in this issue >>>

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The Center for NeuroGenetics, University of Florida

*in*focus

MDF Special Issue

The UF Center for NeuroGenetics

The Center for NeuroGenetics (CNG) performs molecular, genetic and clinical research to define the causes of neurodegenerative disease and to develop effective treatment strategies.

The goal of the Center for NeuroGenetics at the University of Florida is to advance our basic understanding of neurodegenerative diseases, including myotonic dystrophy, so we can develop rational therapeutic strategies for patients. One of the key aspects of our approach is to partner with affected families to identify novel disease genes and to link these patients with researchers and clinicians working to understand these diseases as well as to develop future therapies.

2018 marks the eighth year for the CNG and a period of remarkable progress for our researchers. The Center is growing by recruiting new faculty and occupying new space at the University of Florida. In the past year, CNG faculty have produced some exciting research findings, including publications in ***Molecular Cell, Neuron, PNAS and Nucleic Acids Research***. Many of these findings, which are highlighted in this newsletter and on our website, are focused on potential therapeutic or biomarker development. We also continue to receive outstanding support from the Myotonic Dystrophy Foundation, including MDF Fellowships for numerous CNG postdoctoral researchers. On the clinical front, the CNG has hired a new Clinical Research Coordinator, **Felicia Fitzgerald** (ffitzger@ufl.edu), who will help in coordinating our research and clinical programs with patients and their families. Dr. Subramony and his clinical team also continue their remarkable clinical care program, including three clinical trials, highlighted here.

Our researchers, clinicians, staff and trainees are excited to share these research updates with you!

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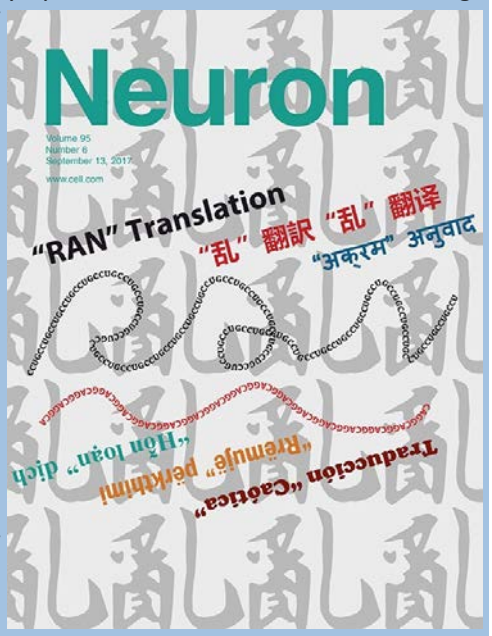
New Research Findings at the Center for NeuroGenetics

Dr. Laura Ranum
Director
The Center For NeuroGenetics

Research Update

Through the analysis of donated human autopsy tissue we have been able to investigate the role of Repeat Associated Non-ATG (RAN) translation in myotonic dystrophy types 1 and 2 as well as other repeat expansion diseases such as amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia (SCA) type 8 and Huntington's disease (HD).

We have recently published some of our findings regarding the role of RAN translation in myotonic dystrophy type 2 (DM2) in the journal ***Neuron*** *(see cover image right)*. In this paper, we identified the presence of RAN proteins in autopsy material from DM2 patients. We also demonstrated that RNA foci and nuclear sequestration of CCUG transcripts by MBNL1 are inversely correlated with RAN protein expression. These data suggest a model that involves nuclear retention of expansion RNAs by RNA-binding proteins (RBPs) early in disease and an acute phase in which expansion RNAs exceed RBP sequestration capacity, are exported to the cytoplasm, and undergo RAN translation. We are proud that this article made the cover of Neuron and was also highlighted with a video abstract.



The team of researchers in my laboratory are making excellent strides across multiple repeat expansion diseases. We are making substantial progress in generating a myotonic dystrophy type 2 mouse model — a project being led by a MDF Fellow, Dr. Kiruphagaran Thangaraju. We have also just published findings in the journal ***EMBO*** describing the role of a novel polySerine RAN protein in SCA8, which may have implications for other CAG/CTG repeat disorders like myotonic dystrophy.

Dr. Maurice Swanson
Associate Director
The Center For NeuroGenetics

Research Update

Our lab studies the potential functions of repetitive DNA and the roles of unstable short tandem repeats (STRs) in neurological and neuromuscular diseases, including myotonic dystrophy. During the past year, our lab has been focused on two major projects relevant to both DM2 and DM1. First, we have uncovered a novel blood biomarker for DM2, intron retention or IR. This data, published in the ***Proceedings of the National Academy of Sciences of the USA***, demonstrated that intron retention is readily detectable in affected tissues and peripheral blood lymphocytes. This screen may be employed to detect DM2 CCTG expansion mutations when they are relatively short and thus very early in the disease course. This work was led by a former MDF Fellow — Dr. Łukasz Sznajder.

Second, we have developed a novel mouse *Dmpk* knock-in model for DM1 that carries the largest uninterrupted CTG expansions mutations reported to date. These mice will provide a key resource for studies on basic disease mechanisms and also serve as an *in vivo model* to test the efficacies of various therapeutic modalities under current development. Work on this project is being aided by current MDF Fellow, Dr. Curtis Nutter. Dr. Nutter is also working on understanding the pathogenesis of congenital myotonic dystrophy and testing the potential of antisense oligonucleotides (ASOs)

Gators on the move !

In widely watched rankings published by U.*S. News & World Report* on the Best Colleges, the University of Florida moved up one spot to eighth place nationally.
Additionally, UFs ranking amongst all universities, public and private, is the highest in the state of Florida!

New Research Findings at the Center for NeuroGenetics

Dr. Eric Wang

Assistant Professor — Department of Molecular Genetics and Microbiology

CNG Executive Committee Member

Research Update

We remain focused on understanding disease pathogenesis in DM as well as finding ways to treat both the root cause and symptoms of this disease. Ever since moving to UF, we have significantly augmented our efforts to better understand central nervous system aspects of DM. New collaborations with neuroscientists and sleep doctors at Emory University, including Gary Bassell, Andy Jenkins, and David Rye, have facilitated these new investigations. We also recently published a paper in ***Molecular Cell***, describing an approach to block transcription of expanded microsatellite repeats such as the CTG repeats found in myotonic dystrophy. This approach is based upon using a deactivated version of the Cas9 enzyme (dCas9) of the CRISPR system. We recruited dCas9 to the expanded CTG repeats in DM1, causing roadblocks to transcription of the toxic RNA. We used adeno-associated virus to deliver the dCas9 protein to a mouse model of DM1, and although delivery of the protein was not especially efficient, we were able to observe partial rescue of myotonia. These studies provide insights into general principles for how to treat repeat expansion diseases, as well as teach us about the extent of molecular rescue required to produce changes in DM phenotypes. We are excited to be at the CNG, working with a team of labs to make progress towards understanding and treating DM and related diseases.

Dr. Andy Berglund

Professor (UF) — Department of Biochemistry

Director (Albany) — RNA Institute, State University of New York at Albany (SUNY)

Dr. Berglund has taken an exciting new position as the Director at the RNA Institute at the State University of New York in Albany (UAlbany). Dr. Berglund will remain closely connected with the Center for NeuroGenetics and will remain a faculty member of the University of Florida.

Research Update

We are pleased to report a set of new research findings from the Berglund lab. First, we have recently published findings in ***Nucleic Acids Research*** regarding an engineered RNA binding protein with improved splicing regulation. Our findings regarding the muscleblind-like 1 protein (MBNL1) showed that the protein's zinc finger domains (ZF1-2) drives splicing regulation while ZF3-4 acting as a general RNA binding domains. These studies suggest that synthetic MBNL proteins with altered splicing activity have the potential to be used as both tools for investigating splicing regulation and as potential protein therapeutics for DM and other repeat diseases. Second, we published in **ACS Chemical Biology,** our investigation of the mode of action of furamidine , a promising small molecule for rescue of mis-splicing in DM1 cells. Our results show that furamidine can affect multiple pathways of DM1 pathogenesis and that it may work through multiple mechanisms to rescue DM1-associated mis-splicing events.

We are adding some new faces at the CNG

The Center for Neuro*G*enetics at the University of Florida (UF) College of Medicine is currently looking to add **TWO tenure/ tenure-track positions** at the **ASSISTANT, ASSOCIATE or FULL PROFESSOR** level. We seek outstanding investigators in the following areas: 1) *Neuroscience, neurological disease mechanisms and/or therapeutic development* with an emphasis on genetic, computational or pathophysiological disease models; 2) *RNA biochemistry* with a current or future focus on central nervous system function and disease. Interviews will begin Fall 2018.

Thanks to the MDF for its support of the ***9th International Conference on Unstable Microsatellites and Human Disease***.

This conference organized by CNG Director, Dr. Laura Ranum along with international researchers Drs. Christopher Pearson and Maria G. Miano, focuses on the most recent advances in understanding repeat instability of nucleic acids and proteins and their relationship to human diseases, inherited and other. Researchers from around the world gathered to discuss myotonic dystrophy and other expansions diseases and to share strategies on how to combat these devastating disorders.

Clinical Research Highlights at the Center for NeuroGenetics

S.H. Subramony, M.D.— Professor of Neurology
CNG Executive Committee Member
Dr. Subramony holds a Myotonic Dystrophy specialized clinic every Wednesday afternoon at the Shands Medical Plaza at UF Health in Gainesville, Florida.
Clinic Contact Info: (Phone) 352-294-5000 (Fax) 352-627-4295.

Current clinical trials and research by Dr. Subramony

(1) **Myotonic dystrophy Clinical Research Network (MDCRN); natural history study of myotonic dystrophy.** Involves 3 visits, each lasting all day. Visits include blood collection for chemistries, complete blood count, DNA testing, and biomarkers; urinalysis test; physical exam; ECG; 4 questionnaires; computerized cognitive testing; muscle strength testing, DEXA (bone density scan); and needle muscle biopsy.

(2) **Skeletal Muscle and Gastrointestinal dysfunction in myotonic dystrophy** – The purpose of this research study is to examine and understand some aspects of muscle activity and gastro-intestinal (GI or stomach). Questionnaires are administered. Electrical and mechanical activity in arm and leg muscles will be performed. One time collection of stool and one blood draw done.

(3) **END-DM1 Establishing Biomarkers and Clinical Endpoints in Myotonic Dystrophy Type 1** - The purpose of this research study is to determine the best ways to assess how people are affected by myotonic dystrophy type 1. The study will examine the effects of DM1 on the subject's muscles, heart, blood, and nervous system. The subject's walking speed, muscle strength, your ability to relax your muscles or myotonia, heart rhythm, and overall health will be assessed by trained study personnel. The subject's thinking and processing information will be assessed using a computerized test. Questionnaires will be administered.

For more information on any of the above trials please contact ***Amanda Cowsert at (352) 294-8778.***

MDF Support of CNG Researchers

Dr. Curtis Nutter works within the laboratory of Dr. Swanson. The goal of Dr. Nutter's research proposal, "*Congenital myotonic dystrophy: pathomechanism and therapeutic development*" is to elucidate the role of MBNL3 in muscle development and its contribution to congenital myotonic dystrophy as well as to test potential therapies to correct RNA mis-processing in congenital myotonic dystrophy. Using mouse KO models and primary myoblasts, Curtis will determine how changes in MBNL3 disrupt muscle development in congenital myotonic dystrophy and identify important pathways that are key to development of patient muscular symptoms. The study will test if correcting the regulation of these key pathways can be developed as treatments for myotonic dystrophy.

Dr. Kiruphagaran Thangaraju works within the laboratory of Dr. Ranum. The goal of Dr. Thangaraju's project "*Molecular characterization of RNA and RAN protein effects in DM2*" is to generate a mouse model of DM2 that will allow us to better understand the contribution of both the mutant RNAs and mutant RAN proteins. To accomplish this task, he has isolated and is using a large piece of human DNA from DM2 patient material that contains a large expansion and all of the normal regulatory sequences. This strategy will help ensure that the RNAs and RAN proteins are made at the right time and place within the mouse, including in the brain, to mimic the human disease.

Dr. Kaalak Reddy works within the laboratory of Dr. Berglund. The goal of Dr. Reddy's research proposal, "Pre-clinical investigations of small molecule-mediated targeting of toxic RNA production in DM2" is to evaluate a novel therapeutic strategy aimed at reducing the production of toxic RNA. In collaboration with members of the Berglund and Ranum laboratories, Dr. Reddy will characterize the therapeutic properties of several small molecules that were recently shown in the Berglund lab to inhibit the production of the toxic DM1 and DM2 RNA and test the efficacy of the most promising lead compound panel in DM2 human cell and mouse models. The study will help determine if lead compounds recently identified in the Berglund laboratory can be developed as treatments for DM.