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Neuroscience 2009 Recap - Wednesday October 21st

10/22/2009

Steven Perrin and Fernando Vieira Present Three Efficacy Reports to Society for

Neuroscience

This morning, Dr. Steven Perrin and Dr. Fernando G. Vieira of the ALS Therapy Development Institute presented data on several recently completed efficacy studies at the Institute. Dr. Perrin's much anticipated talk led the audience through the entire process used to identify, choose and test ALS TDI 00846. Over the past two years, ALS TDI has developed the world's largest gene expression database for ALS. This database includes billions of data points and therefore the Institute set out to organize and prioritize these genes into pathways of interest. Dr. Perrin showed how the Institute used a highly sophisticated series of mathematical equations and interactome networks to accomplish this task. This work led to the identification of 5 pathways containing 95 genes. With this information in hand, ALS TDI was able to identify the molecule known as ALS TDI 00846 and set out to test it for efficacy. ALS TDI 00846 is a protein biologic that blocks a key receptor on the surface of T cells known as CD40L, a key component in the co-stimulatory pathway. The Institute's sole mission is to identify and develop therapeutics to slow and stop disease. This specific route to intervening in the activation of the humoral immune system was chosen, according to Dr. Perrin, because of the precedent in the literature and depth of preclinical work done to block this specific receptor, which would make it likely to have a quicker timeline of development toward the clinic. In summing up the extensive work done on this pathway and molecule at the Institute, Dr. Perrin presented data from efficacy studies that showed ALS TDI 00846 showed statistically significance in all three of the endpoints used to determine efficacy in the SOD1 G93A mouse. The molecule led to an improvement in body weight retention, delayed progression of disease and showed an overall extension of survival in the preclinical studies. Dr. Perrin presented data that clearly linked these results to the administration of ALS TDI 00846. Steve concluded his talk with a dramatic comparison of this result to all other efficacy studies conducted at ALS TDI since its inception. He received several follow-up questions that focused on the enormous data set used to identify this molecule and the reasons that the Institute determined to focus on such pathways with higher statistical significance than others.

Shortly after Dr. Perrin's talk, Dr. Vieira gave two separate discussions on additional efficacy studies undertaken at ALS TDI, first on lithium and then apocynin. To begin his presentation of the lithium studies, Dr. Vieira provided a concise argument for the appropriate use of the SOD1 mouse in preclinical testing by reviewing the potential "confounding variables" which may lead to false positive or false negative results. He suggested that perhaps the most important of these was the need to confirm the actual genetic make-up of the mouse before enrolling it into a treatment or control group. The animals used at ALS TDI are based on a specific genetic form of ALS caused by the over expression of a specific gene; SOD1. Confirming that every subject in the preclinical study has the mutation, and the same number of copies of the mutation of the gene, directly impacts the potential for accurate results across study groups. According to Dr. Vieira, the Institute conducts two counts of this gene – a process known as genotyping – once before the subject is assigned to a group and again afterwards. Statistical calculations are used to account for any loss in copy number which protects the integrity of results. Other variables discussed included the need to consider the importance of gender differences as well as match siblings across study groups. Vieira also briefly described the appropriate number of animals that needed to be used in order to accomplish statistical relevance in results. ALS TDI has conducted more preclinical studies using the SOD1 mouse than all other labs combined and its study design (Scott, et. al 2008) is used broadly by other laboratories throughout the world today.

An Italian group of researchers reported efficacy in treating ALS with lithium. This report (Fornai, et. al, 2008) was published in a major scientific journal. What made this result remarkable as compared to others was that the authors reported benefit in a small clinical trial as well. ALS TDI launched an

identical preclinical study within 6 months of the published findings in an effort quickly reproduce promising preclinical studies on behalf of patients today. Dr. Vieira explained for the audience that the Institute spoke directly with the Italian group and designed an efficacy study based on the exact design performed in the original preclinical study in Europe. However, in the Institute's hands, lithium did not show a positive influence on any of the three end points used to measure efficacy of a potential therapeutic. Furthermore, the results from this retest suggested that chronic lithium dosing may have exasperated disease in the male cohort. This work was published in the NIH's open access journal PLos One (Gill, et.al, 2009).

In 2008, a group of researchers at the University of Iowa (Paulson, et. al, 2008) reported a significant extension of life in SOD1 mice treated with the small molecule apocynin. Dr. Vieira explained that ALS TDI initiated an efficacy shortly after this report and following discussions with the Iowa research team. The major difference between the two studies conducted was the age at which the treatment was given. Dr. Vieira explained that in the Midwestern study the mice were treated with apocynin while they were only a couple weeks old and had not yet been weaned from their mother whereas in the ALS TDI retest the animals received their first dose of the drug approximately 2.5 weeks later. There were several reasons given for the difference in the timing of enrollment which ranged from the logistical to the practical to the developmental. In the end, the apocynin retest showed mixed results, with no statistical relevance shown for body weight, neurological score (used to measure disease progression) or survival. However, Fernando did present data which showed the slight inkling that apocynin had a marginally statistically significant effect in males, but he explained that the data overall did not support additional screening or other evaluation at ALS TDI.

In all, five talks were given by ALS TDI scientists during Neuroscience 2009. More than 30,000 neurologists, biologists and other scientists participated in the weeklong conference. In addition to hundreds of talks, the meeting included thousands of poster presentations and several keynote lectures and workshops. In December of this year, Dr. Steve Perrin will participate in Partnering for Cures, a summit organized by FasterCures, an association designed to connect innovative research programs like ALS TDI will pharmaceutical and biotechnology partners. Dr. Perrin has been selected to provide a high level presentation during that meeting to several major Pharma and biotech partners outlining the Institute's unique and diverse drug development pipeline. Immediately following that meeting, Dr. Perrin will meet Dr. Lincecum and Dr. John McCarty in Berlin Germany for the proceedings of the International Alliance of MND/ALS Associations followed by the International MND/ALS Research Symposium. This symposium is the largest research event devoted entirely to the discussion of ALS in the world. ALS TDI scientists will participate in every aspect of the conference, including giving several talks and several poster presentations.

For more information on the Society for Neuroscience, visit www.sfn.org

For more information on FasterCures, visit www.fastercures.org

For more information on the International Alliance, visit www.alsmndalliance.org

For more information on the MND/ALS Research Symposium, visit www.alsmndalliance.org/meetings