in this issue >>>

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2017

The Center for NeuroGenetics, University of Florida

in focus

MDF Special Issue

UF Center for NeuroGenetics
College of Medicine
UNIVERSITY of FLORIDA

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The UF Center for NeuroGenetics

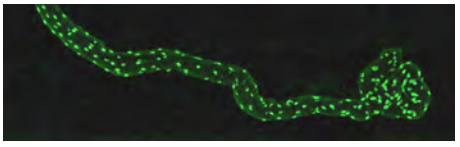
Why we do what we do…

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 in the development of treatments. 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.



DM1 mouse model muscle fiber with hundreds of multiple RNA foci

Research at the Center for NeuroGenetics

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Samples collected from patients and their families are deposited into our CNG Biorepository Bank and can be withdrawn by any UF researcher within the CNG that has Institutional Review Board (IRB) approval. Having a central bank eliminates red tape for individual researchers and helps speed the pace of discovery at the CNG. Samples are used for projects that range from looking at protein or RNA changes in blood, skin, and muscle 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 tissue and blood we are investigating the role of Repeat Associated Non-ATG (RAN) translation in myotonic dystrophy as well as other repeat expansion diseases such as amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia (SCA) type 8 and Huntington's disease (HD). RAN translation was a discovery we made a number of years ago in which we showed that repeat expansion mutations can make unexpected proteins without using the signals previously thought to be required by cells in the body. We have recently published our findings of RAN proteins in patient samples for ALS and HD and have a paper on DM2 and RAN proteins accepted for publication that is coming out soon. We are now investigating how to prevent the production of these proteins and studying the toxic effects of these proteins on the brain. We are also using patient donated samples to isolate the DM2 gene to develop a mouse model for DM2 that will be used to better understand the impact that RAN proteins have in DM and to develop therapeutic strategies. 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.

Dr. Maurice Swanson
Associate Director
The Center For NeuroGenetics

Research Update

In our portfolio of tools for understanding DM1 disease mechanisms, we would benefit from a mouse model where the CTG repeats are expressed in the same molecular context and cellular environment as in the human disease. We are developing a new generation of mouse models that insert a series of CTG repeats into the endogenous *Dmpk* gene. These models, which will reproduce *Dmpk* endogenous expression patterns, will also provide a new mammalian platform for evaluating potential therapies for DM1. Our lab is also interested in understanding the molecular basis of congenital DM (CDM). Using patient samples, we identified prominent alternative splicing and polyadenylation abnormalities in muscle. Many of the targets are also mis-regulated in adult-onset DM1, however the degree of dysregulation is significantly more severe in CDM. Alternative splicing analysis showed that CDM-relevant exons normally go through RNA isoform transitions during human muscle development, which are predicted to be disrupted by CUG^{exp}-associated mechanisms *in utero*. Our study demonstrated that RNA misprocessing is a major pathogenic factor in CDM.

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 they take a stroll to check out new and potentially tasty researchers.

Research at the Center for NeuroGenetics

Dr. Andy Berglund
Professor
Department of Biochemistry and Molecular Biology

Research Update

Using a combination of biochemical, cellular and genomic approaches we continue to focus on myotonic dystrophy with the goal of translating basic science into clinical research. My lab is also beginning to expand our research efforts into other neuromuscular diseases caused by microsatellite expansions to determine similarities and differences in the mechanisms across these diseases to build the necessary foundation of basic understanding that can be used to develop therapeutic strategies for DM, ataxia and ALS. One of our focuses in the lab is the characterization of the many mis-splicing events that occur in the genes of DM1 patients. This could lead to predictions on which splicing events are the best biomarkers for outcome measures in therapeutic studies. We are also developing novel synthetic MBNL1 proteins that have altered activities providing insight into how this protein recognizes RNA and regulates splicing. A synthetic MBNL1 with improved activity could potentially be used in a therapeutic approach. Last but not least, we are screening libraries of small molecules and searching the scientific literature to identify already approved compounds that can be repurposed to inhibit the production of toxic RNAs in DM, ALS and ataxias. Lead compounds that show promise will be studied to understand the mechanisms through which they function to aid in the development of molecules with improved activity. Combining the knowledge from these fundamental studies has allowed us to recently show that small molecules can be used to rescue mis-slicing in cell and mouse models of myotonic dystrophy.

Dr. Eric Wang
Assistant Professor
Department of Molecular Genetics and Microbiology

Research Update

Research in our lab focuses on three main areas - 1) studying the pathogenesis of microsatellite repeat diseases, in particular myotonic dystrophy, 2) studying how RNA is processed and localized in cells in tissues, and 3) combining insights made in both of those areas to develop treatments for patients. To accomplish these goals, we use molecular and cell biological approaches, as well as cutting edge computational and imaging approaches. A critical tool for us is deep sequencing, which allows us to obtain millions of data points in a single experiment, at low cost and time investment. At the same time, we like to take high resolution pictures and videos of molecules moving around in cells, to understand biological pathways that are perturbed in disease. Combining deep sequencing with imaging approaches has allowed us to gain insight into how RNA and protein molecules are perturbed in DM. While we have studied muscle and heart tissue of DM patients, we are also active in studying the central nervous system, and are trying to connect RNA changes to important symptoms such as sleepiness, fatigue, and challenges with learning & memory. We would like to have maximum impact on better understanding and treating DM and related diseases. In order to do so, we work with many other partners at other universities, as well as at biotech and pharma companies. Other important partners for us are the patients who participate in research studies, and donate biomaterial to these studies. We have made many discoveries using this precious material and our progress would not be possible without their valuable contributions.

Donations to the Center for NeuroGenetics

If you would like to join us in the fight to combat neurodegenerative disorders, including myotonic dystrophy, ataxia, amyotrophic lateral sclerosis (ALS), Huntington's disease, and neuropsychiatric disorders, please consider a financial gift. Donations can be made via credit card, check, transfers of stock, real estate, or planned gifts such as wills, trusts, and annuities securely through the donations tab on our CNG webpage at www.neurogenetics.med.ufl.edu/donations/

Donations over $500 can be directed towards something you feel passionate about such as research on a specific disease, student travel award, or a fellowship. Visit the link above for more details. You can also send checks by mail to our address located on the front and back covers of this newsletter. Please indicate in the comments section any specific instructions on how you would like your donation to be used.

You can also send us an email at centerforneurogenetics@health.ufl.edu

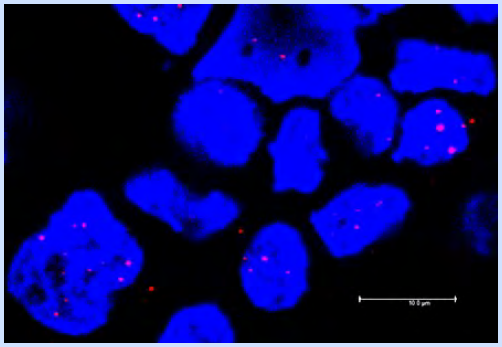
MYOTONIC DYSTROPHY FOUNDATION
Care and a Cure

MDF Support of CNG Researchers

Training the Next Generation of DM Researchers

One of our main focuses at the Center for NeuroGenetics (CNG) is to integrate molecular, genetic and clinical approaches to define the causes of neurodegenerative diseases to further the development of effective treatment strategies. Many of the researchers at the CNG have spent a portion of their careers working specifically on myotonic dystrophy and we have attracted some exceptional scientists dedicated to enhancing the quality of life of people living with myotonic dystrophy. Upon completion of a PhD the next step in a Scientist's career is their continued training as a post-doctoral associate. Financial support during this time is crucial for continued training and the Myotonic Dystrophy Foundation generously provides Fellowships for this type of training.

You can find more information out about this support and all of the recipients and the focus of their work at http://www.myotonic.org/fellows-grant-recipients. We currently have four scientist at the CNG who have been recipients of the MDF Fellowships. We would like to thank the MDF for their continued support to the next generation of DM researchers at the CNG.



RNA foci detected in a human patient lymphoblastoid cell line. The red dots are the RNA foci within the nucleus (blue) of the cells.

MDF Fellowship Support of CNG Personnel

Dr. Eric Wang, a CNG assistant professor, received the MDF Fellowship in 2012, while at MIT, to investigate changes in the myotonic dystrophy transcriptome to increase understanding of DM pathogenesis and identify biomarkers that could be used for the diagnosis of DM.

Dr. John Cleary, an Assistant Scientist in the CNG, joined the Ranum lab in 2010 and received the MDF Fellowship in 2011 to investigate the role of aberrant proteins produced through repeat associated non-ATG (RAN) translation in the pathogenesis of myotonic dystrophy.

Dr. Lukasz Sznajder, a postdoctoral associate in the CNG, joined the Swanson lab in 2015 and received the MDF fellowship in 2016 to generate mouse models for DM2 that could be used for screening potential therapies for DM2.

Dr. Kaalak Reddy, a postdoctoral associate in the CNG, joined the Berglund lab in 2016 and received the MDF Fellowship in 2017 to characterize the therapeutic properties of several small molecules as potential treatments for DM.

MDF DM Family Day in Orlando, Florida

Saturday October 21st, 2017

MDF DM Days are special one-day events that bring together clinicians, researchers and DM family members to share information and resources, and provide close-to-home access to educational sessions. The events offer opportunities for the community to meet local regional clinical staff, hear first-hand research updates and learn more about DM disease management. Additionally, the event provides opportunities to meet nearby community members for networking and support. The next event will held in Orlando on October 21st 2017. A light breakfast and lunch will be served. These events are made possible thanks to a generous MDF donor.

Information for this event can be found at www.http://myotonic.org/mdf-dm-days

CNG Partnership with Promise to Kate

First Annual Promise To Kate Day of Discovery

On Friday, June 9, 2017, Promise to Kate (PTK) held its first "Day of Discovery" at the University of Florida in a partnership with the Center for NeuroGenetics (CNG). The PTK Junior Board offered a field-trip to high school students to travel to the CNG to learn about the exciting research and the many opportunities in the medical research field. They had a great response and filled all 50 slots that were open for the event.

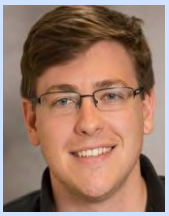
Students and chaperones were chartered from Jacksonville to Gainesville where participants were divided into groups for interactive tours at four scientific research stations. The first station demonstrated how fruit flies are used to study human disease and groups were able to view some of the distinct features of the fruit fly under a microscope. Second was an interactive station where the students isolate genomic DNA from strawberries using a protocol similar to what is used in the lab for research. The third station illustrated how cell culture models are used and some of the tools used in research, including microscopes such as a phase contrast, fluorescence, bright-field, and a confocal microscope. The last station was also interactive with each participant trying to load an agarose gel and why gel electrophoresis is important to research. The stations were a lot of fun for all involved and the students loved the hands on activities.

After lunch two of the CNG lead researchers, Drs. Andy Berglund and Eric Wang, discussed how they each got involved in their respective research fields, the opportunities that are available in research, the difference between basic vs. clinical research, industry vs. academic jobs, and how research is funded. A panel of members of the CNG then answered questions regarding career paths and the various opportunities for education in Science and Medicine. The day finished with a tour of the ShandsCair Critical Care helicopter. We were so excited to partner with Promise To Kate for this event and we hope it gave the upcoming generation of students a unique experience and ignited an interest in research.

PTK Graduate Student Fellowship Awards

Promise To Kate (PTK) has provided very generous support for two Ph.D. level graduate student fellowships at 50% effort for 1 year (2017-2018). These funds will include tuition, benefits, and stipend. Awardees must devote at least 50% of their effort to research that will benefit basic insights into myotonic dystrophy research and/or therapeutic approaches that will benefit DM patients. This years awardees were Melissa Hale from Dr. Andy Berglund's lab and Ryan Hildebrandt from Dr. Eric Wang's lab. Congratulations Ryan and Melissa!!

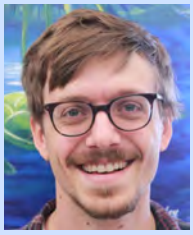
Melissa Hale



Ryan Hildebrandt

PTK Trainee Travel Awards

Traveling to scientific meetings and conferences is an important component of scientific training. Students and postdocs require opportunities to network, present their research, and form new collaborations with scientists in other locations around the world. These interactions are essential for developing new hypotheses, practicing scientific communication, and identifying future training and career opportunities. In an effort to facilitate this process, funding from Promise to Kate is being provided to support travel to scientific meetings related to Myotonic Dystrophy research. Five travel awards of $1000 each will be awarded to students and postdocs to help defray costs of travel and attendance at these meetings. Two of the PTK trainee travel scholarships have been awarded for attendance to the IDMC to Melissa Hale from Dr. Andy Berglund's lab and James Thomas from Dr. Maury Swanson's lab. Congratulations Melissa and James!!



James Thomas, PhD

Melissa Hale

Clinical Studies at the Center for NeuroGenetics

S.H. Subramony, MD
Professor of Neurology
Director, Adult MDA Clinic

Dr. James Wymer, MD, PhD
Professor of Neurology
Chief, Neuromuscular Division

Miguel Chuquilin, MD
Assistant Professor
Fellowship Director

Adult patients with muscular dystrophy, including myotonic dystrophy, are seen all day Tuesday and Thursday morning every week at the Center for Movement Disorders at UF Health in Gainesville Florida. The adult Neurologists medical team work closely with the Pediatric MDA clinic, which meets every Wednesday afternoon. The clinics are multi-disciplinary with added services from physical therapy, occupational therapy, pulmonary therapy, a social worker, and a mobility devices representative. In addition, coordinated appointments are available from cardiologists and cardiac electrophysiologists with expertise in muscular dystrophy, gastrointestinal motility service and others as needed. For clinical appointments please call 352-294-5000 (fax# 352-627-4175).

Current Clinical Research Protocols

(1) Studies of Skeletal Muscles and Gastrointestinal Dysfunction in Myotonic Dystrophy and Controls
This study will research the contractile muscle properties in DM using non-invasive recording methods. The study will also examine the association of gastrointestinal dysfunction with changes in gut microbiome of DM subjects. Includes one study visit with a skeletal muscle assessment (i.e. muscle biopsy) as well as a stool sample kit provided to patients that will need to be mailed within 2-3 weeks after the initial visit.

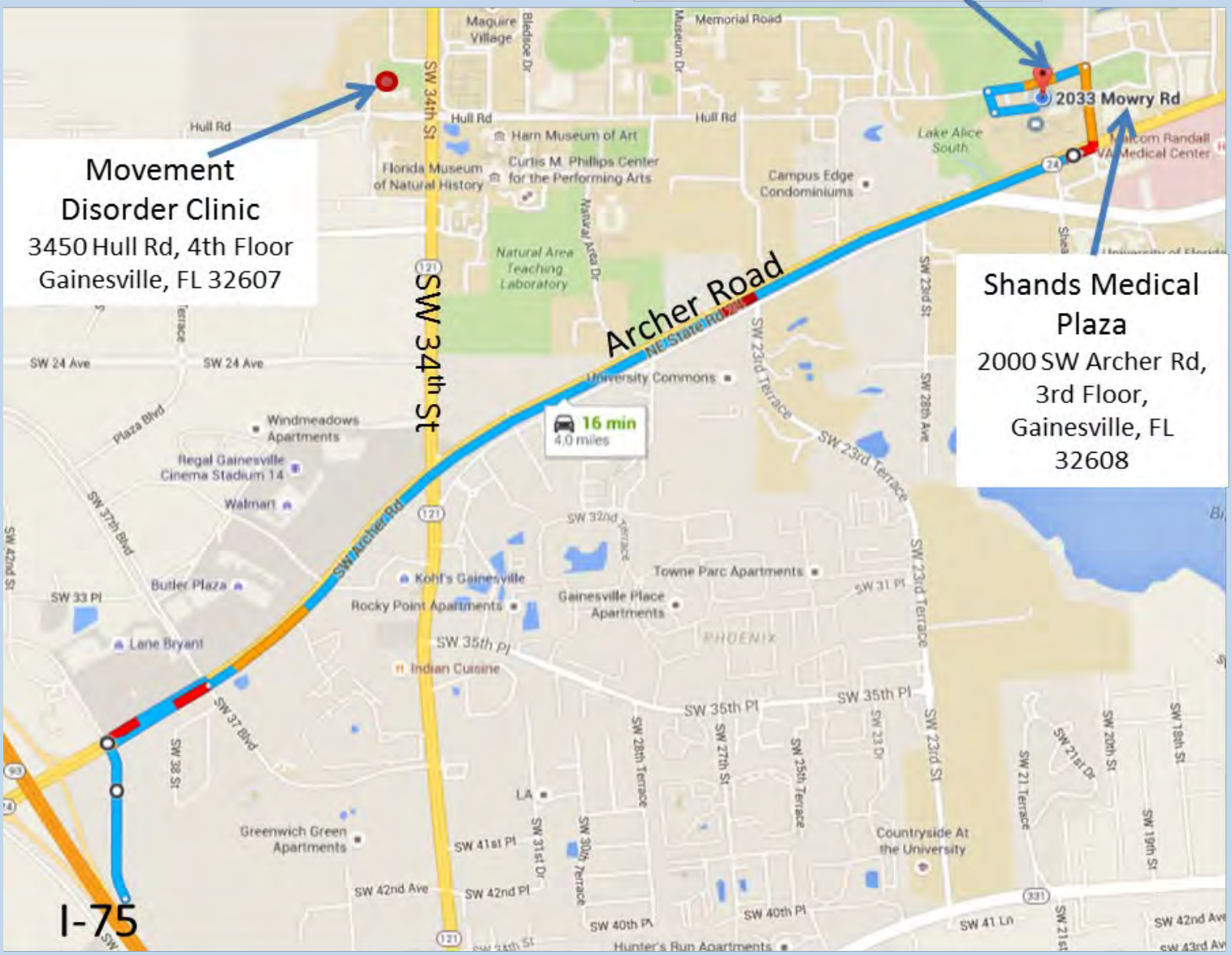
(2) Myotonic Dystrophy Clinical Research Network; Natural History Study of Myotonic Dystrophy– Funded by MDF
This is a follow-up of the previous natural history study of DM1 in which UF with participate with many other centers in the US. The study is in the process of being approved and will study the disease progression over 2 years. It will include analysis of genetic modifiers and biomarkers so patients will be asked to give muscle and blood samples.

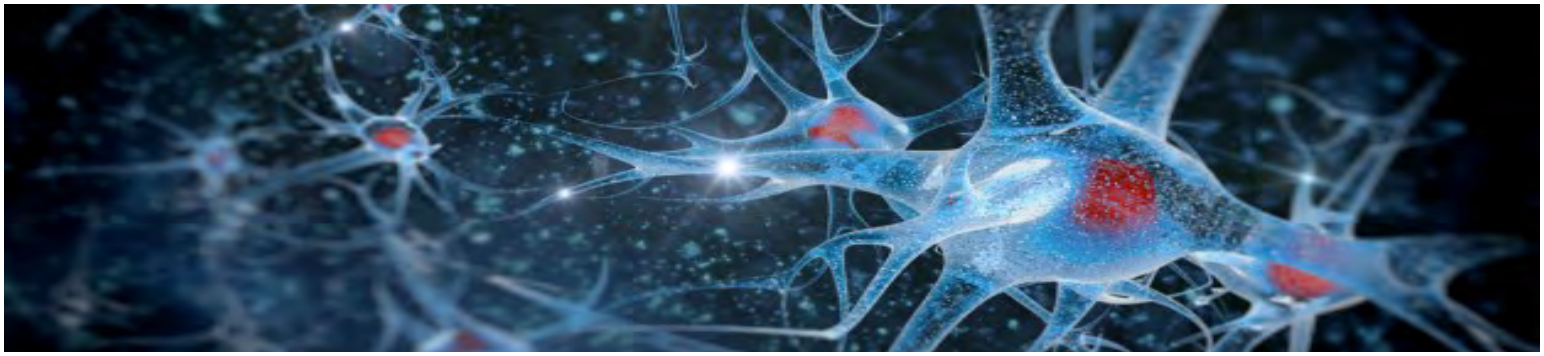
The data will be essential as we move forward towards more clinical trials in DM.
For more information on the above trials please contact **Aika Konn**- **Clinical Research Coordinator,** UF Department of Neurology, 352-273-6003, Email: aika.konn@neurology.ufl.edu or **Amanda Cowsert, Clinical Research Coordinator,** UF Department of Neurology, (352) 294-8778, amanda.cowsert@neurology.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 the MRI study is Donovan J. Lott, PT, PhD, CSCS,
Research Assistant Professor, (352) 273-9226, djlottpt@phhp.ufl.edu.

CNG Clinical Contacts

Map of the CNG and Associated UF Health Clinics





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UF Health Center for Movement Disorders and Neurorestoration
Specialized clinics for MDA , Ataxia , ALS , and Huntington's Disease

3450 Hull Rd, 4th Floor
Gainesville, FL 32607

For appointments call 352-294-5400

https://ufhealth.org/uf-health-center-movement-disorders-and-neurorestoration

Center for NeuroGenetics Retreat Group Photo December 2016 Florida

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