The UF Center for NeuroGenetics

Why we do what we do...

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

Genetic disorders that affect the nervous and muscular systems are responsible for a large number of devastating diseases including amyotrophic lateral sclerosis (ALS), myotonic dystrophy (DM), Huntington disease (HD) and the spinocerebellar ataxias (SCAs).

Each of these diseases progresses over a period of years and results in lifestyle impairments and a variety of medical complications. Although there has been a significant effort to understand and treat these disorders, progress has been slow. A major reason for the limited advancement in our understanding and treatment of these disorders is that we have not developed sufficiently integrated and multidisciplinary approaches to understand the causes and common pathways of these diseases.

The goal of the Center for NeuroGenetics is to advance our basic understanding of these disorders so we can develop rational therapeutic strategies for patients. Key aspects of our approach are to partner with affected families to identify novel disease genes and to link these patients with scientists working to understand these diseases using both clinical and basic science approaches.
The Center for NeuroGenetics Biorepository Bank.

Samples collected from patients and their families are deposited into our CNG Biorepository Bank and can be withdrawn by any UF researcher within the CNG that has IRB approval. Having a central bank eliminates red tape for individual researchers and helps speed the pace of discovery at the CNG. These samples are used for projects that range from looking at protein or RNA changes in the samples to making cell lines from patient blood. Samples can also be used to assess possible treatments for diseases, such as antisense oligo nucleotides (ASOs), small molecules or already approved FDA drugs. Here are some examples of new and exciting research from our Center for NeuroGenetics scientists and clinicians and how patient samples are being used to study neurogenetic diseases.

Dr. Laura Ranum
Director
The Center For NeuroGenetics

Research Update
Through the analysis of donated human autopsy tissues 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 are investigating the mechanism by which RAN translation occurs in these diseases and the toxic effects of RAN proteins in the brain and other organs. Using patient derived cell lines we have also been able to develop mouse models for some of these diseases. These mouse models are used to better understand the impact these proteins have in disease and these models can be used to develop therapeutic strategies. We have recently published our findings of RAN proteins in patient samples for ALS and HD and we are preparing manuscripts for DM2 and SCA8. Many of the scientific breakthroughs made in the Ranum laboratory over the years would not have been possible without the participation of patients and their families in the research studies. Continued sample donations such as blood, autopsy tissue, skin, and muscle biopsy samples are essential for our research studies.

First Annual Community Symposium

We held our first Annual Center for NeuroGenetics Community Focus Symposium on July 22nd at the University of Florida. This Symposium highlighted for the community what we are learning through interdisciplinary basic and clinical research efforts among Center for NeuroGenetics faculty and students across campus.

Our program for this meeting included an overview of CNG research efforts, CNG faculty presentations, short talks and poster presentations by Postdoctoral Fellows, Graduate Students and a group of seven Undergraduate Summer Research Students that are being funded through a new philanthropically supported undergraduate scholarship effort.

We invited community members that have previously participated in or were interested in our efforts to fight neuromuscular disease to our Center where they were able to meet our team of interdisciplinary scientists. The entire event was live-streamed for patients and families that were unable to join us. A video of the event can also be found at the Center for NeuroGenetics webpage. (http://neurogenetics.med.ufl.edu). Click on events for our video and more information about similar upcoming events and opportunities to learn more about the CNG.

Are there really alligators at the Center for NeuroGenetics?
You bet, the CNG is located next to Lake Alice which has several resident alligators. They rarely venture from the lake area but occasionally take a stroll to check out new and potentially tasty researchers.
Research Update

We are developing a new generation of mouse models for DM1 and DM2 that will be essential to elucidate the differences and similarities in the disease mechanisms involved in these two types of myotonic dystrophy. To generate these new models, we have inserted a series of CTG expansions in the mouse \textit{Dmpk} gene to model DM1 and a CCTG series in the \textit{Cnbp} gene for DM2. These models, which will reproduce the endogenous expression patterns of the \textit{Dmpk} and \textit{Cnbp} genes, will also provide a new mammalian platform for evaluating potential therapies for DM1 and DM2.

We are also investigating the impact of DM repeat expansions on T cell development and maintenance—an important component of the body's immune system. Results from our animal models have demonstrated defects in T cell signaling, suggesting a potentially compromised immune system in DM patients. We are collecting fresh blood samples to investigate T cell signaling in both DM1- and DM2-affected individuals to determine the effect of repeat expansions on the immune system.

Research Studies at the Center for NeuroGenetics - Bedside to Bench

The Next Generation of Researchers

This year also marked the start of our new philanthropically supported undergraduate scholarship effort. Thanks to generous donations from DM community members, several undergraduate students were able to undertake research at the CNG this summer. These students, mentored by CNG researchers, worked on projects ranging from analyzing large bioinformatics datasets to discovering new disease genes. These exciting young scientists will make significant contributions to research in years to come.
S.H. Subramony, M.D.  
Professor of Neurology  
Committee Member of the Center for NeuroGenetics

Dr. Subramony holds a Myotonic Dystrophy specialized clinic every Wednesday afternoon at the Shands Medical Plaza at UF Health. For clinical appointments please contact Brittany Ferry (Ferryb@shands.ufl.edu) at 352-265-8477. Clinic Contact Info: (Phone) 352-294-5000 (Fax) 352-627-4295.

Current clinical trials and research by Dr. Subramony

(1) ASO treatment study
A Phase 1/2a Blinded, placebo-controlled study to assess the safety, tolerability, and dose-range finding of multiple doses of ISIS 598769 administered subcutaneously to adult patients with Myotonic Dystrophy Type 1.

(2) Myotonic dystrophy Clinical Research Network (MDCRN); natural history study of myotonic dystrophy
Natural history study for patients with 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.

Future studies will include the following (IRB approval in progress):
- Cognition in DM patients
- Motor physiology of DM patients
- Analysis of gastro-intestinal features in DM patients

For more information on any of the above trials please contact Aika Konn- UF Department of Neurology, 352-273-6003, Email: aika.konn@neurology.ufl.edu or Tracie Kurtz –UF CTSI - (352) 273-8517, tlkurtz@ufl.edu.

(3) Development of Magnetic Resonance Imaging (MRI) as an Endpoint in Myotonic Dystrophy Type 1 Study.
Investigating the use of MRI as a clinically relevant diagnostic tool in people with DM1 that could be used in future clinical trials investigating new therapies for the DM1 patient population. It involves the use of quantitative MRI measurements of the lower and upper extremity muscles. Contact for this study is: Donovan J. Lott, PT, PhD, CSCS Research Assistant Professor, (352) 273-9226, djlotpt@phhp.ufl.edu.

The lab/clinic of Guangbin Xia
Dr. Xia is using patient-derived skin tissue (obtained through a skin biopsy) to generate fibroblast cell lines. These fibroblast lines can be used to establish induced pluripotent stem cells, which will be used for mechanistic studies, drug screen studies and as a cell-based therapy for DM1. Dr. Xia is also using patient-derived muscle samples (obtained from a muscle biopsy) to generate myoblast cell lines to study muscle degeneration/regeneration in DM1 affected muscles. Please contact Dr. Xia at (352) 294-5144 or email him at guangbin.xia@neurology.ufl.edu for more information on these studies.

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