keep in mind here in terms of the timeline. This research was conducted on mouse models, and there are a few steps that still need to happen. These are early results. They already have a lot of information collected on the drug: where it acts, whether it enters the brain, how long does it stay in the brain, these are the things we call PK or pharmacokinetics of the drug. It's great that they have this information.

Now they need to make sure that the chemistry of the compound is such that it can be given to humans. They would also need to make sure that the drug is safe and tolerable, and generally that is done in two different species of animals. And once they have that data, they can then submit a package to the FDA to ask to do a clinical trial. And

when the FDA looks at the data package and grants them a go ahead, that is when they can start to test the treatment in humans for safety and efficacy.

To listen to the entire interview with Dr. Dave, "Finding Hope on the Horizon Through ALS Research…" on Connecting ALS, visit ConnectingALS.org HERE.