

# DUKE NEUROLOGY











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# FROM OUR CHAIR

I'm excited to share our annual report with you. As our partners, colleagues, and generous benefactors, you are a crucial part of our current success and future aspirations as we endeavor to reduce the crippling burden of neurologic disorders. This year we have made tremendous progress in our ability to provide patient care, conduct ground-breaking research, and train the next generation of neurologists.

As a Department we have adopted the core values of excellence, generosity, and learning that inform both our daily actions and plans for the future. I'd like to thank all of our faculty, staff, residents, and fellows, as well as Drs. Eugene Washington, Bill Fulkerson, and Nancy Andrews, and our other partners within Duke Health and the Duke School of Medicine, who have worked countless hours to help us achieve these goals. I'd also like to thank the alumni, patients, philanthropic partners, academic colleagues, and family members that keep our Department strong and moving forward.

#### This report focuses on four stories from this year:

- » **"Unlocking Alzheimer's disease"** focuses on the research of Carol Colton, PhD, who is investigating how an unexpected culprit--the body's immune system--may play a major role in the formation of Alzheimer's disease.
- » **"Opening eyes in Eldoret"** follows two of our stellar graduating residents, Chen Lin, MD, and Ravi Vakani, MD, who traveled to Eldoret, Kenya, to help doctors there provide better neurological care.
- » "Getting the best stroke care--wherever you are" tells the story of Juanita Grant, a Danville, Virginia stroke patient who received life-saving care thanks to our telestroke network, which allows our doctors to remotely provide Duke-level stroke care to patients across North Carolina and Virginia.
- » "Cultivating innovation" explores the Clinical Laboratory Interface Program, or CLIP, a multidisciplinary group investigating new potential breakthrough therapies for traumatic brain injury and other conditions.

These stories represent only a sliver of the progress we made this year. We expanded our residency and fellowship programs for physicians. We also launched the nation's first residency program to provide neurology training for physician assistants and nurse practitioners, and we founded the Duke Center

for Research in Autoimmunity and Multiple Sclerosis (DREAMS), a multidisciplinary group of basic and clinical researchers dedicated to improving our understanding of multiple sclerosis and autoimmune brain diseases.

In all, it's been a wonderful year, and momentum towards the future is building every day.

RICHARD O'BRIEN, MD, PHD CHAIR, DUKE DEPARTMENT OF NEUROLOGY

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Fiscal Year 2016

## At a Glance









Total clinic visits: 41,000

## Research



Clinical trial research: \$6.8M

Laboratory research: \$3.2M

\* Total budgeted costs for FY 2016

Published peer-reviewed journal articles: 59



# LEADERSHIP

## Department Chair

Richard O'Brien, MD, PhD



## Vice Chairs



Julian Yang, MD Vice Chair, Clinical Operations



Saurabh Sinha, MD, PhD Vice Chair, Education



Brad Kolls, MD, PhD Vice Chair, Technology



Daniel Laskowitz, MD, MHS Vice Chair, Academics

## **Division Chiefs**



Joel Morgenlander, MD | General and Community Neurology Carmen Graffagnino, MD | Critical Care and Vascular Neurology | Stroke Timothy Collins, MD | Headache and Pain Mark Skeen, MD | Multiple Sclerosis and Neuroimmunology Mark Stacy, MD | Movement Disorders James Burke, MD | Memory Disorders Rod Radke, MD | Epilepsy and Sleep Vern Juel, MD | Neuromuscular Disease

## UNLOCKING ALZHEIMER'S DISEASE

Internationally renowned neuroscientist Carol Colton explains why the immune system may hold the key

Despite decades of research, science has yielded almost no treatments for Alzheimer's disease. That's why Carol Colton, PhD, professor of neurology at Duke, is leveraging her expertise in immunity to develop a new approach for understanding this devastating disease.

## Alzheimer's in a new light

Most Alzheimer's research has focused on amyloid plaques, clumps of protein that accumulate in the brain that are a distinctive sign of Alzheimer's disease. But while attempts to cure the disease by eradicating these plaques were initially promising in mouse models, such therapies have proved ineffective and even dangerous in treating humans.

Rather than focusing on amyloid plaques alone, Colton has taken a broader view at what is happening within the brains of people with Alzheimer's disease. The answer is a complicated one, involving many factors—including the body's own immune system.

"Alzheimer's disease is the disregulation of a system," she said. "You can't just focus on a single pathological event when a plethora of disease-based changes are observed, and then hope to find a magic bullet to hit a single target and stop the disease."

Colton was one of the first scientists to study brain immunity and, particularly, the microglia, which are the cells responsible for protecting the brain against disease. Her groundbreaking studies provide a different view of how the immune response in the brain contributes to Alzheimer's disease.

## Lessons from the liver to understand the brain

One of Colton's key insights into Alzheimer's disease came from an unusual source—the body's response to a liver parasite. Macrophages, giant immune cells that neutralize threats throughout the body, can exist in either a repair mode, walling off the threat and preserving the body's healthy cells, or in a toxic mode, destroying the invader as well as healthy cells caught up in the attack. An urgent threat such as a parasite would usually be dispatched swiftly with a toxic response.

However, in this case, the liver parasite communicates with the macrophages and convinces them to enter the repair phase instead. As a result, the macrophages wall off the parasite, protecting the body but allowing the parasite to survive.



"AFTER 20 YEARS OF FAILED DRUG TRIALS FOR ALZHEIMER'S DISEASE, WE CANNOT BE BLIND TO THE FACT THAT THESE TRIALS ARE NOT WORKING, AND THERE MUST BE A REASON WHY," SAID COLTON. Colton posited that a similar process could be taking place in the brain. Her team identified genes that would indicate whether microglia were in the repair or toxic phase when amyloid deposits began to form. In tests using mice with an Alzheimer's-like condition, they found that the microglia did not attack the amyloid deposits; as with the liver parasite, the deposits remained intact and accumulated.

#### Sapping resources

Researchers studying Alzheimer's had postulated that Alzheimer's-related brain cell death was due in part to collateral damage that results when microglia, operating in toxic mode, attack amyloid deposits. Colton's evidence, however, indicated that microglia react to amyloid deposits in repair mode. The next step was to figure out what was causing the neurons to die.

As it turned out, the microglia were not killing neurons outright, but sapping them of resources. As the microglia maintain a repair phase, they use critical amino acids such as arginine within the surrounding area, slowly starving the brain of these resources. When deprived of arginine and other nutrients, the stressed neurons die, triggering other pathologies associated with Alzheimer's.

## New hope for treatments

With this insight Colton studied ways to interrupt these detrimental immune processes. Her research led her to investigate a drug called Difluoromethylornithine, or DFMO, that is approved for treating cancerous tumors. Colton's initial experiments in mouse models of Alzheimer's disease demonstrated that the drug is able to prevent Alzheimer's pathology if started early, and is able to reduce pathology if started after the onset of the disease.

## Colton hopes to advance to human clinical trials within the next year. "Moving forward, there is now a new avenue of therapeutics, which is why we are so excited," she said.

Colton also has her sights set on better understanding the Alzheimer's disease process by focusing experiments on the events that initiate the abnormal immune response in microglia. To pursue this, she recently submitted a multi-million dollar grant to the National Institutes of Health for a university center to produce animal models of Alzheimer's disease that can improve the development of novel therapeutics.

A silver-bullet cure for Alzheimer's is likely impossible. But research like Colton's offers the possibility that scientists may yet find new ways to prevent or slow the course of the disease, giving renewed hope to patients and families desperately seeking the ability to live a fulfilling life and enjoy close relationships with loved ones.



"ALZHEIMER'S DISEASE HAS A VERY REAL POTENTIAL TO AFFECT EACH OF OUR LIVES," SAID COLTON. "WE ALL NEED A SENSE OF URGENCY TO SOLVE THIS WORLDWIDE PROBLEM."

# OPENING EYES IN ELDORET

Duke residents provide neurology training in Kenya

A disoriented, groaning man in a crowded hospital bed gave Ravi Vakani, MD, and Chen Lin, MD, a stark lesson in the realities of medicine in sub-Saharan Africa. Vakani and Lin, two Duke Neurology residents who graduated this year, traveled to Eldoret, Kenya for a month with Duke neurologist Carmen Graffagnino, MD, last summer to provide care and train local health-care providers about treating neurological conditions.

Vakani and Lin were discussing the morning's cases with a group of Kenyan doctors when, from across the hospital wing, they noticed a man who appeared to be undergoing a seizure. When asked about the man's condition, one of the doctors casually remarked, "He was found in a ditch last night. He's just psychotic." Lin and Vakani performed an examination and found the man in status epilepticus, a recurring seizure that can last for hours. They filled out the paperwork to initiate treatment and waited for it to arrive.

After nearly twenty minutes without an official response, Lin and Vakani dashed to a nearby pharmacy. Realizing that the hospital paperwork for paying for the medications would delay treatment, Vakani and Lin paid for it themselves and administered it to the patient, who eventually recovered.

The apparent indifference Vakani and Lin observed in their fellow providers occurred not from a lack of skill or desire to help, but from limited exposure to specialties like neurology and an overworked health system, Vakani said.

"The doctors we worked with were phenomenal when it comes to general internal medicine. They've developed fantastic clinical skills without the luxuries of equipment we take for granted," Vakani said. "They're also working in conditions where resources are scarce and the only compensation is the joy of providing care. However, their skillsets in neurology and other areas are less well developed. Although there is an abundance of patients with neurological disease, there are no full-time neurologists to train providers to recognize and treat these conditions." "THAT MORNING WAS A REAL EYE-OPENER. IT HIGHLIGHTED THE GULF BETWEEN HOW NEUROLOGICAL CARE IS PRACTICED IN KENYA AND HOW IT'S PRACTICED AT DUKE" RAVI VAKANI, MD

*Chen Lin, MD, (third from left) poses with a group of doctors and nurses in one of Eldoret's public hospitals.* 



In addition to lacking training, the sheer number of patients doctors face throughout Eastern Africa leads them to pass over difficult cases. In Eldoret, one part-time neurologist is on hand to provide care for all the public hospitals for a population the size of Durham (Duke alone has more than 70 full-time specialists). The 900 beds in Eldoret's major public hospital are typically filled with two or three patients each; personnel, medicine and equipment are in short supply. With demand for care greatly outstripping supply, many doctors naturally focus on the patients they can help quickly and easily.

During their visit, Vakani and Lin worked to improve that dynamic. Along with Graffagnino, they rounded with Kenyan providers, gave lectures on key "high-yield" neurological topics, and conducted surveys to identify areas for improvement. They also worked to develop effective standards of care for common neurological diseases and injuries. These standards were adapted to fit the realities of health care in sub-Saharan Africa, relying on doctors or nurses rather than modern machinery to make diagnoses, or recommending older, more widely available medications than those used in the United States.

"THERE'S A LOT THAT CAN BE DONE TO TREAT NEUROLOGICAL INJURIES OR CONDITIONS, EVEN WITHOUT A MILLION-DOLLAR MACHINE," LIN SAID.

"Getting doctors and patients to recognize basic conditions and treat them quickly can make a huge difference in the lives of patients and relieve the sense of futility many providers feel. One of the most rewarding parts of the trip was finding physicians interested in becoming future neurologists and potentially helping them fulfill this dream."

Vakani and Lin said their efforts made a real difference. "In our time there we saw a real paradigm shift, with providers becoming more confident in diagnosing cases and asking questions. One provider said he diagnosed epilepsy more in the one month we were there than he had in the past year," Vakani said. Graffagnino plans to return to Kenya with other residents to continue this work.

He is also working with Duke neurosurgeon Michael Haglund, MD, PhD, to improve infrastructure and training for neuroscience care in Kenya and neighboring Uganda. Their efforts are part of the Academic Model Providing Access to Healthcare (AMPATH), a medical partnership of American and African universities and government agencies working to improve health care in sub-Saharan Africa through care, research, and training.



Ravi Vakani, MD, examines the charts of a patient who was in an automobile accident. Eldoret, a city with the population the size of Durham, has only one practicing neurologist in its public hospitals (Duke alone has more than 70).



# CULTIVATING INNOVATION

Neurologist Daniel Laskowitz discusses the collaborative team behind Duke's translational research program

On an early weekday morning, an ambulance brings another patient to the emergency room at Duke University Hospital. The patient, a high school student who had an accident on the way to school, has serious head injuries and has not regained consciousness. But after tending his wounds and stabilizing his breathing and heart rate, there is little for his medical team to do, except wait. And hope.

Duke neurologist Daniel Laskowitz, MD, MHS, has seen scenarios like this many times.

While advances in medical research have yielded new diagnostic tools and preventative treatments for heart disease, cancer, and other conditions, major new treatments for brain injuries—such as a neuroprotective drug that could prevent devastating loss of brain cells after a trauma—have remained elusive. After more than two decades treating and studying brain injuries, Laskowitz said that medical treatment for traumatic brain injury and other neural insults has remained virtually unchanged since the early days of his career. "THE HOPE BACK THEN WAS THAT SOME KIND OF NEUROPROTECTIVE THERAPY WOULD BE RIGHT AROUND THE CORNER. THE REALITY IS THAT 21 YEARS LATER, WE STILL DO NOT HAVE A SINGLE NEUROPROTECTIVE DRUG. IF WE WANT TO SEE MEDICAL IMPROVEMENT IN PATIENTS WITH TRAUMATIC BRAIN INJURY, INTRACRANIAL HEMORRHAGE, OTHER STROKES OR ANY OF THESE LIFE-THREATENING NEUROLOGICAL INJURIES, THERE ARE VERY LIMITED OPTIONS THAT WE CAN OFFER RIGHT NOW."



At the other end of the spectrum, laboratory neuroscience research has advanced our understanding of how the brain grows and functions, but often at the microscopic or genetic level, without direct applications to patient care. Many researchers who study brain injuries rely on animal models, primarily rodents, which provide valuable information but are still very different from the real-world neural traumas that come into the emergency room.

Laskowitz is working to bridge this divide between laboratory research and improved patient care through his leadership with Duke's Clinical Laboratory Interface Program (CLIP). His vision is to bring together researchers, staff, and administrators with diverse expertise to advance clinical improvements.

Researchers and administrators involved with CLIP have expertise in neurological conditions, such as traumatic brain injury, neurovascular disease, and epilepsy, as well as other specialties such as anesthesiology, animal surgery, basic laboratory research, administering human clinical trials, and navigating the FDA's drug approval process.



DANIEL LASKOWITZ, MD, MHS

"CLIP CROSSES TRADITIONAL DEPARTMENT BOUNDARIES. IT IS DESIGNED TO REACH OUT TO FACULTY WHO HAVE IDEAS THAT MIGHT REALLY MAKE A DIFFERENCE, BUT DON'T CURRENTLY HAVE A PATH FORWARD." DANIEL LASKOWITZ, MD, MHS



In facilitating this translational research, CLIP dwells in the high-risk, high-reward realm where new experimental treatments are tried for the first time, an area where pharmaceutical companies and traditional venture capitalists are reluctant to investigate.

#### FROM GENETIC CLUES TO AN EXPERIMENTAL DRUG

One CLIP project has its roots in Laskowitz's early research into how genetics influence healing after a neural trauma. His research revealed that a gene known as apolipoprotein E (APOE) could modify brain inflammatory responses and influence whether the patient was more likely to fully recover or to experience fatal swelling or significant cognitive impairment after an acute brain insult.

With this underlying knowledge, Laskowitz sought to create a drug that would mimic the positive effects of APOE and increase a person's chance of recovery. Years of research yielded a compound known as CN105. Recently, CN105 completed the first in-human trials (a process known as escalating dose Phase 1 trials), in which it was found to be safe in healthy volunteers. The next step will be a proof-of-principle trial in which CN105 will be given to patients suffering from intracranial hemorrhage, a neurological trauma for which there is currently no effective drug.

#### ROOM TO GROW

CLIP researchers are investigating other leads, from additional neuroprotective drugs to safer contrast agents for Magnetic Resonance Imaging (MRI) that would allow doctors to peer into patients' brains while reducing their exposure to toxins. While some of CLIP's projects are focused within Duke, others include collaborations with other academic institutions, including the University of Kentucky, and private companies such as NeuroOp, a company cofounded by researchers from Duke and Emory Universities.

Laskowitz hopes that CLIP's team-based approach will inspire others in addition to directly yielding results that influence patient care. "It's not about basic science, like in neurobiology, but rather helping to understand the disease, understand what a clinical trial would look like, developing a potential commercialization path and really trying to bring new therapies to bear," Laskowitz said. "Many things will fail, but some may succeed. Hopefully this program can be a 'call to arms' for people who really want to see important clinical improvements, advance the practice of medicine, and help people."



"ALL OF THESE EFFORTS REPRESENT NOVEL COMPOUNDS THAT NEED THOUGHTFUL GUIDANCE, IN TERMS OF TEAM MEMBERS WHO UNDERSTAND THE SCIENCE, DISEASE PROCESS, COMMERCIAL DEVELOPMENT AND CLINICAL TRIALS. IT'S NOT ONE PERSON WHO DOES IT ALL."

## DUKE TELESTROKE EXPANDING THE REACH OF LIFE-SAVING DUKE CARE

Duke's Telestroke Network offers remote diagnosis and ensures expert treatment across the region

Somewhere in Juanita Grant's body, a blood clot broke loose. Forced through her veins with the surge of her heartbeat, it quickly became lodged in one of the vessels supplying blood to her brain. Within seconds, brain cells began to die.

It was a stroke.

By the time Juanita Grant, 87, entered Danville Regional Medical Center near her home in Danville, Virginia, she was completely paralyzed on her left side. Things looked grave.

A robotic mobile cart wheeled into the room. From his office at Duke, Carmelo Graffagnino, MD, appeared on the screen, ready to examine Grant. He guided a nurse at Danville Regional through tests, remotely accessed her CT scan through a secure connection, and recommended a medication to dissolve the clot. Grant was soon boarded onto a Life Flight helicopter bound for Duke.

Grant's friends were told that she might not even survive the flight. But after emergency surgery at Duke, she was able to leave the hospital just five days later, her cognitive functioning nearly normal and only in need of speech therapy. Without the quick 9-1-1 call her friends made and the rapid transfer to Duke, Grant could have died or survived only with severe cognitive and physical impairments.

"YOU GET VERY COMPLETE AND QUICK CARE," GRANT ATTESTED DURING HER RECOVERY AT DUKE. "THIS IS THE PLACE TO COME IF YOU HAVE A STROKE."

## The right care, at the right place

Duke was the place to come for Grant, who experienced a massive stroke that required immediate specialty care. But for most cases of stroke, care from a local hospital is sufficient or even preferable. Regional medical centers can adequately treat most strokes, and an emergency transfer to a larger, distant medical center means a stressful (and expensive) ambulance or helicopter ride, additional medical bills, and increased worry

for patients and families. Enabling routine stroke patients to remain at their local hospitals also helps to ensure that staff and beds are available at specialty centers like Duke when more severe stroke cases come in.

However, regional medical centers are not always equipped to distinguish between routine strokes, with a straightforward treatment plan, and massive strokes like Grant's.

Enter Duke's Telestroke network. An extension of the Duke Stroke Center, Telestroke enables doctors at affiliated regional hospitals to get immediate, expert opinions from Duke stroke specialists 24 hours a day, seven days a week via a secure, two-way audio and video connection. This consultation allows doctors to quickly sort out which patients will benefit from a transfer to Duke and which ones can receive the care they need near home.



Telestroke allows Duke neurologists like Brad Kolls, MD, PhD, to talk to remotely evaluate stroke patients.

## A win-win

The Telestroke network includes five medical centers across North Carolina and southern Virginia and has facilitated 1,500 consultations since its launch in 2013.

Duke faculty said they are proud to share their stroke expertise via the network. "One of our main goals was to try to provide a higher quality of care to stroke patients beyond our own ER," said Brad Kolls, MD, director of Telestroke and associate professor of neurology at Duke.

About 90 percent of Telestroke patients have been able to stay at their local facilities, saving thousands of dollars in transfer costs, as well as time and productivity for family who would otherwise have to travel hours by car to be with their loved ones. "That's a big win for the local hospital, as well as for the patients, because they are getting all the care they need right there in their own community," said Kolls.

Kolls talks to a patient in Danville, Virginia, during a telestroke demonstration.



In addition to making stroke triage decisions easier, joining the Telestroke network also allows Duke stroke experts to help medical personnel at smaller regional hospitals to improve their practices and medical care. For example, during early site visits, Duke stroke experts observed that many regional hospitals were administering tissue plasminogen activator (tPA), a common stroke medication, too infrequently or too late for it to be effective. After promoting tPA use and training staff through the Telestroke partnership, Kolls said tPA administration rates have doubled or tripled in some partner hospitals.

Annual satisfaction surveys also speak to the program's success. The Telestroke program has scored at least 4.7 out of 5, on average, in annual surveys from network hospitals. In addition to these formal surveys, the Telestroke team visits each affiliated medical center quarterly and is always looking to improve the program.

Inspired by Telestroke's success, Duke Health has opened a telemedicine office to develop similar programs for other medical conditions. The Duke ALS clinic has also followed suit and now offers telemedicine services for patients with amyotrophic lateral sclerosis (ALS).

"THE TELESTROKE PROGRAM FORGED A LOT OF NEW TERRITORY," SAID KOLLS. "TELEMEDICINE AT DUKE HAS BEEN STRUCTURED AROUND WHAT WE LEARNED FROM TELESTROKE, WHICH HAS BEEN ABLE TO PROVIDE INSIGHT AND GUIDANCE TO THE INSTITUTION AT LARGE."

# GIVING TO THE DEPARTMENT

The Duke Department of Neurology relies on individual gifts and philanthropic partnerships to support our missions of providing transformational patient care, conducting research into neurological conditions, and training the next generation of neurologists.

Your contributions are a vital part of our work, allowing us to:

• Investigate the mechanisms behind Alzheimer's disease, multiple sclerosis, Parkinson's disease, movement disorders, chronic pain, and other conditions, as well as new treatments for these conditions.



NICOLE CALAKOS, MD, PHD, is conducting research to isolate and better understand how obsessive-compulsive disorder and habits form at the neuronal level. • Provide new and innovative forms of patient care such as telemedicine for stroke and amyotrophic lateral sclerosis (ALS), and the use of smartphone apps to help multiple sclerosis patients record their symptoms and reactions to treatment.



**RICK BEDLACK, MD, PHD,** is pioneering a telemedicine program for patients with ALS.

• Train and nurture medical students, residents, fellows, and junior faculty. The newly established Donald B. Sanders Residents and Fellows Research Fund, or Sanders Fund, provides funding for research projects, travel, and other work for residents and fellows within the Department of Neurology.



**CHRISTA SWISHER, MD,** a 2014 recipient of the Donald B. Sanders Fund, joined our faculty this year.

There are many ways to support our work. To discuss your options for giving, or to suggest a contribution area, contact:

#### Holli Gall

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# OUR FACULTY AND RESIDENTS



THE DUKE DEPARTMENT OF NEUROLOGY OFFERS EXCEPTIONAL PATIENT CARE FOR PATIENTS WITH CONDITIONS AFFECTING THE BRAIN AND NERVOUS SYSTEM. WE ALSO CONDUCT CUTTING-EDGE BASIC, TRANSLATIONAL, AND CLINICAL RESEARCH, AND TRAIN THE NEXT GENERATION OF LEADERS IN NEUROSCIENCE.

#### CREDITS

Stories	"Unlocking Alzheimer's Disease" by Sarah Banducci and Anne Frances Johnson "Opening Eyes in Eldoret" by Will Alexander "Telestroke: Expanding the Reach of Lifesaving Care" by Kathleen Pierce, with additional reporting from Maryann Fletcher "Cultivating Innovation with CLIP" by Sarah Banducci and Anne Frances Johnson Graphic Design by Agata Rocka Edited by Will Alexander
Photos	Front Cover: Photo 1: Carol Colton; Photo 2, 4: Emily Critchfield, Photo 3: Ravi Vakani § Page 7: Carol Colton § Page 8: Chen Lin § Page 9: Photo 1: Ravi Vakani, MD; Photo 2: Cordelia Person § Page 11: Earl Nelson § Page 12, 13: Emily Critchfield § Page 15: Jared Lazarus

Department of Neurology Duke University School of Medicine

AN ENVIRONMENT OF GENEROSITY, LEARNING, AND EXCELLENCE

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