

# ADVANCES IN NEUROLOGY AND NEUROSURGERY

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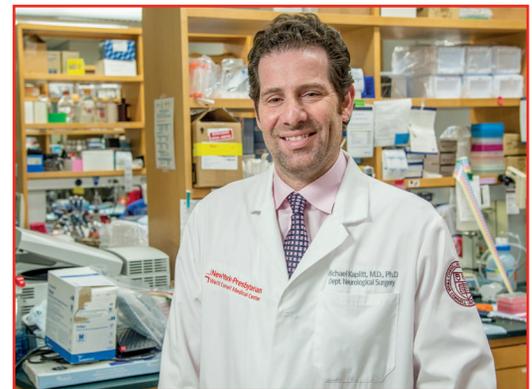
NewYork-Presbyterian  
Neurology and Neurosurgery  
ranks #4 in the nation.

## HIFU: Heralding New Hope for Movement Disorders

In July 2106, the FDA approved the use of high-intensity focused ultrasound (HIFU), a noninvasive technology, for treatment of essential tremor. This was a particularly defining moment for **Michael G. Kaplitt, MD, PhD**, a neurosurgeon and Director of Movement Disorders at the Weill Cornell Brain and Spine Center, who was the first in New York to perform HIFU to relieve a patient's essential tremor.

"Focused ultrasound has the potential to transform treatment by gaining access deep within the brain without harming healthy tissue," says Dr. Kaplitt, who continues to evaluate the approach in a clinical trial. "It also enables surgeons to ablate targeted tissue without exposing the brain to the effects of ionizing radiation and makes possible the reversible opening of the blood-brain barrier to deliver therapeutic agents to targeted diseased areas."

Performed while the patient is awake, focused ultrasound involves no anesthesia, no incisions in the scalp, and no burr holes through the skull or insertion of electrodes. During focused ultrasound



Dr. Michael G. Kaplitt

therapy, target cells in the thalamus are visualized in real time using MR imaging. The highly precise treatment uses focused beams of acoustic energy to heat and destroy target lesions as small as one to two millimeters, thereby eliminating or greatly diminishing the tremor.

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## A Commitment to Conquering ALS

Clinicians and scientists at the Eleanor and Lou Gehrig ALS Center in the Department of Neurology at NewYork-Presbyterian/Columbia University Irving Medical Center are leading efforts on a number of fronts to combat amyotrophic lateral sclerosis (ALS) and related forms of motor neuron disease. In addition to providing the latest therapies, they are conducting integrated translational research that ranges from the genetics and basic biology of ALS to the testing of promising therapeutic candidates in clinical trials.

"There are well over 25 genes that have been implicated in ALS, and the challenge to the research world is to understand how it is that mutations in so many genes can cause a stereotyped motor neuron disorder like ALS."

— Dr. Neil A. Shneider

### Eleanor and Lou Gehrig ALS Center

Each year, approximately 500 patients with ALS, primary lateral sclerosis, and progressive muscular atrophy come to the Eleanor and Lou Gehrig ALS Center at NewYork-Presbyterian/Columbia.

"Beginning with diagnosis and continuing through each stage of the disease, our subspecialty-trained neurologists and multidisciplinary team members strive to optimize and support the highest possible level of functioning, independence, and quality of life for our patients and their families," says Neil A. Shneider, MD, PhD, a physician-scientist with expertise in neuromuscular disease and Director of the ALS Center.

At the same time, Dr. Shneider has engaged basic scientists, cell biologists, molecular biologists, and geneticists to advance the pace of therapeutic discovery in the science of ALS.

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## A Commitment to Conquering ALS (continued from page 1)



Dr. Neil A. Shneider

“In the last 10 years, we have gained considerable insight into the genetics of ALS, a very complicated disease,” says Dr. Shneider. “There are well over 25 genes that have been implicated in ALS, and the challenge to the research world is to understand how it is that mutations in so many genes can cause a stereotyped motor neuron disorder. What is genetics telling us about pathways and mechanisms of disease shared by all these different forms of ALS? You would think that the genes would all point to a very clear causal mechanism, but they have not.”

In recent years, Dr. Shneider and his colleagues have begun to iterate a unifying theory about ALS. “I think that we are making real progress in our understanding of disease mechanisms that will enable us to take a rational approach to therapy using both traditional and non-traditional approaches.”

With the discovery in late 2011 of the C9orf72 gene mutation as the single most common cause of familial ALS and a related disease, frontotemporal dementia (FTD), Dr. Shneider and his colleagues realized that ALS and FTD are clinically, pathologically and genetically related and that many of their patients have some degree of frontotemporal dysfunction, if not dementia.

“This provided researchers with a genetic target and, as a result, a great deal of effort is focused on this one form of ALS,” says Dr. Shneider. “For example, antisense oligonucleotides technology used to treat spinal muscular atrophy – a related motor neuron disease – is now being tested in C9-ALS patients in the hope that it will prevent or stop the disease by targeting it at its source. There has been a great amount of success in this arena, which will facilitate its application to other diseases.”

### Precision Medicine Sets its Sights on ALS

Tom Maniatis, PhD, is Director of the Columbia Precision Medicine Initiative and a co-founder and currently Scientific Director and Chief Executive Officer of the New York Genome Center, of which Columbia is a partner. Dr. Maniatis, who is also a molecular neuroscientist with Columbia’s Mortimer B. Zuckerman Mind Brain Behavior Institute, pioneered the gene-cloning methods that gave a generation of scientists the tools necessary to identify the genes that cause disease. Today he uses advanced genetics and molecular and cellular biology to identify potential causes of neurological and neurodegenerative diseases,

including ALS, which has been a particular focus of his research for nearly 15 years.

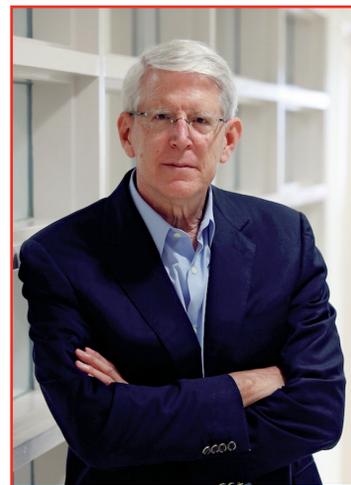
“A great deal of effort involving a number of people at Columbia has led to the establishment of initiatives that are directed towards the genetic analysis of ALS and the use of that genetic information to understand its disease mechanisms,” says Dr. Maniatis. “About 10 percent of ALS cases are familial; the remaining 90 percent are sporadic.”

In 2015, Columbia researchers identified a new gene associated with sporadic ALS called TBK1 through a major study co-led by David B. Goldstein, PhD, Director of the Institute for Genomic Medicine at Columbia, involving next-generation genetic sequencing of the exomes of nearly 3,000 patients with sporadic ALS. Subsequently others showed that genetic changes in TBK1 also cause familial ALS. TBK1 is among several “autophagy” pathway genes identified by ALS genetic studies. Thus, this critical cellular pathway has emerged as an “Achilles heel” for ALS disease mechanism studies. A better understanding of how mutations in this pathway cause motor neuron death could lead to finding a cure.

Dr. Maniatis and his colleagues recently reported that autophagy suppresses disease progression early on, but in later stages accelerates the deadly spread of the disease through the spinal cord. Their findings in mouse models, which were recently published in the *Proceedings of the National Academy of Sciences*, provide a window into

ALS’s earliest stages, as well as new insights into its complexity, namely the differing roles that autophagy plays in its progression. In addition, this study can help scientists search for ways to detect and even treat the disease before the onset of devastating symptoms that gradually rob patients of movement, speech, and life.

“One of the biggest barriers to treating ALS is that its progression is dynamic – many different cell types and mechanisms are involved – so treating it at one stage of



Dr. Tom Maniatis

the disease might have very different, and potentially harmful, consequences at a different stage,” says Dr. Maniatis, the study’s senior author. “Here, we’ve identified a cellular process that likely plays a central role at the very beginnings of the disease, which could open the door to treatments that stop ALS before it has a chance to gain a foothold in motor neurons.” Autophagy is governed by many genes working in concert across every cell in the body, so Dr. Maniatis and his team are now studying how mutations in these genes affect disease progression in an ALS mouse model.

Matthew B. Harms, MD, a clinician-scientist in neurophysiology and neuromuscular medicine, directs the ALS Center’s genomics program. “Our relationship with Columbia’s Institute for Genomic Medicine and our proximity to the New York Genome Center have allowed us to make the ALS Center the country’s foremost research

resource for ALS and genetics,” says Dr. Harms. “At the ALS Center, we are endeavoring to create the first genomically characterized patient cohort that pairs with Columbia’s precision medicine initiative. Patients who come here have the opportunity to participate in whole-genome sequencing projects. We ask if they are interested in learning the results about known ALS genes if we find a causative mutation and we will provide them with any genomically actionable findings that come out of our research. We don’t know of any other clinic in the country that’s doing this.”



*Dr. Matthew B. Harms*

“As we learn more about genotype correlations, we’re hoping to be able to provide information on prognosis based on those genetic findings, and eventually to tailor therapy based on the patient’s genetic profile,” adds Dr. Harms. “If we find someone with a mutation or a set of mutations in a gene that regulates autophagy, then we could use a drug to ramp up or inhibit autophagy depending on the scenario.”

Dr. Harms also leads a multisite effort using whole-genome and transcriptome sequencing to bring precision medicine to ALS. He serves as the Principal Investigator for the ALS Precision Medicine Initiative through the Genomic Translation for ALS Clinical Care (GTAC) project in which researchers are seeking to identify common and distinct features of ALS cases, and to better understand how genes influence the clinical features of the disease. In collaboration with the ALS Association, GTAC involves a combination of next-generation genetic sequencing and detailed clinical phenotyping in 1,500 people with ALS gathered at 10 sites across the country. The goal is to provide a basis for the development of more individually tailored therapies for ALS.

“The GTAC project grew out of the ALS Exome Consortium that Dr. Goldstein and I led in previous years, which was the first study to use whole-exome sequencing to identify a new ALS gene using burden collapsing analysis,” says Dr. Harms. “This technique uses algorithms to identify regions of the genome that are more abnormal in people with the disease than in people without the disease. GTAC will allow us to look for abnormal genes and gene expression profiles that help determine why a person develops ALS and related motor neuron diseases and why their symptoms present and progress with a particular pattern.”

In addition to sequencing the genomes, the researchers are also doing transcriptome profiling, examining the expression level of RNAs in a given cell population. “This gives us a snapshot of the person’s blood cells – what genetic programs are turned on or turned off at that moment,” says Dr. Harms. “We suspect that there will be subgroups of patients, based on those profiles, that will allow us to group people biologically as opposed to clinically. We have to know this if we are going to be able to stratify patients into clinical trials and target autophagy drugs to those with autophagy profiles or those who have an axonal transport problem.”

Antisense oligonucleotide therapy is already impacting the gene therapy landscape for SOD1-associated mutations linked to ALS, the most common of which is C9orf72. SOD1 is in phase 2 human trials and Dr. Harms anticipates C9orf72 to move into clinical trials this year.

“It feels like we’re always on the verge and that something is always just around the corner,” says Dr. Harms. “We are optimistic that genomically characterizing and determining the subtypes of ALS and then pursuing genetically targeted therapies is the most viable idea that we’ve had in a long time.”

### **ALS Clinical Trials: Bringing Therapeutics Closer to Home**

Jinsy A. Andrews, MD, MSc, is Director of Neuromuscular Clinical Trials in the Department of Neurology at Columbia. Prior to joining Columbia, Dr. Andrews was Head of Neuromuscular Therapeutics at Cytokinetics, where she focused on developing novel, small molecule skeletal muscle activators as a potential therapy for neuromuscular diseases, bringing the therapy from phase 1 to phase 3 in clinical trials for ALS, and subsequently, spinal muscular atrophy.

“My experience in industry has enabled me to see beyond the academic development of clinical research,” says Dr. Andrews. “I learned more of the regulatory process and interacted with clinical researchers and experts within the field in the U.S., Canada, and Europe, and also collaborated both nationally and internationally on specific compounds. I characterize my academic development as unconventional and a little bit out of the box, which is how I approach developing clinical trials in ALS and neuromuscular disorders.”

**Many of the compounds being tested at Columbia are in phase 2 or phase 3 development and are targeting different mechanisms of motor neuron degeneration, including hyperexcitability in both the peripheral and cortical motor neurons.**

Many of the compounds being tested at Columbia are in phase 2 or phase 3 development. The compounds are targeting different mechanisms of motor neuron degeneration, including hyperexcitability in both the peripheral and cortical motor neurons. “These are compounds that are looking at reducing microglial activation or processes involved in its inflammation that might be causing motor neuron degeneration, as well as trying to enhance the activation of the skeletal muscle in the setting of reduced nerve input,” explains Dr. Andrews, who is participating in an international collaboration to gain consensus in updating clinical trial guidelines in ALS.

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## HIFU: Herald New Hope for Movement Disorders (continued from page 1)

“Historically, we would make a hole in the skull and put a probe in and ablate the ventral intermediate nucleus [VIM] of the thalamus that is central to regulating the control of stability,” says Dr. Kaplitt. “That approach was then supplanted over the years by deep brain stimulation, which we’ve been doing for nearly 18 years at Weill Cornell. Brain stimulation gave us a little bit more flexibility intraoperatively. With focused ultrasound, however, we can actually lesion the abnormally functioning area of the brain completely noninvasively with MR thermometry, which allows us to measure the temperature inside the tissue to confirm its accuracy. We are also able to get real-time responses from the patient, so as we send more and more energy to the target, we can see the patient’s tremor becoming better.”

“While the VIM has proven to be an ideal target for tremor control using a number of minimally invasive techniques, delineating its anatomy is limited on traditional MRI sequences, resulting in technical challenges in selecting appropriate VIM coordinates to target this area,” explains Dr. Kaplitt. In a recent investigation, Dr. Kaplitt and his colleagues in radiology, neurology, neurosurgery, and anesthesia evaluated the utility of diffusion tensor imaging (DTI) tractography-based targeting of the dentatorubrothalamic tract (DRT) for MRI-guided focused ultrasound thalamotomy in a small sample of patients with essential tremor.

Their findings, published online in the October 20, 2017 issue of the *Journal of Neurosurgery*, showed that DTI performed pre- and post-procedure aided in optimal selection of the ablation site and showed loss of DRT fiber tracking immediately following the procedure. “We believe DTI-based functional imaging techniques provide significant benefits in procedural planning, performance, and follow-up for MRI-guided focused ultrasound thalamotomy,” says Dr. Kaplitt.

### On the Horizon for HIFU

With the success of HIFU with essential tremor, Dr. Kaplitt envisions potential applications for the treatment of other brain and movement disorders. “We have already demonstrated in our laboratory that we can expand the use of focused ultrasound to hone in on an exact location where we need to deliver gene therapy or chemotherapy, create temporary holes in the blood-brain barrier that normally prevents molecules from crossing from the bloodstream into the brain, then deliver the agents to the precise locations where they are needed,” he says. “This has tremendous implications not only for movement disorders, but also for Alzheimer’s disease, metastatic brain tumors, and other disorders that may benefit from our delivering genes and drugs to the exact location where they’re needed without invasive surgery.”

“There are going to be limitations to HIFU for some patients because of certain physical characteristics of their skull that make it difficult to perform the procedure,” continues Dr. Kaplitt. “Some patients may need it done on both sides of the brain, including the majority of Parkinson’s patients, and we don’t yet know if this is safe. It’s only approved for one side now.”

**“I think over time as we understand more about ultrasound that this is where our field is going. The idea that we can move toward less-invasive surgical procedures for patients and they can get the same result without having their brain penetrated is obviously very attractive to them.”**

— Dr. Michael G. Kaplitt

Weill Cornell is about to begin a clinical study of HIFU for patients with Parkinson’s whose symptoms are predominantly on one side of the body, though as Dr. Kaplitt notes, deep brain stimulation therapy will still be a very valuable adjunct to Parkinson’s patients who have symptoms on both sides.

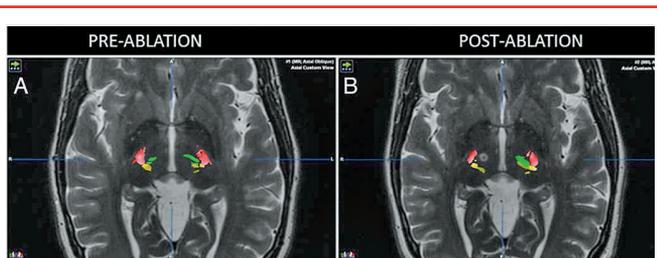
“These are exciting times in neuroscience, with new advanced treatments being developed at a rapid pace,” says Dr. Kaplitt. “Over the past 15 years, the Department of Neurological Surgery at Weill Cornell has led a revolution in the treatment of neurological diseases, from the first application of gene therapy to the human brain to pioneering work in new applications of brain stimulation and use of precise lasers for certain forms of epilepsy, and now HIFU. Ultrasound to treat tremor without surgery, gene therapy to change brain function in Parkinson’s disease, and lasers to eliminate sources of epilepsy truly sound like science fiction, and yet they are all examples of the cutting-edge treatments being brought to our patients.”

#### Reference Article

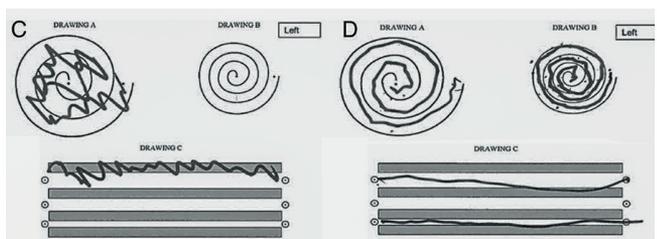
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#### For More Information

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*Imaging findings provide a direct correlate to the clinical improvement of tremor. A and B: Pre- and post-ablation DTI tractography overlaid on T2-weighted sequences. CST (red), ML (yellow), and corticothalamic tract (green) are shown from DTI. Post-ablation imaging reveals the T2-weighted hyperintense MRgFUS lesion in the location of the right DRT that could no longer be successfully tracked.*



*C and D: Results of the pre- and post-procedure Archimedes spiral drawing tests.*

Source: *Journal of Neurosurgery*. 2017 Oct 20

## NIH Director's Pioneer Award Bestowed on Weill Cornell Researcher

In October 2017, renowned neuro-oncologist **Howard A. Fine, MD**, Director of the Brain Tumor Center at NewYork-Presbyterian/Weill Cornell and Associate Director for Translational Research at the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine, was awarded a five-year, \$6 million National Institutes of Health Director's Pioneer Award for brain cancer research. This is the first Pioneer Award received by Weill Cornell Medicine and complements the productive brain cancer research program at the Meyer Cancer Center and the Brain Tumor Center.

The Pioneer Award will allow Dr. Fine and his Weill Cornell colleagues to pursue a brain cancer modeling strategy that represents a bold departure from traditional approaches, which may lead to new and more effective treatments and therapies for patients. The researchers have been using advanced stem cell techniques to grow large clusters of cerebral organoids in the laboratory. Cerebral organoids, with their brain-like environments, have enabled them to model brain cancers more accurately on the molecular level. With support from the NIH award, Dr. Fine and his team are now working to enhance the realism of their organoid models by adding two vital components: blood vessels with key properties of cerebral vessels and immune cells that normally reside in or can enter the brain.



*Dr. Howard A. Fine*

Recent research from Dr. Fine and others has found that glioblastoma tumors typically harbor genetic mutations that differ from patient to patient and offer no obvious common target for therapies. Part of his organoid-based research will involve the development of personalized brain cancer models using cerebral organoids derived from the cells of patients, which may lead to the development of precision medicine treatment strategies.

## NeuroNEXT

### NN107 FX-LEARN: A Study of AFQ056 in Fragile X Syndrome

Fragile X syndrome is a single-gene disorder and the most commonly inherited cause of intellectual disability. Effects range from learning disabilities to severe intellectual impairment. This study will examine if drug therapy with AFQ056 can improve communication and learning in children with Fragile X syndrome. The study will also determine the most effective dosing to improve neural plasticity, which is the core deficiency in Fragile X, as well as the safety of the therapy.

Participants between the ages of 32 months and six years of age will be randomized to either receive the drug therapy or a placebo for the initial period of about one year. All participants will be evaluated by speech language therapists, who will analyze and measure change in language skills in response to the intervention and deliver language therapy sessions to the family. In the study's extension phase, all participants will be treated with the

active drug for a period of about 8 months. The study is the first of its kind to evaluate whether a treatment aimed at improving a core deficit of brain connectivity can change the ability to learn in young children with Fragile X syndrome.

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#### Study Location

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21 Bloomingdale Road  
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### NN108 TopCSPN: A Study of Oral Topiramate as a Therapy for Cryptogenic Sensory Peripheral Neuropathy

The TopCSPN trial is a 96-week, double blind, randomized, placebo-controlled trial of oral topiramate at a target dose of 100 mg daily (50 mg twice daily) as a potentially disease altering therapy for cryptogenic sensory peripheral neuropathy (CSPN). Adults, ages 18 to 75, diagnosed with CSPN who also have metabolic syndrome (defined by the ATPIII criteria) and do not have an alternative cause for neuropathy are potentially eligible. Randomized participants will return to the clinic for follow-up visits every 16 weeks. The treatment phase will last 24 months.

Primary outcome measures are change in the Norfolk Quality of Life-Diabetic Neuropathy (NQOL-DN) Scale and intraepidermal nerve fiber density (IEFND) at the distal thigh.

#### For More Information

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**A Commitment to Conquering ALS** *(continued from page 3)*



*Dr. Jinsy A. Andrews*

According to Dr. Andrews, traditionally, many compounds have targeted different singular mechanisms of motor neuron degeneration. In recent years, however, compounds are being developed to target the neighborhood cells – the astrocytes – as well as the skeletal muscle to enhance the skeletal muscle function, thereby improving physical function in these diseases that are chronic and progressive. Parallel

to those efforts, Dr. Andrews is pursuing experimental therapies in clinical trial settings to find a drug that can be effective in mitigating the disease.

“Our group is also involved in epidemiological studies to evaluate environmental risk factors that are associated with the sporadic forms of ALS,” says Dr. Andrews. “For me, it’s about trying to introduce innovation to clinical trials. I am heavily involved in collaborations in developing predictive algorithms or outcomes measures since we don’t have a good way of predicting how the disease progresses in ALS.”

In order to find effective therapies for rare neurological disorders, Dr. Andrews believes the only way is through collaboration. “And not just on a national scale, but an international scale,” she says. “Some of these phase 2 trials may be multicenter national studies, but the phase 3 clinical trials we are conducting are international. There must be a global shift in the way we do clinical trials and engage multiple stakeholders in that development process.”

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