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Miller School Studies Pave the Way for the First Pre-Symptomatic ALS Trial for Individuals with SOD1 Genetic Mutation

For more than a decade, investigators at the University of Miami Miller School of Medicine have been studying the earliest signs of amyotrophic lateral sclerosis (ALS). Now, armed with biomarkers and findings from their *Pre-Symptomatic Familial ALS (Pre-fALS)* study, these researchers are collaborating with Biogen to design a clinical trial that aims to evaluate whether the investigational drug tofersen can delay onset or slow progression of ALS when initiated in pre-symptomatic SOD1 mutation carriers.

“The overarching goal of the ALS Research Program at the University of Miami is to advance therapy development for people with ALS,” said Michael Benatar, M.D., Ph.D., professor of neurology, the Walter Bradley Chair in ALS Research, and executive director of the ALS Center at the University of Miami. ALS, which is also known as Lou Gehrig’s disease, is a rapidly progressive, fatal neurological disease that attacks the nerve cells responsible for controlling voluntary muscles.

Dr. Michael Benatar

A major challenge in ALS therapy development is that diagnosis

is often delayed, and treatment typically begins at a later stage of the disease. Overcoming this challenge was the impetus for *Pre-fALS*, led by Dr. Benatar and Joanne Wuu, Sc.M., research associate professor of neurology at the University of Miami and associate director of research at the ALS Center.

Pre-fALS is a longitudinal natural history and biomarker study of unaffected carriers of a wide variety of gene mutations known to cause ALS. According to Dr. Benatar and Wuu, these individuals, who are family members of patients with genetic forms of ALS, have an elevated *risk* for developing the disease, and are the only population in whom it is feasible to study ALS before symptoms begin.

“Our goal, when initiating *Pre-fALS* in 2007, was to lay the foundation to someday delay the onset of ALS, or perhaps even prevent disease,” said Dr. Benatar. “We have made remarkable progress since then. And it is incredibly exciting to have reached the important milestone of gearing up for the first-ever interventional trial in pre-symptomatic ALS.”

Since ALS symptoms can begin at any age, a critical obstacle to pre-symptomatic intervention has been the inability to predict which individuals carrying gene mutations will develop disease and when that will occur. The game changer came in 2017 when the UM researchers and their collaborators discovered that, in individuals with mutations in the SOD1 gene that lead to the most aggressive forms of ALS, neurofilament levels rise in the six to 12 months prior to emergence of clinical disease.

“The neurofilament discovery was pivotal because we may now be able to use the increase in blood neurofilament levels to

identify individuals with these gene mutations who are at the greatest short-term risk of developing ALS, and enroll them in a pre-symptomatic trial," said Dr. Benatar.

Dr. Benatar then reached out to Biogen, which, together with Ionis Pharmaceuticals, has been at the forefront of studying antisense oligonucleotides (ASOs) as potential treatment options for ALS patients with specific genetic forms of disease. Tofersen, an investigational ASO designed to target SOD1 mRNA, is currently being tested in SOD1 ALS patients in a phase 3 clinical trial.

Now Dr. Benatar is excited to be working with Biogen on the first interventional trial in pre-symptomatic carriers of an SOD1 mutation associated with rapidly progressive disease in which study treatment will be initiated once neurofilament levels become elevated.

"Additional details will be made available in advance of study initiation, which is expected to occur in 2021," said Dr. Benatar. "This trial for pre-symptomatic SOD1 mutation carriers will hopefully illuminate a path towards early intervention for other forms of ALS as well."