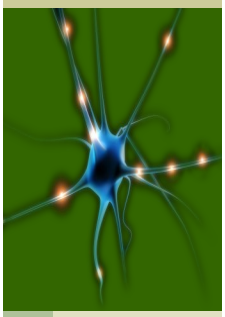
Winter, 2016



WASHINGTON UNIVERSITY DEPARTMENT OF NEUROLOGY

ALS Research Update

C9 Natural History Study

Dr. Timothy Miller is currently conducting a C9ORF72 Natural History Study, which will help researchers analyze the natural progression of C9ORF72-related ALS. This study will establish an extremely important historical control population that will be used to design and assess the effectiveness of C9ORF72-targeted therapies in future clinical trials.

The C9ORF72 gene in humans contains repeating units of 6 DNA bases, called hexanucleotide expansions, or simply "C9ORF72 repeats". Normal human adults typically have 2 to 35 C9ORF72 repeats, but it was recently discovered that 30% of inherited ALS and 5-10% of non-inherited ALS cases are caused by an abnormally large amount of over 50 C9ORF72 repeats. Researchers have been unable to determine how the large number of C9ORF72 repeats causes ALS, but recent data suggests that lowering the amount of C9ORF72 may be an effective therapy for ALS patients with C9ORF72 repeats.

Dr. Timothy Miller received a NeuroBank Award at the recent NEALS conference for innovative contributions by his clinical research team. He is pictured here with team members Jennifer Jockel-Balsarotti, Caroline Drain and Ted Hyman.

One therapy that could accomplish this goal involves antisense oligonucleotides (ASOs), which are DNA-like chemicals that lower the abnormally large amount of C9ORF72 to successfully treat ALS. Dr. Miller has tremendous experience with ASOs and previously developed a therapy for another form of ALS using these chemicals. Before this type of therapy can be implemented to treat C9ORF72-related ALS, however, we need to understand how the large number of C9ORF72 repeats contributes to ALS. The purpose of the C9ORF72 Natural History Study is to collect more information about C9ORF72 repeats and document disease course in this population of ALS patients.

Growing attention to this study has provoked the launch of 5 new sites in addition to 3 existing sites. The participation of ALS patients from the Washington University Neuromuscular Clinic is greatly appreciated and we welcome new volunteers as this study continues to grow. Please call the Neuromuscular Clinical Studies line, 314-362-6159, or email neuroclinicalstudies@neuro.wustl.edu for more information.

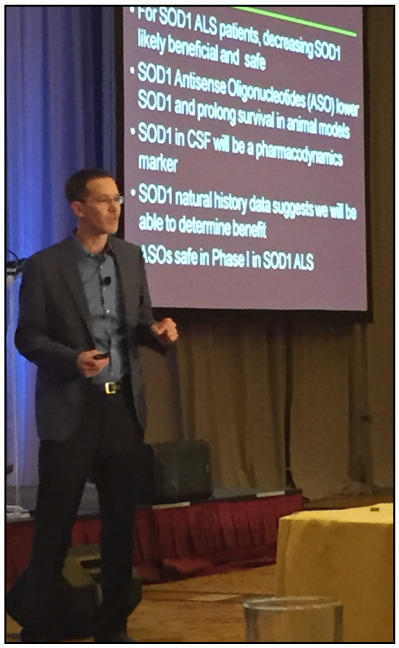
Collaboration with Dr. Urano

Proteins are the products that form after C9ORF72 repeats are processed in the body, and several of these C9ORF72 proteins were discovered to be harmful. ALS researchers are now investigating the harmful C9ORF72 proteins and how their interactions in the human body manifest in ALS.

Dr. Fumihiko Urano, Professor of Medicine in the Division of Endocrinology, Metabolism, and Lipid Research at Washington University, is currently studying how C9ORF72 proteins cause neurodegeneration in ALS patients. If we can understand the role of C9ORF72 proteins, we can develop drugs that target them and stop their harmful effects.

C9ORF72 ALS patients from the Washington University Neuromuscular Clinic have donated tissue to the Miller Laboratory and samples have been shared with Dr. Urano for his research study. Using these samples, Dr. Urano has identified a specific job that is performed in normal cells, but is stopped by C9ORF72 proteins in ALS patients. When the job is canceled by C9ORF72 proteins, the cell dies and the muscles of the ALS patient are weakened. Dr. Urano speculates that one therapy could involve getting rid of the harmful C9ORF72 proteins, so that the job can continue to be performed and keep the cells alive in ALS patients.

Each participant who donates tissue samples provides a valuable resource to the ALS community and furthers many different types of ALS research. The continued support of participants is appreciated and vital to future research.



Dr. Timothy Miller spoke earlier this year in Boston at a joint investigators meeting regarding the SOD1 ASO and ALS Methodology studies.

New SOD1 ASO Clinical Trial

Collaborators Biogen Idec and Isis Pharmaceuticals announced the launch of a Phase 1/2 Clinical Trial of an antisense oligonucleotide (ASO) administered to ALS patients with mutations in the superoxide dismutase 1 (SOD1) gene. SOD1 mutations account for approximately 20% of inherited ALS, making it the second largest ALS population. The ASO, called ISIS-SOD1Rx, works by binding to disease-causing SOD1 proteins in the body and destroying them, thereby slowing disease progression. The clinical trial will assess the safety and tolerability of the drug in humans with SOD1 mutations and will provide important dosage information.

Dr. Timothy Miller is leading this clinical trial as the overall Principal Investigator and Washington University will be enrolling participants. Pre-clinical studies from the Miller Lab formed the basis for the development of the ASO through research sponsored by the ALS Association, the Muscular Dystrophy Association, and a UO1 grant from the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Miller also completed the first-in-man Phase 1 Clinical Trial using a similar ASO in ALS patients in 2013, which provided crucial information about the drug's interactions in the body. Pre-clinical and clinical studies from the Miller Lab were essential to the development of ISIS-SOD1Rx.

Dr. Miller is enthusiastic about the launch of the second ASO Clinical Trial in SOD1 ALS patients. Study sites from across Europe and the United States will begin recruiting patients in early 2016. Dr. Alan Pestronk and Dr. Robert Bucelli will be leading this study at Washington University. More information can be found by going to ClinicalTrials.gov and searching for Clinical Trials Identifier NCT02623699, or by contacting us (314-362-6159, or neuroclinicalstudies@neuro.wustl.edu).

WU Neuromuscular

http://millerlab.wustl.edu/
http://neuromuscular.wustl.edu/
neuroclinicalstudies@neuro.wustl.edu

We gratefully acknowledge the support of the following organizations:

Project 5 for ALS
www.project5forals.org

Muscular Dystrophy Association
www.mda.org

The ALS Association
www.alsa.org

NEALS-Northeast ALS Consortium
www.alsconsortium.org/

National Institutes of Health
www.nih.gov/

Robert Packard Center for ALS

Target ALS

U. of Missouri Spinal Cord Injury Research Program

Isis Pharmaceuticals

Biogen Idec.

How can you help Miller Lab?

Charitable donations support ALS research

For contributions to the Washington University ALS program, please contact Zach Silvers, Director of Development, at 314-935-3498 or email zsilvers@wustl.edu.

Those who wish to send a check should write it payable to Washington University. In the memo section indicate the gift is to ALS Research Support Fund. Checks should be sent to:
Medical Alumni and Development, Attn: Zach Silvers
7425 Forsyth Blvd., Suite 2100 St. Louis, MO 63105

Contribute to the CSF Biorepository Study

Persons who have been diagnosed with a disease of the nerve, muscle, or brain and healthy volunteers are needed to participate in this study.

The purpose of this research is to gather, study and store cerebrospinal fluid (CSF) and serum (blood) to provide a resource for future investigation in neurodegenerative diseases such as ALS. Normal control samples of CFS are valuable to provide a comparison between the CSF of those with neuromuscular disorders and those without neuromuscular disorders, helping us to better understand neurologic and neuromuscular diseases. The study involves two visits to the Clinical Research Unit, located in the Barnes Hospital complex.

Please call the Washington University Neuromuscular Clinical studies line at 314-362-6159 for additional information.