NYU Langone Health

Neurology

2018 Year in Review

MESSAGE FROM THE CHAIR

As our understanding of neurological disorders expands, new tools and treatments are enhancing patient care while simultaneously advancing our impact in the field of neurology.

Our clinicians and researchers have taken critical steps forward with developments in the management of epilepsy, multiple sclerosis (MS), and Parkinson's disease. We're breaking new ground in diagnostics with new screening approaches for concussion, MS, and autonomic disorders, and we're continuing to lead the push toward effective immunotherapies for Alzheimer's disease and other neurodegenerative conditions.

These efforts reflect the shared commitment of forward-thinking experts who collaborate across disciplines to advance neurological practice for the benefit of our patients.

STEVEN L. GALETTA, MD

Philip K. Moskowitz, MD Professor and Chair of Neurology
Professor of Neurology and Ophthalmology

CAMPUS TRANSFORMATION

In 2018, NYU Langone Health opened a new, 830,000-square-foot inpatient facility, the **Helen L. and Martin S. Kimmel Pavilion**, featuring 374 exclusively single-bedded rooms, an outdoor terrace, and 30 operating rooms and image-guided labs.

(Photo credit: Jeff Goldberg)

DEPARTMENT OF NEUROLOGY

236

NEUROLOGY FACULTY
with

18

joining in 2018

80K+

OUTPATIENT VISITS

$23.4M

IN NEW AND CONTINUOUS GRANT FUNDING

70

RESIDENCY AND FELLOWSHIP POSITIONS

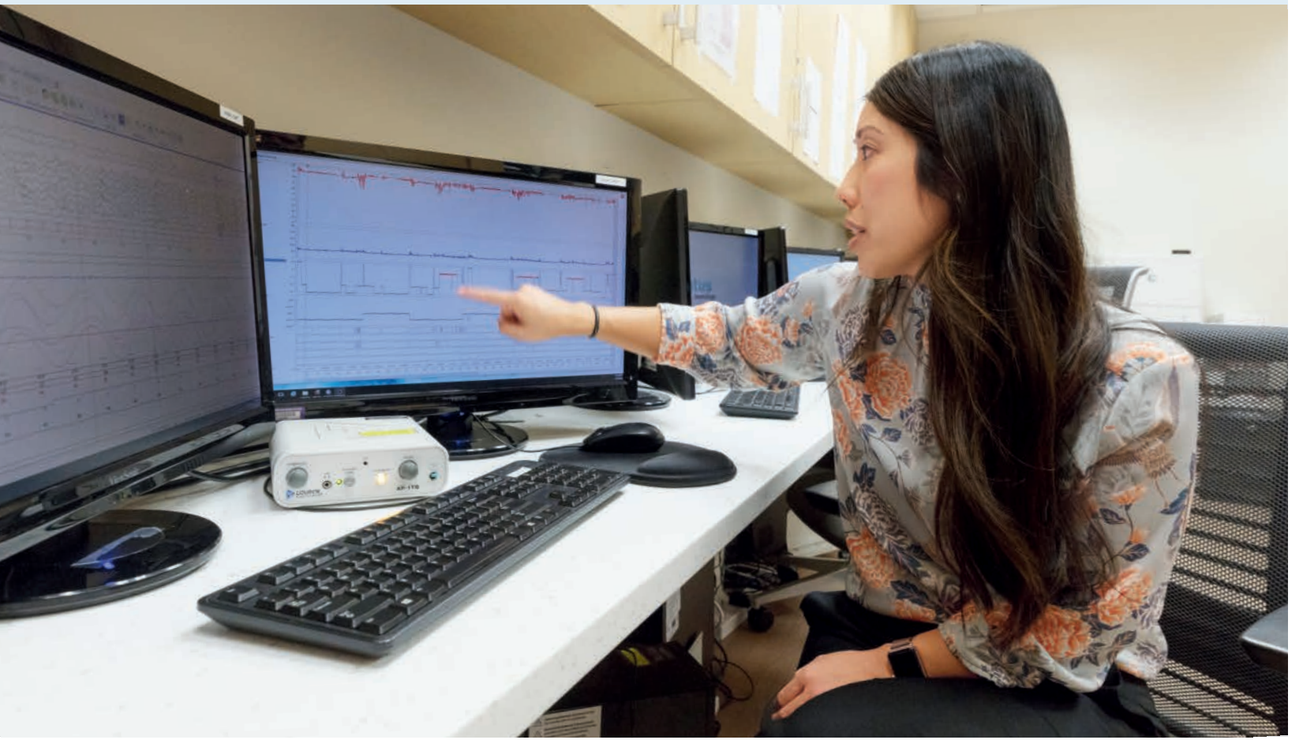
19

SUBSPECIALTY DIVISIONS
that enhance our clinical, teaching, and research missions

Numbers represent FY18 (Sept 2017–Aug 2018)

Using New Genetic Therapies and Sleep Expertise to Advance Epilepsy Treatment and Research

At the Comprehensive Epilepsy Center, a new understanding of epilepsy's genetic roots—and insights linking epilepsy, sleep, and memory—are giving rise to new treatments for patients.



Karen L. Lee, MD

NOVEL MEDICATIONS TARGET EPILEPSY'S CELLULAR ORIGINS

NYU Langone Health researchers continue to demonstrate leadership in the development and evaluation of new epilepsy drugs. In 2018, researchers led two single-site phase II trials of ataluren—a small-molecule medication approved in Europe for Duchenne muscular dystrophy—to examine its effectiveness in treating Dravet syndrome and CDKL5, which are expected to conclude in early 2019. Additional center research includes a single-site trial exploring the use of fenfluramine to treat CDKL5, an international trial studying ganaxolone as a treatment for CDKL5 and PCDH19, and a trial investigating the off-label use of the plant-derived supplement vinpocetine to suppress seizures in patients with a GABA receptor mutation.

"The opportunity to host these trials puts us in a unique position to vastly expand available treatments and significantly improve quality of life for individuals with epilepsy and related disorders," says Orrin Devinsky, MD, professor of neurology, neurosurgery, and psychiatry and director of the Comprehensive Epilepsy Center.

NYU Langone researchers are working on early-stage CRISPR therapies for epilepsies caused by mutations in DHPS, SCN1A (Dravet syndrome), and CDKL5 genes; these therapies will soon move to animal testing. The team's additional investigations into new genetic approaches for these and other genetic disorders could have extensive impact. "We're targeting the gene mutations that trigger these conditions," says Dr. Devinsky. "The resulting therapies could have far-reaching efficacy for other genetic disorders, such as blood disorders and cancers."

Epilepsy Center Achieves Milestone with FDA Approval of Cannabidiol

The Comprehensive Epilepsy Center's role in the clinical testing of liquid cannabidiol (CBD) for seizure disorders culminated with the June 2017 FDA approval of the cannabis derivative as a seizure-reducing medication for Lennox-Gastaut syndrome and Dravet syndrome. "The story of CBD is a remarkable one," says Orrin Devinsky, MD, professor of neurology, neurosurgery, and psychiatry and director of the Comprehensive Epilepsy Center. "With the established safety profile and efficacy data, CBD has made it into pharmacies as of late 2018, available for people with these severe disorders." Additional 2018 investigations support CBD as an off-label treatment for CDKL5 deficiency disorder, as well as for Aicardi, Dup15q, and Doose syndromes.

Dr. Devinsky is collaborating with Richard Tsien, PhD, the Druckenmiller Professor of Neuroscience, professor of neurology, and chair of the Department of Neuroscience and Physiology, to take CBD research even further, exploring the drug's seizure-control mechanisms in the context of other epilepsy syndromes, as well as in conditions such as autism and anxiety.

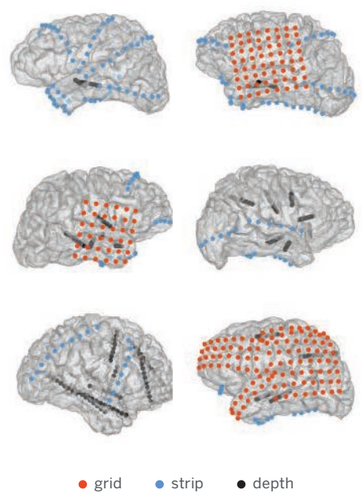
Orrin Devinsky, MD, was named one of *TIME* magazine's 50 Most Influential People in Health Care for 2018.

Using New Genetic Therapies and Sleep Expertise to Advance Epilepsy Treatment and Research

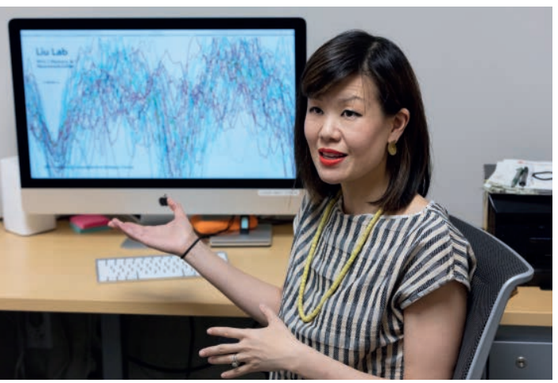
STUDYING THE LINKS BETWEEN SLEEP, MEMORY, AND BRAIN ABNORMALITIES

For individuals with epilepsy, sleep disturbances are often a major issue—poor sleep can elicit seizures, and epilepsy itself can exacerbate sleep problems. This cycle was a driving factor in integrating the Sleep Center into the Comprehensive Epilepsy Center, where all epilepsy patients are screened for sleep disorders. "The ready availability of screening data supports both our collaborative research and our targeted clinical approach," notes the sleep center's pediatric sleep specialist, Karen L. Lee, MD, clinical assistant professor of neurology.

Center research is focused on the links between epilepsy, memory impairment, and sleep. One study, supported by an NIH Career Development (K) Award given to Anli A. Liu, MD, assistant professor of neurology, records intracranial EEG activity in epilepsy patients as they participate in memory tasks. Study subjects include epilepsy patients undergoing invasive EEG monitoring for surgery, as well as patients with brain-implanted responsive neurostimulation devices that provide chronic EEG monitoring in an ambulatory setting. The goal is to understand how pathological electrical events such as interictal epileptiform discharges and high-frequency oscillations disrupt learning.



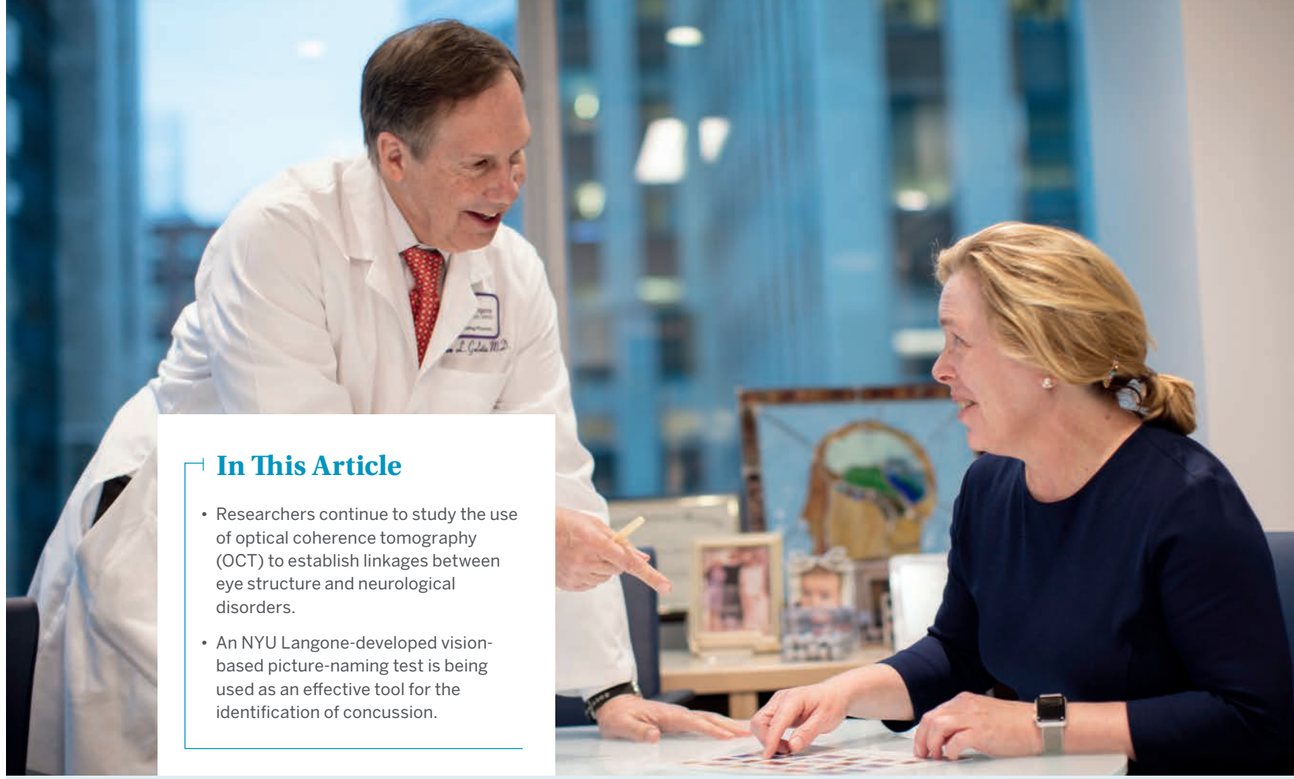
Images of the brains of epilepsy surgical patients undergoing EEG monitoring in order to localize a seizure focus and determine candidacy for surgical resection. The configuration of the electrode grid (red dots), strips (blue dots), and depth electrodes (black dots) are tailored to possible locations of the patients' seizure onset zone.



Anli A. Liu, MD

"Epilepsy patients commonly have impaired short- and long-term memory," explains Dr. Liu. "If we discover that initial encoding of information is disrupted by abnormal brain waves, we could then administer treatments to inhibit these events and restore memory."

A separate, R01 grant–funded collaboration between Orrin Devinsky, MD, Comprehensive Epilepsy Center researchers, and György Buzsáki, MD, PhD, the Biggs Professor of Neuroscience and professor of neurology, uses techniques such as transcranial electrical stimulation (TES) and acoustic stimulation to enhance brain rhythms critical to sleep-dependent memory consolidation. Recently, Dr. Liu's team has been working to enhance sleep-dependent brain rhythms through a closed-loop acoustic driving approach.



In This Article

- Researchers continue to study the use of optical coherence tomography (OCT) to establish linkages between eye structure and neurological disorders.
- An NYU Langone-developed vision-based picture-naming test is being used as an effective tool for the identification of concussion.

Vision-Related Biomarkers Provide New Clues for Diagnosing and Monitoring Neurological Disorders

Advanced neuro-ophthalmic research has identified changes in the condition and function of the eye that could lead to enhanced diagnosis and management of neurological disease and brain injury.

Steven L. Galetta, MD, and Laura J. Balcer, MD, MSCE

Vision-Related Biomarkers Provide New Clues for Diagnosing and Monitoring Neurological Disorders

NEURO-OPHTHALMOLOGISTS IDENTIFY TELLING NEW LINKS BETWEEN EYE STRUCTURE, FUNCTION, AND NEUROLOGICAL DISEASE

Research into optic neuritis as a manifestation of multiple sclerosis (MS) took a major step forward in 2018 with the publication of a pilot study by NYU Langone Health researchers establishing a threshold for the amount of retinal thinning considered predictive of an MS-related lesion in the optic nerve, the pathway connecting the eye with the rest of the brain.

Using optical coherence tomography (OCT), a high-resolution retinal scanning technique pioneered at NYU Langone, the new study builds on earlier research aimed at identifying patients with a history of optic neuritis. The higher resolution of OCT scans may be better able to detect both asymptomatic and symptomatic MS-related optic nerve lesions—a defining MS symptom currently omitted from standard diagnostic criteria—and measure the progression of MS and response to treatment over time.

The 2018 study, published in the *Journal of Neuro-Ophthalmology,* compared OCT scans of 124 individuals diagnosed with MS to scans of healthy controls. It found that an inter-eye difference of five microns to six microns in retinal nerve fiber layer thickness most closely correlated with patients who had an optic nerve lesion, which was defined for the study as a clinical history of prior optic neuritis. This NYU Langone–based investigation led to an international, multi-site study of 1,500 MS patients, which confirmed these inter-eye difference thresholds for the identification of an optic nerve lesion within a larger and more diverse study cohort.

"Many MS patients eventually develop optic nerve lesions—which is why we feel strongly that the presence of such lesions should be one of the imaging criteria used in diagnosing MS," explains Steven L. Galetta, MD, the Philip K. Moskowitz, MD Professor and Chair of Neurology and professor of ophthalmology. "The next step is to see how our OCT data fare in modeling and predicting who ultimately gets MS, by establishing a meaningful benchmark for retinal nerve thickness and monitoring the outcomes of those with clinically isolated demyelinating syndromes."

BEYOND MS: USING OCT TO DIAGNOSE AND MONITOR OTHER NEUROLOGICAL DISORDERS

In light of OCT's relative ease of use and low cost as a diagnostic tool, clinicians in the Division of Neuro-Ophthalmology are expanding the applications of OCT to the evaluation of other conditions, such as suspected chronic traumatic encephalopathy (CTE) in contact sport athletes. "The goal is to determine whether this visual pathway can serve as a potential living biomarker for CTE or cognitive decline among those who have a history of contact sports exposure," notes Laura J. Balcer, MD, MSCE, professor of neurology, ophthalmology, and population health, and vice chair of the Department of Neurology.

Steven L. Galetta, MD, and Laura J. Balcer, MD, MSCE with a patient.

This research joins other ongoing OCT studies of patients with Parkinson's disease and Alzheimer's disease, all with the common goal of providing new insight into the effects of these disorders on the eye and the visual pathway and potentially helping to predict disease progression.

MULES ADDS TO CONCUSSION ASSESSMENT ON THE SIDELINES

As concussion continues to grow as a concern in youth, collegiate, and professional sports, the Mobile Universal Lexicon Evaluation System (MULES), a vision-based picture-naming test developed by NYU Langone neuro-ophthalmologists, is proving to be an effective tool for the sideline assessment of concussion, and it could be effective in identifying other neurodegenerative conditions as well. Designed as a series of 54 grouped color photographs that integrate color perception, eye movements, and contextual object identification, MULES is a subtype of the rapid automatic naming measures that have been used for more than 80 years to capture vision-based aspects of cognition.

"We're employing the test on a research basis with a number of local athletes," notes Dr. Galetta. "By comparing sideline performance with an athlete's preseason score, we've found that it identifies concussion with a high level of sensitivity."

MULES also has potential as a vision-based assessment tool for other neurological disorders, since it captures a wide distribution of neural networks involving color vision, object recognition and categorization, and speed of object identification. One study, published in 2018 in the *Journal of the Neurological Sciences*, correlated MULES performance with vision changes found in patients with MS. The study found a link between slower MULES picture-naming times and low-contrast letter acuity—the perception of gray letters on a white background—established for two decades as a marker of MS-related visual dysfunction.

Laura J. Balcer, MD, MSCE, uses optical coherence tomography to obtain a high-resolution image of a patient's retina.

Researchers are now studying the effectiveness of MULES in Parkinson's and Alzheimer's diseases, and investigators in the Eye Movement Testing Lab have added the test to their groundbreaking repository of data linking eye movement abnormalities with various neurological conditions to look for new patterns and potential diagnostic clues.

The expanding applicability of vision-related evaluation tools suggests that changes in visual structure and function truly reflect what is happening with the rest of a patient's nervous system. "The eyes are a window into the brain, and we're continuing to explore that connection," notes Dr. Balcer.

Allal Boutajangout, PhD, and Thomas M. Wisniewski, MD

Novel Oligomer-Targeting Immunotherapies Offer a Promising New Direction in Alzheimer's Treatment

Researchers at the Center for Cognitive Neurology continue to focus on therapies for Alzheimer's disease, targeting the condition's molecular roots and isolating highly neurotoxic molecules in order to reduce pathology without evoking toxic side effects.

By isolating neurotoxic molecules and creating synthetic oligomers, NYU Langone Health researchers have advanced their search for a new lead in Alzheimer's immunotherapy. The researchers' investigations, described in a pair of 2018 articles, use antibodies that attack the characteristic beta-sheet structure created when monomers combine into oligomeric form—a key step in Alzheimer's progression. Because this beta-sheet structure is shared by many types of oligomers, these antibodies can be used to target toxic proteins, including the amyloid-beta and tau proteins that predominate in the brains of Alzheimer's patients. These studies build on the researchers' original animal studies, published in 2017 in *Scientific Reports*, which demonstrated that oligomer-fighting antibodies could be created from p13Bri, a protein associated with the rare genetic disease British amyloidosis, and then be used to target the structure of the oligomers rather than proteins to avoid a toxic autoimmune response.

"These antibodies offer a more focused approach compared to existing immunotherapy treatment options for Alzheimer's," says Thomas M. Wisniewski, MD, the Gerald J. and Dorothy R. Friedman Professor of Neurology, professor of pathology and psychiatry and director of the Center for Cognitive Neurology. "In addition to their reduced risk of toxic side effects, they allow the simultaneous targeting of multiple pathologies and proteins—versatility that is vital considering the variable characteristics of dementia-causing pathology from person to person."

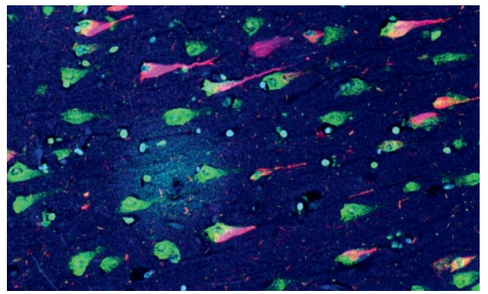
NEW STUDIES AFFIRM THE EFFECTIVENESS OF OLIGOMER TARGETING

In 2018, Dr. Wisniewski and colleagues published a pair of animal studies in *Alzheimer's Research & Therapy* that evaluated the efficacy of two monoclonal antibodies developed in the lab. The drugs, GW-23B7 and TWF9, both significantly reduced oligomeric forms of amyloid-beta and tau and also improved cognitive performance in aged mice with extensive Alzheimer's disease pathology.

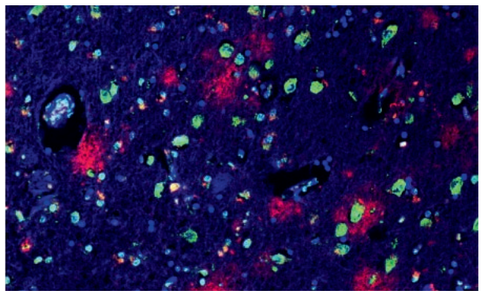
"In both studies, we began treatment in animals whose Alzheimer's disease was quite advanced," says Dr. Wisniewski. "In many previously published immunotherapeutic approaches, the antibodies were given at the onset of disease pathology, but we were seeking to demonstrate therapeutic efficacy in late-stage disease." Researchers plan to test the monoclonal antibodies in nonhuman primates and are submitting grant proposals for phase I human trials of the drugs.

NIH-Funded Fellowship Program Trains Next Generation of Alzheimer's Researchers

A new NYU Langone fellowship program is training select MDs and PhDs in bench and translational research on therapeutic approaches to Alzheimer's and other neurodegenerative diseases. The program, funded by an NIH T32 research training grant, launched in late 2017 and has four fellows enrolled. "There's a pressing need to train researchers in Alzheimer's disease—a chronic illness without effective treatments that is quickly becoming recognized as the most expensive condition in healthcare," says Dr. Wisniewski. "This fellowship will play a key role in meeting that critical need."



To determine if TWF9 neuronal staining was seen in neurons containing neurofibrillary tangles (NFTs), researchers performed double immunostaining with TWF9 and a phosphorylated tau marker (pSer404).



To determine if TWF9 recognized amyloid plaques in formalin-fixed-paraffin-embedded tissue, researchers performed double immunostaining with TWF9 and an Aβ42 marker (rab42) in the entorhinal cortex.

Novel Oligomer-Targeting Immunotherapies Offer a Promising New Direction in Alzheimer's Treatment

Center researchers also plan to expand their approach to other neurodegenerative disorders. One investigation will examine the impact of the antibodies on traumatic brain injury, where neurodegeneration appears to be driven mainly by toxic tau protein. Another will test their approach in Parkinson's disease—which, along with Lewy body disease, is caused primarily by alpha-synuclein oligomers—and a third investigation will study diseases linked to prions, such as mad cow disease.

Researchers are also collaborating with neuroradiologists to examine the effectiveness of a novel imaging tool to complement this oligomer-targeting drug development approach. The new technology uses a ligand that binds to oligomers, allowing them to be visualized on PET scans. "This ligand could enable us to visualize and quantify the oligomeric species in animal models as well as in Alzheimer's patients themselves," notes Dr. Wisniewski.

OTHER IMMUNOLOGICAL ALZHEIMER'S DRUG INVESTIGATIONS HOLD PROMISE

Researchers continue to advance investigations into other promising Alzheimer's drugs, including CpG ODN, a novel molecule developed at NYU Langone that boosts activity of the brain's primary immune cells by stimulating the immune system–mediating protein toll-like receptor 9 (TLR9). "We've completed one full set of animal experiments, treating squirrel monkeys for two and a half years with this TLR9 agonist," says Dr. Wisniewski. "We're seeing significant cognitive benefits and a reduction in Alzheimer's related pathology without any evidence of toxicity." A second set of grant-funded primate experiments is under way, and application for funding for a human phase I clinical trial is planned.

These studies are in addition to Alzheimer's immunotherapy trials already in progress. Researchers are conducting phase III trials of aducanumab, a monoclonal antibody that is derived from healthy aged donors with no cognitive impairment and that appears to be effective at reducing amyloid plaque in the brains of patients with early Alzheimer's disease. In addition, NYU Langone will be part of an upcoming TANGO study, a phase II trial of another novel immunotherapy agent, BIIB092, which targets tau proteins in the brain.

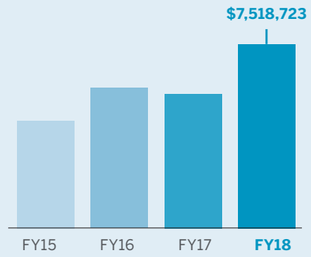
Portfolio of Total Awarded Grants

FY15
$4,405,825

FY16
$5,735,075

FY17
$5,509,845

FY18
$7,518,723



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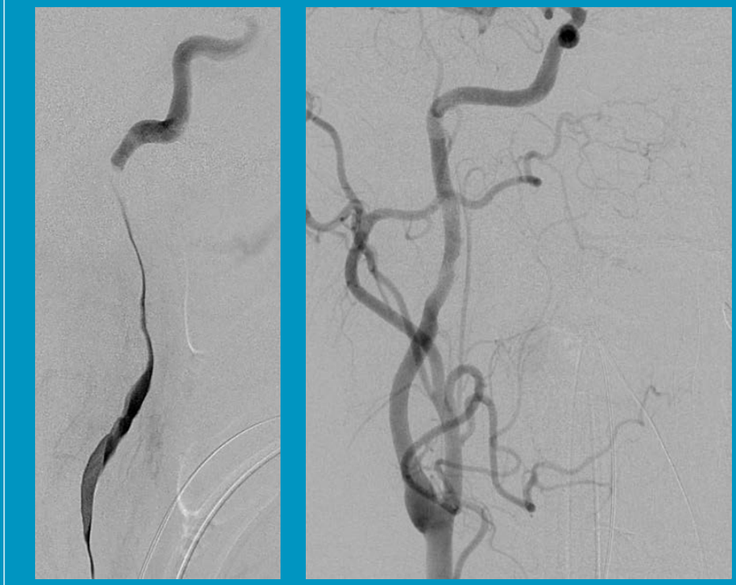
ONGOING ALZHEIMER'S INVESTIGATIONS

Complex Case: Swift Neurovascular Intervention Prevents an Impending Stroke

A woman in her late 40s presented to physicians at the Ronald O. Perelman Center for Emergency Services with tingling and numbness in her right hand, accompanied by imaging obtained at an out-of-state institution where she had presented with similar symptoms while traveling a few days earlier. With her symptoms recurring, she was referred to vascular neurologist Jose L. Torres, MD, assistant professor of neurology, who ordered repeat vascular imaging based on earlier findings of left carotid artery dissection. The new scan revealed that her left carotid artery dissection had worsened, with new dissection in the right carotid artery and irregularities in the left vertebral artery.

Although a subsequent MRI showed no brain injury or stroke, Dr. Torres and the attending neuro-interventional radiologist, Maksim Shapiro, MD, clinical associate professor of radiology and neurology, performed a conventional angiogram, which demonstrated that all major arteries to the brain—now including the right vertebral artery—were deteriorating. "Based on the appearance of the vessels as well as the risk associated with intervention, we decided to stent the two carotid arteries on the spot, leaving the two vertebral arteries to be managed medically," explains Dr. Torres.

The successful procedure was completed in less than five hours, and the NYU Langone team's swift, multidisciplinary intervention prevented what could have been a major stroke. "She could have easily been disabled for life," he says. "But our emergency department physicians, nurses, stroke doctors, and interventional radiologists mobilized as a team, responding to a troubling set of symptoms and imaging results with the most advanced intervention available."



Severely reduced blood flow in the patient's right internal carotid artery (left), with normal blood flow restored after intervention (right).

Innovative Therapies Could Improve Treatment Options and Quality of Life for MS and Parkinson's Patients

Novel treatment approaches developed and enhanced at NYU Langone Health hold potential for both reducing symptoms and strengthening rehabilitation protocols for patients with complex neurological disorders.

Lauren B. Krupp, MD; Leigh E. Charvet, PhD; Robert W. Charlson, MD

In This Article

- Remotely supervised transcranial direct current stimulation (RS-tDCS) for patients with MS continues to produce promising results.
- Researchers are investigating RS-tDCS for patients with Parkinson's disease and other neurological conditions.
- A novel art therapy protocol targets abnormalities in visuospatial function in Parkinson's patients.

AT-HOME TRANSCRANIAL STIMULATION PROVIDES SUSTAINABLE RELIEF FOR MS-RELATED FATIGUE

Remotely supervised transcranial direct current stimulation (RS-tDCS), a novel NYU Langone–developed protocol designed to relieve a range of symptoms associated with multiple sclerosis (MS), is gaining momentum as clinicians at the Multiple Sclerosis Comprehensive Care Center uncover new applications for the telemedicine technology.

RS-tDCS safely influences the brain's neuronal activity by applying low-level electric current through electrodes placed on the scalp, with treatments carried out at home under remote video supervision. Findings from a 2017 clinical trial indicated that RS-tDCS can alleviate intractable MS-related fatigue, a common and troubling symptom that has been without treatment options until now.

The remote capability is critical to the technique's effectiveness, notes Leigh E. Charvet, PhD, associate professor of neurology, who leads the MS-related tDCS research. "For optimal long-term effect, tDCS treatments need to be administered five days a week for four weeks or more—and traveling to a clinic can be difficult for people with advanced MS or Parkinson's," she says. "We've spent a lot of time working with biomedical engineers to make our tDCS headsets easy to use so MS patients can operate them unassisted."

Following these encouraging results, a 2018 study, published in *Neuromodulation*, revealed enhanced gains in complex attention and response variability among MS patients who received tDCS during cognitive training exercises. "Because tDCS influences the resting potential of the brain's neurons to fire and form connections, reinforcing neuroplasticity, the hope is that it can reinforce the learning process," explains Dr. Charvet. "When paired with rehabilitation, this should produce quicker, stronger, and more lasting results."

Together, these promising results have bolstered a number of additional studies. Researchers are now conducting a large-scale controlled trial of RS-tDCS's benefits for MS-related fatigue, and they have launched another study, funded by the Department of Defense, which is investigating the effects of applying tDCS to the motor cortex of patients with progressive MS while they perform hand exercises designed to improve manual dexterity.

Researchers are also conducting an NIH-funded pilot study using real-time functional MRI scans during patients' tDCS treatments to gain insight into the brain changes elicited by the treatment protocol. Collectively, these trials will provide insight into who benefits from tDCS and which parameters work best when administering it.

Leigh E. Charvet, PhD, shows a patient how to use the remotely supervised transcranial direct current stimulation headset.

Innovative Therapies Could Improve Treatment Options and Quality of Life for MS and Parkinson's Patients

STUDYING THE IMPACT OF REMOTELY SUPERVISED TDCS ON PARKINSON'S AND OTHER NEUROLOGICAL CONDITIONS

NYU Langone researchers are also looking into the benefits of RS-tDCS for other neurological conditions in several open-label studies.

A study conducted in collaboration with researchers at the Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, published in 2018 in the *Journal of NeuroEngineering and Rehabilitation*, demonstrated the applicability of this methodology in Parkinson's disease, with improvements in fatigue and cognition similar to those seen in MS. Further, as published in 2018 in the *Journal of Clinical Neuroscience*, patients with moderate Parkinson's disease experienced a notable reduction in symptoms from using RS-tDCS in combination with cognitive training.

"The use of telemedicine to supervise at-home tDCS will allow us to reach more patients and also to bypass common obstacles that prevent populations with mobility impairment or other accessibility barriers from participating in clinical trials and receiving health services," says Milton C. Biagioni, MD, assistant professor of neurology and co-investigator on the study. "This is the first time an RS-tDCS protocol has been designed for and tested in these patients."

These early positive findings sparked a separate clinical trial, funded by the Parkinson's Foundation, that studied the use of RS-tDCS to alleviate fatigue and cognitive slowing in Parkinson's patients—with encouraging findings submitted for publication. Case histories compiled from this study also detail RS-tDCS's potential as a treatment for depression and cerebellar ataxia, as well as for stroke-related damage and head injury—demonstrating its far-reaching promise as a treatment modality for neurological disease.

Although studies currently focus on patients with moderate Parkinson's disease, researchers at the Fresco Institute anticipate expanding these investigations in the near future to include patients with advanced disease. "The specific effects of tDCS depend on its applications and frequency of use, and these telemonitored trials play a critical role in defining those parameters so we can reach and help as many patients as possible," Dr. Biagioni concludes.

Landmark MS Center Study Confirms Extended Natalizumab Dosing Safety

In the first study quantifying the risk reduction associated with less frequent dosing of natalizumab, an extended dosing protocol was found to sharply reduce patients' risk of developing progressive multifocal leukoencephalopathy (PML), a rare but potentially fatal brain infection. Lana Zhovtis Ryerson, MD, assistant professor of neurology, and Ilya Kister, MD, associate professor of neurology, examined the impact of a 300 mg infusion of the drug every five to 12 weeks—rather than every four weeks, the current protocol.

"Natalizumab is one of the most effective medications available to treat relapsing-remitting MS," says Dr. Ryerson. "But until now, patients have had to consider stopping it after two years to ensure their safety, as approximately half of all MS patients harbor the JC virus—putting them at risk of developing PML." In a retrospective analysis of more than 90,000 patients on the medication, Dr. Ryerson found that less frequent dosing resulted in up to a 94 percent reduction in the risk of developing PML; she is now co-developing a protocol for a prospective, international, randomized trial to confirm extended-interval dosing efficacy.

Milton C. Biagioni, MD, with a patient.

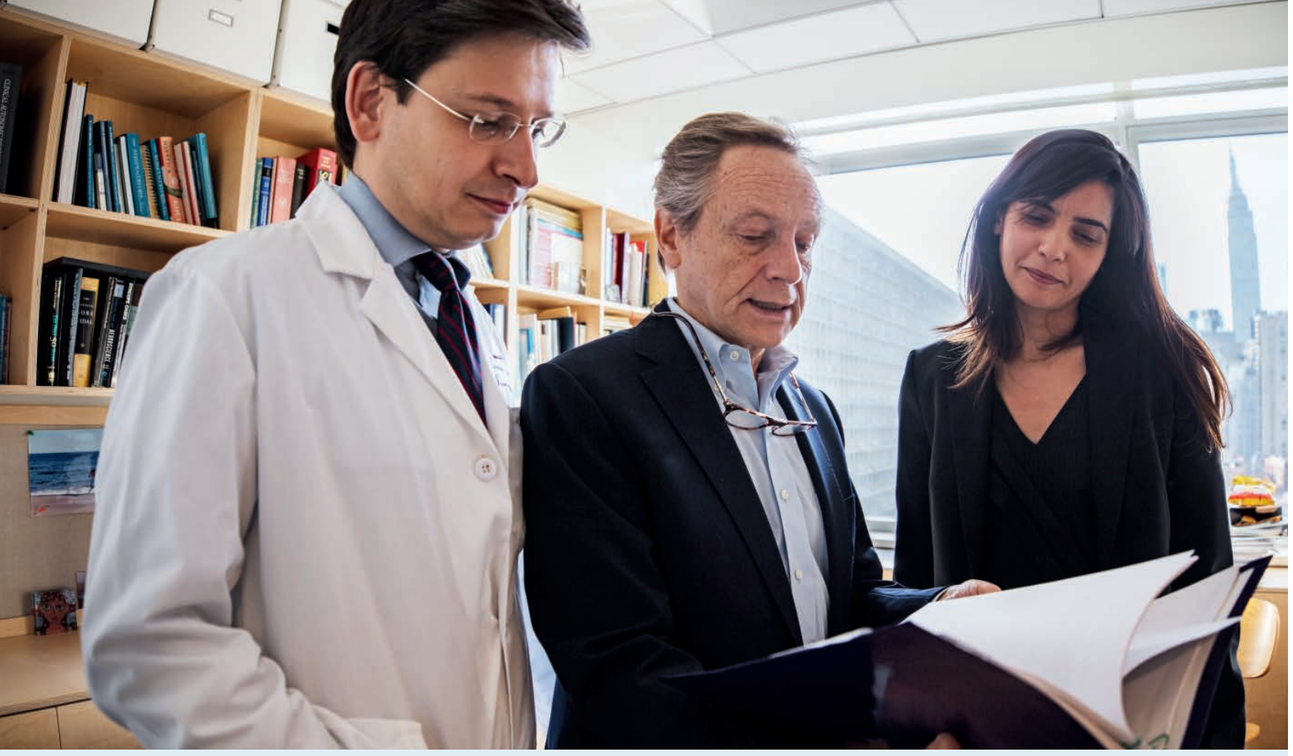
Art Therapy Protocol Aims to Address Visuospatial Deficits in Parkinson's Patients

A novel Parkinson's protocol developed by clinical researchers at the Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders in partnership with Rusk Rehabilitation and the NYU Steinhardt Art Therapy Program involves using art therapy techniques such as paint, clay, and origami to target abnormalities in visuospatial function—which influences everything from color perception and contrast sensitivity to gait and hand dexterity.

Researchers, led by Milton C. Biagioni, MD, assistant professor of neurology, are measuring the impact of art therapy through MRI-based brain connectivity analysis and eye movement efficiency, as well as through behavioral, neuropsychological, and gait kinematic assessments. "Creating art relies on complex and interconnected mechanisms such as visual processing and motor-sensory integration, and this study tracks its impact on the visual network," explains Dr. Biagioni.

Because visuospatial dysfunction is associated with deficits in a wide range of daily activities, the hope is that this approach will provide an early intervention that can help prevent downstream impairment in areas such as balance and spatial navigation. "I like to think of it as prehabilitation," adds Dr. Biagioni. "In addition to its potential neurological benefits, art therapy enables subjects to understand their emotions and manifest them through creative thinking and artistic expression, promoting self-awareness, relaxation, and self-confidence without stigma."

A painting created by a patient taking part in the Parkinson's art therapy protocol.



Harnessing Expertise in Autonomic Disorders to Yield New Approaches to Long-Standing Challenges

Researchers at NYU Langone Health's Dysautonomia Center are building on significant advancements made in the last year to inform new approaches to the diagnosis and treatment of autonomic disorders.

Jose Alberto Palma Carazo, MD, PhD; Horacio Kaufmann, MD; Lucy J. Norcliffe-Kaufmann, PhD

In This Article

- A simple bedside screen provides insight into possible autonomic causes of orthostatic hypotension.
- A groundbreaking NYU Langone trial explores the use of an FDA-approved medication for patients with multiple system atrophy (MSA).

BEDSIDE DIAGNOSTIC TOOL REVEALS ORIGINS OF ORTHOSTATIC HYPOTENSION

NYU Langone researchers have identified a simple calculation that can help clinicians identify a neurogenic etiology for orthostatic hypotension, a chronic and substantial drop in blood pressure upon standing, often resulting in dizziness, lightheadedness, visual blurring, or fainting.

The research was developed out of the need for clinicians to readily distinguish between neurogenic and non-neurogenic causes of orthostatic hypotension in order to guide patients' prognosis and treatment. Although the problem has a number of benign, non-neurological causes, it can also be linked to a family of serious neurodegenerative disorders known as synucleinopathies, including Parkinson's disease, multiple system atrophy, and some types of dementia. Orthostatic hypotension may be an early indicator of these diseases, but currently the differential diagnosis requires time-consuming, specialized autonomic testing in the laboratory. The newly developed algorithm—dividing a change in heart rate by a drop in blood pressure after a patient stands—provides a simple shortcut that signals a need to look into autonomic causes.

"This simple, effective bedside screen for autonomic disorders may lead us to identify patients with disorders such as Parkinson's disease years before they suffer movement or memory difficulties—and enable intervention before severe brain damage has occurred," says Lucy J. Norcliffe-Kaufmann, PhD, associate professor of neurology and neuroscience and physiology and lead author of the paper published in *Annals of Neurology* in March 2018.

Individuals with neurogenic orthostatic hypotension typically have little or no increase in heart rate after standing, while those with the non-neurogenic form have a marked increase in heart rate. To create the analytical shortcut to distinguish the two, the researchers identified more than 400 patients diagnosed with either type of orthostatic hypotension based on detailed autonomic testing and measured their blood pressure while on a tilt table in a supine position, as well as in the head-up position to mimic standing up. This test indicated that when the increase in heart rate was less than half a beat per minute for each unit of drop in systolic blood pressure, the condition almost invariably had a neurogenic cause. "For the first time, we are able to systematically show that patients whose blood pressure drops after standing up, without a specific increase in their heart rate, may have autonomic dysfunction caused by a synucleinopathy," says Horacio Kaufmann, MD, the Felicia B. Axelrod Professor of Dysautonomia Research, professor of medicine and pediatrics, and director of the Dysautonomia Center and of the Division of Autonomic Disorders. "This research should have widespread applicability."

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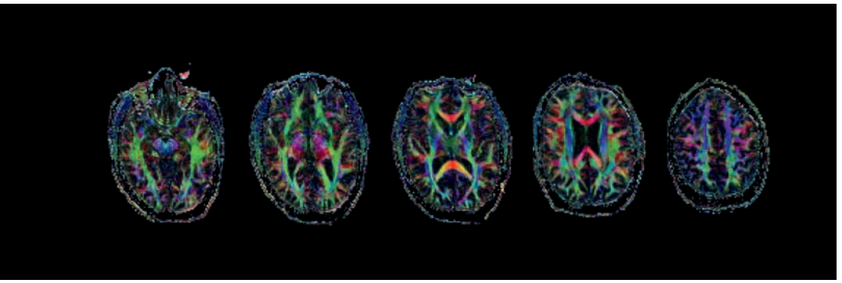
Harnessing Expertise in Autonomic Disorders to Yield New Approaches to Long-Standing Challenges



Magnetic resonance diffusion tensor imaging sequences in a patient with multiple system atrophy, evaluating subtle changes in the brain after one year of treatment with either sirolimus or a placebo.

NOVEL APPLICATION OF APPROVED IMMUNOSUPPRESSANT COULD TARGET MULTIPLE SYSTEM ATROPHY

A clinical trial exploring a potential new use of an FDA-approved medication could offer hope for patients with multiple system atrophy (MSA). No effective treatment to date has addressed the underlying pathology of MSA—a general breakdown of the body's motor and autonomic nervous systems that typically strikes people in their 50s and invariably causes death, usually within eight to 10 years.

The groundbreaking three-year NYU Langone trial, which began recruiting participants in 2018, is being led by Jose Alberto Palma Carazo, MD, PhD, assistant professor of neurology and assistant director of the Dysautonomia Research Laboratory. Dr. Palma's team will study the anti-MSA effects of the immune suppressant medication sirolimus, also known as rapamycin. In addition to being used to prevent rejection of transplanted organs, sirolimus promotes autophagy, the process by which toxic, misfolded proteins are removed from the body.

This controlled, double-blind study will enroll 56 patients with MSA, and Dr. Palma and colleagues will explore whether sirolimus can reduce levels of alpha-synuclein, the toxic protein that causes the disorder. Of the study subjects, 75 percent will receive sirolimus and 25 percent will receive a placebo, with researchers monitoring disease progression over time with neurological examinations, regular MRI scans of the brain, and regular measurements of subjects' retinal nerve thickness using optical coherence tomography.

Dr. Palma's study—the first ever to employ an autophagy-stimulating drug against a neurodegenerative disorder—received funding from the NIH through an R01 grant. "Fortunately, sirolimus is an FDA-approved drug with a well-known safety profile to support its use in our research," he notes. "We are building on robust evidence that sirolimus reduces alpha-synuclein accumulation and associated neurodegeneration in animal and cell models of synucleinopathies."

Looking beyond MSA, the investigators believe that sirolimus may also hold promise as a treatment for other neurological conditions associated with the accumulation of toxic proteins, including Parkinson's disease and Alzheimer's disease. "If this approach works, sirolimus could not only benefit our MSA patients but also potentially be tested as a treatment for the entire range of neuro-degenerative diseases," says Dr. Palma.

NYU Langone's Dysautonomia Center treats the **largest population of multiple system atrophy patients** in the United States.

Disclosure: Pfizer kindly donated the study drug to Dr. Palma, but they had no involvement in the study design, or provided any funding.

Enzyme Replacement Breakthroughs Bring Hope to Patients with Lysosomal Storage Disorders

Researchers in NYU Langone's Division of Neurogenetics played a central role in the FDA's recent approval of two life-changing medications for the enzyme deficiencies caused by lysosomal storage disorders (LSDs). Under the leadership of Heather A. Lau, MD, assistant professor of neurology and director of the Lysosomal Storage Disorders Program, NYU Langone was a lead site in evaluating the first-ever therapy for mucopolysaccharidosis type VII (MPS VII)—also known as Sly syndrome—which can affect growth and cardiac and pulmonary function in children. Researchers will continue to monitor MPS VII patients across the eastern United States over the next decade to gather additional data on the drug's efficacy.

The division also played an integral role in the development of a breakthrough oral medication for Fabry disease—an LSD that affects the heart and lungs—which offers an alternative to infusion-based treatment. The first FDA-approved LSD chaperone drug, this medication enhances activity of Fabry patients' own deficient enzymes, rather than providing enzymes from an external source.

In 2018, the division began enrolling patients in phase I trials of MPS I and MPS II medications—both drugs developed through a novel gene-editing technique using viral vectors and zinc-finger nucleases to insert the gene for each condition's missing enzyme directly into patients' genomes. The liver's albumin promoter then expresses the enzyme, effectively correcting the deficiency and potentially eliminating the need for weekly enzyme infusions. With an encouraging safety profile to date, the viral vectors' approach used in these trials could be applied to future treatments across all LSDs.

Heather A. Lau, MD

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11
ONGOING FELLOWSHIPS
that provide advanced neurological training to the department's

18
FELLOWS

36
NEUROLOGY FACULTY AND RESIDENTS
involved in ongoing quality and safety projects

Awards & Recognition

Steven L. Galetta, MD
was given the 2018 A.B. Baker Award for Lifetime Achievement in Neurological Education by the American Academy of Neurology for his career contributions to the field.

Aaron Nelson, MD
received the 2018 A.B. Baker Teacher Recognition Award from the American Academy of Neurology.

Jacqueline A. French, MD
was appointed to the board of directors of the American Neurological Association.

Laura J. Balcer, MD, MSCE
was named editor-in-chief of the *Journal of Neuro-Ophthalmology*.

Orrin Devinsky, MD
was named one of *TIME* magazine's 50 Most Influential People in Health Care for 2018.

Janet C. Rucker, MD
was appointed to the board of directors for the North American Neuro-Ophthalmology Society.

Koto Ishida, MD
was appointed to the American Academy of Neurology Guideline Development, Dissemination, and Implementation Subcommittee, and received the Rising Star Award in Education from NYU School of Medicine.

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vizient.

5
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ANNOUNCING

Tuition-Free Initiative Addresses High Student Debt

NYU School of Medicine announced in August 2018 that it will begin offering full-tuition scholarships to all current and future students in its MD degree program regardless of need or merit—a bold effort to simultaneously address the rising costs of medical education and still attract the best and brightest students to careers in medicine. "This decision recognizes a moral imperative that must be addressed, as institutions place an increasing debt burden on young people who aspire to become physicians," says Robert I. Grossman, MD, the Saul J. Farber Dean of NYU School of Medicine and CEO of NYU Langone Health.

(Photo credit: Juliana Thomas Photography)

Visit **med.nyu.edu/school** for more information.

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80

ONGOING CLINICAL TRIALS

30+

ONGOING RESEARCH STUDIES

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