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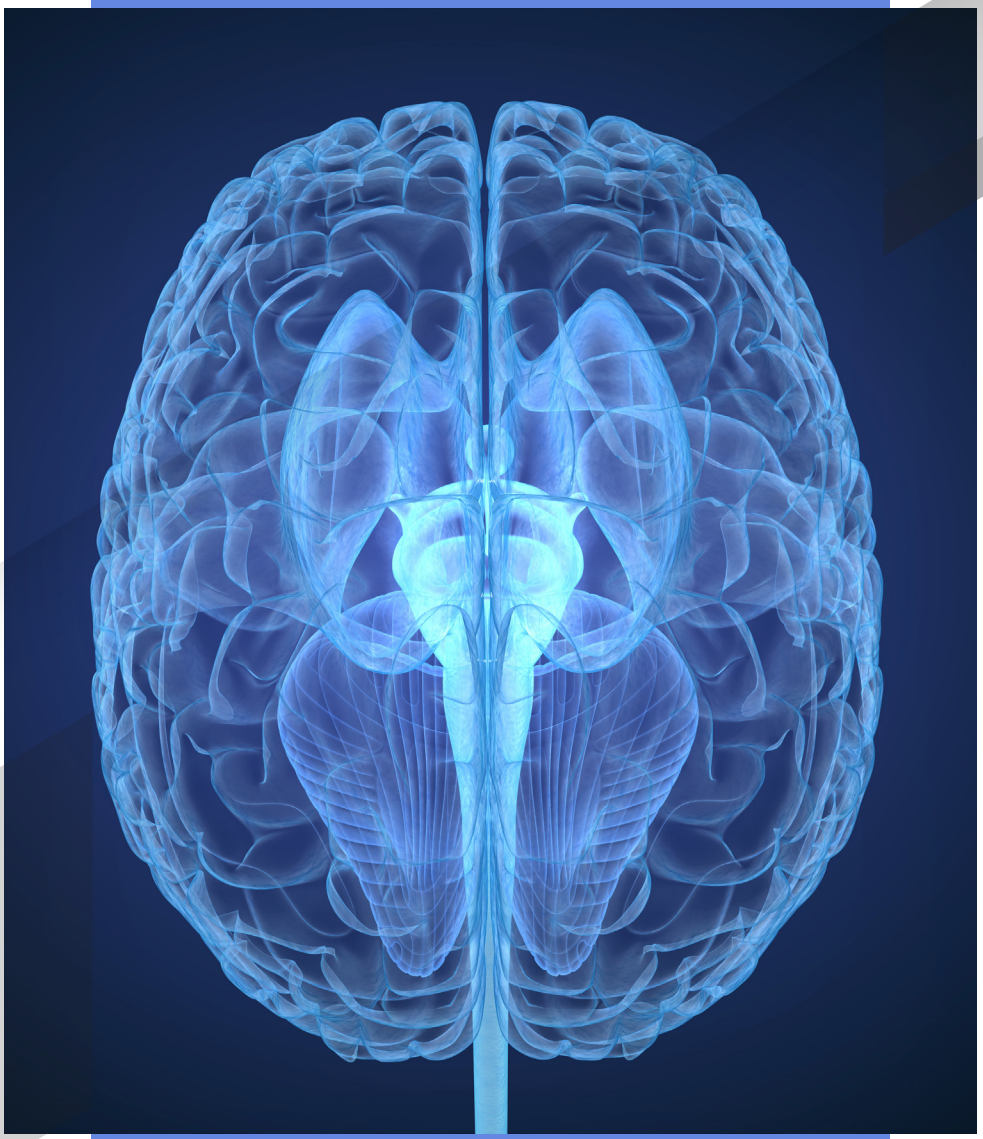

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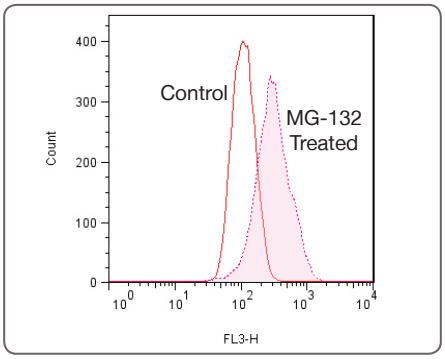

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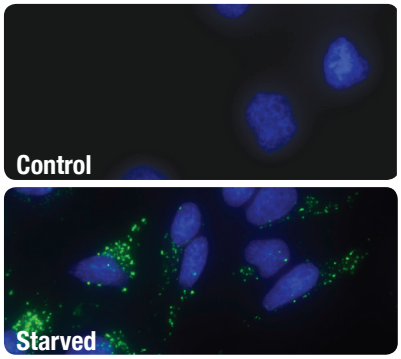

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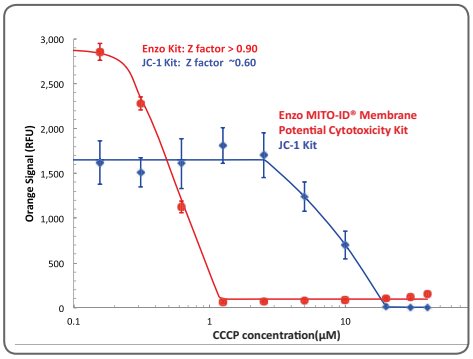

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Peering Into the Brain

DARCIE L. MOORE

Assistant Professor
Department of Neuroscience
University of Wisconsin-Madison

As a trained classical vocalist, Darcie Moore didn't expect to end up in a scientific career. But after a series of setbacks and opportunities eventually landed her in a research lab, her interest in science became undeniable.

Now in her lab at the University of Wisconsin-Madison, she studies how asymmetric inheritance impacts dividing neural stem cells. Often, one daughter cell ends up "cleaner" than the other, which receives less desirable cargo[1]. As individuals age, this segregation may become more symmetric, potentially leading to cell death and cognitive impairment. Once a challenging phenomenon to visualize, Moore developed an innovative method for imaging cell division that opened the door to understanding asymmetric cell division.

What prompted you to change your career from vocal performance to science?

I have always been interested in science, but I had focused on music since I was 10 years old. Sometimes the reality of a career does not fit with what you expected. With opera singing, you audition for jobs that are short-term. The rest of the time, you are trying to find ways to support your "habit." I realized that this would frustrate me long-term, so I decided to go back to school for science.

I thought a good entry point was to get a master's degree in music therapy because I was already a musician. My first year was mostly science classes. I had two amazing mentors who recognized my interest and saw my potential. They took me under their wings and suggested that I transfer to a master's of science program.

I was extremely curious about the brain. This program got me very excited about research, and the next thing I knew, I was a full-blown scientist.

Has your performance training helped you in your science career?

Absolutely. Studying to be a classical musician requires an enormous amount of self-discipline and motivation. You don't have someone leaning over your shoulder, telling you what to prepare and when to practice. You have to plan effectively for each performance—learn your music and your words—so there's a focus on self-direction. That made the transition to science very easy for me because I was used to being self-motivated and disciplined.

How did you become interested in neural stem cells and aging?

Stem cells are so fascinating because they are constantly making decisions. Am I going to divide? Am I going to stop dividing? Am I going to become a different type of cell? Am I going to move?

During my postdoctoral fellowship, I started to look at stem cells in the brain and I became curious about how changes occurred during aging. There's a continuum of function, with the only difference being the passage of time. I'm interested in how these changes translate into cell behavior.

What was it like when you first detected asymmetric cargo segregation during cell division?

Everyone always assumed that when a cell divided, it split all of its components equally between the daughter cells. In fact, it's fairly impossible for those cells to look exactly the same, even if they have the same fate, so we had a bit of a dogma to overcome.

We had done some immunostaining on fixed samples when we first saw this result. We were excited, but we didn't know if we could mimic it in vivo. When we looked at the cargo in an embryonic brain slice, we saw asymmetric division in a live situation, where cells were actively moving and dividing. We got incredibly excited; this wasn't an artifact, but it occurred regularly in the brain.

What role does stem cell division play in human aging and development?

This is quite controversial and we don't have the techniques available to say what is happening in the human brain. Some researchers feel that neural stem cell proliferation does not occur in adults; it only occurs during development. However, some of the most recent studies suggest that neurogenesis does occur throughout life, including in the aging brain. There is also potentially a disease connection in Alzheimer's disease, Parkinson's disease, and depression, where proliferation is decreased in neural stem cells.

We are trying to understand what happens to the daughter cell that gets the "garbage" cargos, and it's not black and white. These cells could get cargo that helps take care of them. They could either re-enter the cell cycle if everything goes well, or they may die if it doesn't. It isn't clear how the cells will utilize this cargo in terms of differentiation and fate. In the adult rodent brain, there is a huge amount of cell death at an early stage among the neural stem cell progeny and no one knows why this is happening.

This phenomenon has been very difficult to study in the past. What has your team done to overcome these hurdles?

The tools and the time required to study dividing cells are challenges. You can't synchronize actively dividing primary neural stem cells, so you have to wait for the pleasure of the cells to do your experiments. We've been developing automated imaging techniques to find these rodent-derived dividing cells without having someone sit for 12 hours at the microscope to find six or seven cells.

We use software within our microscope that is trained to recognize a nuclear signal when chromosomes are getting ready to divide. The machine can scan for cells that are dividing and zoom in to visualize changes throughout mitosis. When that process is over, the machine starts scanning again for other dividing cells.

What is on the horizon for your work?

Being able to visualize changes in cells is fascinating. What we would like to do is understand the controls that regulate neural stem cell decisions to divide or not divide. These controls can potentially be manipulated in disease or aging—getting those cells to divide to make more stem cells rather than depleting the population. This is a perfect example of needing a basic science understanding of a process so that you can develop therapeutic strategies later.

Interviewed by Niki Spahich, PhD

Exploring the Limits of Knowledge

DANIEL A. COLÓN-RAMOS

HHMI Scholar

McConnell Duberg Professor of Neuroscience and Cell Biology

Yale School of Medicine

Daniel Colón-Ramos' fond childhood memories of chickens, ants, and turtles in rural Puerto Rico directly led him to his career. Now as an associate professor of neuroscience at Yale University, he works with *C. elegans* to understand how synapses are precisely assembled to build the neuronal architecture underlying animal behavior.

What inspired you to pursue neuroscience?

As a young child, I was fascinated by animal behavior. Puerto Rico is a tropical country and there are a lot of insects and spiders. I found their behaviors fascinating—particularly those of ants. My family is from a rural part of the country, and I spent a lot of time near farms. There was a chicken that used to follow me around, which made me wonder, why does it know to follow me and nobody else? I also had an interest in sea turtles and how they came out of their nests and went straight towards the ocean, knowing what to do from the moment they hatched. I was intrigued by the fact that they were capable of performing pretty complex behaviors although they hadn't trained in those behaviors. Leatherback turtles go all over the world and then come back to the beach where they were born; I was amazed that they could remember where they were born. At one point, I thought that I would become a veterinarian because I liked animals so much. That later led to my interest in science.

What challenges have you overcome during your career?

I think roadblocks are endemic to the job. Rejection, for example, is so much a part of the job that I don't see it as a difficulty anymore, much like gravity is a difficulty for flying an airplane. It's just a reality. There's actually an excellent book about this by Stuart Firestein from Columbia University called Failure: Why Science Is So Successful. It's a discussion about the role of failure in science and how they are intricately connected.

For every success I've had, every paper I've had published, or grant I've received, I estimate that I have had two to four rejections. But what's great about science is that the successes count, not the rejections. Science pushes us to our very limits of knowledge, so failure is to be expected. It's like being a high-performance athlete; you are constantly at the very edge of what you can do or what is known. And I think that is what's most exciting, but it's also what's hardest. You're constantly feeling ignorant, constantly facing biases, and constantly reframing what you know, or what you think you understand. As a scientist, you're actually identifying a question to generate knowledge, rather than having an answer for everything. It can be a difficult transition to think like that.

At this point in my career, difficulties are now something that I expect. Certain experiences are so internalized that I don't see them as negatives or roadblocks at all. Our job as scientists is to solve problems; but to solve problems, you have to face them. I'd say that the more successful we are, the more we get rejected; the more shots you take, the more you're going to miss. But you need to take shots, otherwise you're not going to make them. I don't think that's unique to our lab. I think it's consistent with science; the most successful labs out there are really the ones that are getting rejected the most.

What do you consider to be your biggest accomplishment?

My biggest accomplishment in terms of my development as a scientist has been realizing that all of the knowledge we have is, at best, incomplete. I need to put myself into spaces where I am feeling ignorant to be able to grow. Realizing that ignorance is the first step towards learning has led to really exciting opportunities.

In terms of scientific questions that we have answered, there are a number that I'm really proud of, some of which are published and some of which are still unpublished. They include studies

where we found surprising answers to questions that we thought we understood, but didn't. So, for example, one of the early things we discovered was that glial cells can guide the assembly of neural circuits[1]. That was completely outside of our conceptual framework at the time.

There was another project we did later, where we looked at how synaptic positions develop, involving a concept called synaptic allometry. When animals grow, their tissues grow at different rates. We wanted to investigate how an animal maintains synaptic positions between different cells during growth. We found that glia were important for this, which was very exciting to us[2].

We also have some interesting results showing that glycolysis is localized to synapses when they are under energy stress in *C. elegans*[3]. What we saw blew my mind because we had a preconception that this ancient energy pathway would be active all over the place, but we saw glycolytic enzymes condensing in certain areas instead. It speaks to making sure we don't let our own preconceptions affect the experiments that we do. All of the projects that have been really exciting for me have been projects where I've had to really check my biases and reframe the way I was thinking of them.

What do you like to do when you are not working on research?

I'm the father of triplets who are nine years old, and a toddler who's three. Right now, my life is in multiples of three. That's what occupies most of my time! I like reading when I have free time for myself too, especially the history of science. Recently, I really enjoyed a book written by a French researcher, François Jacob, who worked with Jacques Monod in the early days of molecular biology. They won the Nobel Prize for their work about genetic control of enzymes and virus synthesis. It is a beautiful book about the history of Western science called The Logic of Life. It covers the 16th century to the mid-nineties, and it was a fascinating read.

Interviewed by Kathryn Loydall, PhD

A Mind for Science

MICHELLE MONJE

Associate Professor

Neurology, Neurosurgery, Pediatrics, Pathology, Psychiatry, and Behavioral Sciences

Stanford School of Medicine

Michelle Monje discovered her passion for neuroscience in an unconventional way; it all began with ice skating. After navigating gender discrimination, she made her way to neuroscience where she now serves as an associate professor of neurology and neurological sciences at Stanford University, focusing her research on high-grade gliomas. As a practicing neurologist and board-certified neuro-oncologist, she is especially interested in the roles of neural precursor cell function in the origins of pediatric brain tumors and the consequences of cancer treatments.

Will you describe your educational journey and the role Stanford played?

I became interested in neuroscience as an adolescent. It was kind of an odd path. I was a figure skater and I started a skating program to teach kids with disabilities, mainly Down syndrome, to ice skate. That experience got me interested in medicine and the nervous system. Then as an undergraduate student at Vassar, I had the opportunity to work with a wonderful neuroscientist, Kate Susman, and do research in her lab. I fell in love with the nervous system.

I came to Stanford in 1998 for medical school and for a neuroscience PhD, and I loved the collaborative research environment. I've been here ever since, with the exception of leaving for a neurology residency to train at the Harvard Hospital in Boston for three years.

What was it like to work with Dr. Susman?

She was a fantastic role model. She's a mother; she's a professor; she's a scientist. She helped redirect me.

Growing up, I was interested in science and medicine, but I had a very discouraging experience in my high school biology class. My teacher once said to me, "Don't worry sweetheart, it's a rare woman who has a mind for science," after I attempted to ask a question. I remember thinking, "He's just being kind and telling me that I'm not smart enough to understand this." So I continued my education and focused on other things.

When I went to Vassar as an undergraduate, I wrote an essay about my interests that said I was thinking about pursuing disability advocacy, or perhaps law, but I'd always had a dream of pursuing medicine. Kate, who was my pre-major advisor, asked me about it. I started talking about my experience and said, "I don't have a mind for science." She looked at me and asked, "Who told you that?" When I told her, I remember very clearly; she looked extremely determined and said calmly, "You had a bad teacher. We're really good here. We're going to fix this. I want you to sign up for my class."

She took me under her wing. I rediscovered my love for biology that year and went on to major in it. I have stayed very close to her over the years and she continues to be a touchstone in my life. I was lucky. I was rescued from a bad experience and I got a second chance. Not everybody who faces gender discrimination gets that chance.

How did you decide to pursue pediatric neuro-oncology?

While I was at Stanford, I became interested in neuro-oncology, the seeming intractability of many forms of brain cancer, and our inability to effectively treat them, together with the long-term cognitive effects of many cancer therapies. My PhD focused on understanding cellular and molecular mechanisms underlying cognitive impairment after cranial radiation therapy for cancer. The biology led me to think about the way that different cells interact with each other to modulate their function and how important the microenvironment is for the function of any cell type. I decided to make that my sub-specialty when I came back to Stanford.

These cancers are tragic diseases. They strike previously healthy children, and are nearly universally lethal. I found high-grade gliomas the most compelling because they're so difficult to treat, and we don't understand the biology well enough. They are so devastating.

The first time I saw a child with the form of high-grade glioma that my laboratory focuses on, called diffuse intrinsic pontine glioma, I felt like I couldn't turn away from it. It seemed so clearly to be a disease of dysregulated neural development in some way. These tumors occur in very specific places, and at very specific time points in childhood development. What that developmental process is, how it goes awry, and how we could use knowledge of normal neurobiology and neural development to create better therapies, seemed like a set of questions that I needed to tackle.

What do you think is the most promising emerging therapy in the field?

If you're going to fight a war, you're going to need the Army, Navy, and Air Force. Similarly, I think we're going to need to effectively target cell-intrinsic vulnerabilities, look for immunotherapeutic opportunities, and explore microenvironmental dependencies.

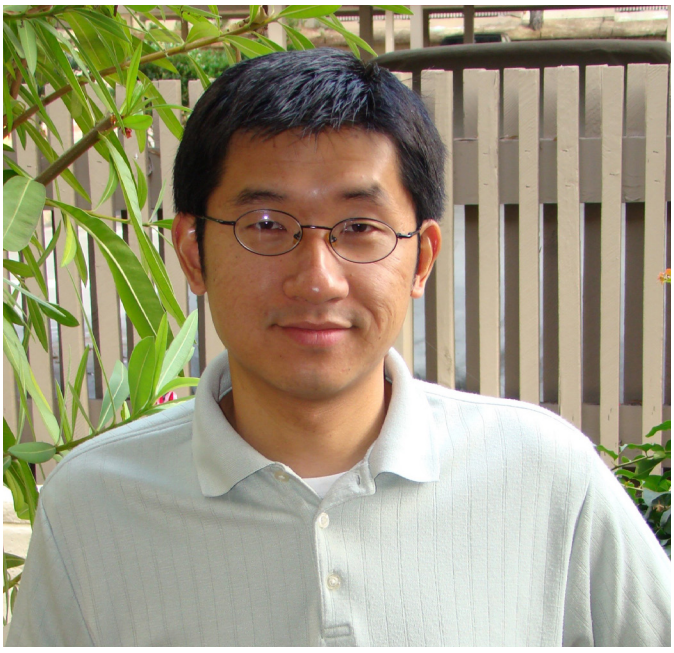
The cell-intrinsic vulnerabilities seem to be quite different from those of adult cancers, in that epigenetic dysregulation seems to play a much more prominent role in pediatric brain malignancies. As we understand more about epigenetic regulation and dysregulation in cancer, new therapeutic strategies emerge.

The opportunities for effectively leveraging the immune system to fight cancer are enormously exciting. There are some specific challenges in immunotherapy for brain tumors because of the closed physical space of the cranium and the ability of the central nervous system to tolerate edema and swelling.

The third part, which my lab focuses on, is the way that the brain microenvironment regulates the function of precursor cells. Microenvironmental interactions are critically important for regulating both normal and neoplastic stem cell function. The nervous system strongly regulates the cancers that emerge from those cells. Our work focuses on the neural regulation of high-grade gliomas, and I think it will be exciting over the next few years to see how the nervous system interacts with other subtypes of brain malignancies in kids. I think that treatment strategies incorporating all three of these approaches might be able to eradicate these seemingly intractable brain cancers in children.

Interviewed by Meaghan Brownley

Seeking out the Unexpected



MINGSHAN XUE

Assistant Professor

Department of Neuroscience, Baylor College of Medicine

Caroline DeLuca Scholar

Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital

Always fascinated by basic science, Mingshan Xue broke from his family mold to research the intricacies of neural circuits. The series of mishaps and obstacles that plagued his early days instilled the technical and personal skills necessary for him to excel as a scientist. His innate curiosity guided his response to witnessing a medical emergency—a response that changed the course of his research and the outlook for children suffering from a devastating genetic disorder.

Looking back across your scientific career, what has been your biggest challenge?

I spent more than 8 years in graduate school, which is not typical. I worked for two and an half years in a lab at the University of Texas at Austin, but things didn't work out. Not only did I have to change labs, but I had to change schools and research fields.

Typically, a PhD student has the opportunity to rotate in different labs before they choose one. But because I had already completed two years when I arrived at my new program at Baylor College of Medicine, I had to contact individual advisors and ask them if I could join their lab. I met Christian Rosemann, who had just moved to Baylor, and asked if I could join his lab. We talked, and I guess he liked me, so he said yes.

On the day I started in the lab, I was setting up some physiology work at the microscope and I dropped an objective lens and broke it. This was my first day and the first thing I did was drop the objective on the floor! I showed it to Christian, and he just said, “Yeah, it happens.” That was it.

Christian’s reaction changed how I see things. Now I'm an advisor, and when people in my lab make mistakes or break things, that's exactly the same attitude I show. I am supportive.

What has been the biggest surprise in your research so far?

In graduate school, I studied a pre-synaptic protein’s structure-function relationship. One day, I noticed that all of the previous studies published in the last 15 to 20 years focused on one side of the protein. No one had looked at the bottom part, so I made some mutations. To my surprise, the first data from these experiments showed a dramatic change in the protein’s function. When I noticed this, I literally ran into Christian’s office to tell him what I found. Later, he told me that I was shaking because I was so excited. This was odd because I tend to be pretty calm. But this finding opened up a whole new area in terms of understanding this protein. Of course, I hoped to find something, but I didn't expect it to be so dramatic.

Why did you decide to switch from protein studies to neural circuitry dysfunctions?

Shortly after starting my postdoctoral fellowship, I met a 16-year-old young woman by chance while traveling for the holidays. While I briefly spoke with her and her mother, she had a seizure right in front of me. I grew up in a physician family; my mother, father, and sister were all physicians. They wanted me to become a physician too. We lived close to the hospital, so I'm used to patients. But it never occurred to me that somebody would have a seizure, in such a short time, in front of me. It had a profound impact on my decision to go into this field. I decided to study her disease.

At that time, scientists had just figured out the genetic cause for her seizure disorder. It was considered a rare disease because she was one of the first patients diagnosed. Now we know that this gene mutation is one of the most common for pediatric epilepsy.

How did you begin to research epilepsy?

I was extremely lucky to start my lab at the Jan and Dan Duncan Neurological Research Institute at Baylor College of Medicine. The first thing I did when I arrived was build a mouse model for this particular disease.

I had never built a mouse model before, nor had I done any behavior characterization. My first postdoctoral fellow and I learned everything together. We were so naive. Now we are experts in this area.

The young woman's mutation is in a gene that can cause a variety of diseases that share some common features. Ninety-five per cent of the patients have epilepsy. Nearly all have intellectual disability, and most have motor impairments and motor dysfunction. Some of the patients also have anxiety and autistic features. We recaptured these phenotypes in our mouse model.

Now that you have the mouse model, how are you using it?

We want to use this model to do two things: study what went wrong in this animal model and try to reverse the symptoms. For example, a simple question would be why does this animal have seizures? What is wrong with the cells and synapses?

For reversing the symptoms, we are considering multiple approaches. One is working already! I hope this strategy we are developing will make it into the clinic. That is my hope for the next ten years.

Interviewed by Kristie Nybo, PhD

Growing Results in an Open Field

KATHERINE L. THOMPSON-PEER

Assistant Professor

Department of Developmental and Cell Biology

University of California, Irvine

Katherine Thompson-Peer's curiosity got the best of her when a literature search for neuron regeneration revealed an unappreciated research question: How do dendrites regrow their branches after injury? That curiosity eventually led her to her new lab at the University of California, Irvine, where she uses modern techniques to study this old mystery.

How did you come to study dendrite regeneration?

My graduate work focused on nervous system development, but I wanted to switch it up and study something more clinically relevant. I converted from studying how neurons develop under normal conditions to how they recover after injury. My postdoctoral lab had decades of expertise studying development of dendrite arbors—the highly branched structures that receive information from the environment or neighboring neurons. I was interested in utilizing their experimental tools and insights to study what happens to this arbor after injury.

I started a number of literature searches to learn what was known about neuron recovery. At the time, there were about 1,200 papers on axon regeneration. In contrast, when I searched for dendrite regeneration, there were three hits. I was confused about this disparity because a neuron works as a circuit to process information with both input from dendrites and output from axons.

This seemed to be a blind spot in the field, so I started asking why nobody had studied dendrite regeneration before. My best guess is that it is due to the history of techniques used to study neuroregeneration. Traditionally, this field was built using surgical injury to long bundles of axons. An axon is a bigger target to hit with a scalpel than a dendrite branch.

How do you injure dendrites?

We use an optical injury technique with a two-photon laser microscope to burn the dendrite arbor. We do this in the peripheral nervous system that surrounds the body wall of *Drosophila* larvae. With the two-photon microscope, we deliver a high-power laser precisely to a small spot. We focus the laser initially at the primary dendrite branch points from the cell body and then repeat this with all of the branches to obtain the strongest effect. Then we follow the same neuron in the larva over many days to see how it recovers.

After injury, the neurons robustly regenerate new dendrites—they grow an arbor with about the same number of branches as uninjured controls[1]. However, when you take a closer look you see that the regrowth fails to perfectly recreate the uninjured neuron. The arbor is smaller in diameter and how the branches interact with adjacent cells is different. Their touch response is only about 50-60% that of normal neurons. Right now, we're teasing apart both what allows the dendrites to regenerate as well as they do and what intrinsic cell factors prevent them from fully recreating an uninjured neuron.

What are your main considerations now that you're starting your own lab?

One of my favorite things is learning who the budding young scientists coming into my lab are—what are their particular strengths and interests, and how can we find projects to match. Science is a long process and you have to enjoy setting up the experiment and troubleshooting, in addition to getting the end result.

A really important aspect of my career has been engaging in outreach and advocacy work to make science more inclusive for people from all backgrounds. I'm highly motivated when thinking about the culture in science and how different

populations should be encouraged to become scientists. In my lab, I'm trying to establish a culture where everyone's voice is valued and everyone is on a level playing field so that we can all be encouraged to thrive.

What do you hope to accomplish with the dendrite regeneration project?

We are studying this on a cell-by-cell basis right now, but we don't know the effect for the animal as a whole. My lab is currently piloting techniques to injure many dendrites at the same time to get more insight into the behavioral consequences.

In human tissue surrounding a stroke site, researchers have seen defects in dendrite architecture. It would be good to know how we could improve regeneration after any sort of injury so that the new arbor could function properly as part of its neural circuit.

Generally, I hope to get researchers to think more about the basic science of dendrite regeneration and how that influences how neurons recover. I want to bring more attention to this blind spot in the field. This field is nothing but fundamental open questions ready for big-picture exploration.

Interviewed by Niki Spahich, PhD

Decoding Decision-making

ANNE CHURCHLAND

Associate Professor of Neuroscience
Cold Spring Harbor Laboratory

In Anne Churchland's lab at Cold Spring Harbor Laboratory, animals are hard at work making decisions while performing trained tasks. Her team of researchers are working equally hard, monitoring and tracking the animals' behavior, trying to understand the neural circuits underlying those decisions. Churchland's latest work shows that mice and humans aren't so different when it comes to decision-making; mice fidget too[1]. Hind limb movements, pupil dilations, facial movements, nose movements, and whisker movements may be the equivalent of a human scratching their head, shaking a leg, or tapping their fingers. Churchland's research has neuroscientists thinking differently about decision-making. One intriguing hypothesis is that the movements may be integral to the process of thinking and deciding.

How did you first become interested in neuroscience?

When I was an undergraduate, I did some volunteer work at a local elementary school. It was really interesting to me to watch how the kids learned and sometimes how they struggled with learning. Through that, I became interested in cognitive development, which was an area that I pursued a little bit as an undergraduate. After completing my degree, I got a job as a technician, where I got my first taste of systems neuroscience in a non-human primate lab. I really love the ability to collect data, analyze data, and test different hypotheses.

What kind of big picture questions does your research help to answer?

We want to understand how humans and animals make decisions when they're faced with uncertainty. We're particularly interested in the kinds of decisions that put multiple sources of information together. For many complicated decisions, there are lots of different things that weigh in. And we want to understand how the brain clicks those different sources of information together to allow the subject to decide what to do.

Have you encountered any great difficulties during your research?

Wide-field imaging was developed by a few other groups and we brought it to our lab as a pretty new technique. Traditionally, we focused on one brain area at a time, but developing this new approach allowed us to look at the activity in lots of areas across the cerebral cortex. When we got the results, we realized that they were not what we expected at all! We found that the modulation by decision-making signals was actually pretty weak, and the modulation by movement was much larger. This was a big surprise. It was a real challenge to interpret because it didn't support or refute our hypothesis; instead, it made us realize that we were looking at the activity in the wrong way. In the end, we came to understand this activity much better and to understand that it related to movement. So, what started out as a big challenge really led us to an exciting and interesting discovery.

What would you say is your biggest achievement in the field of neuroscience?

I've had a number of influential publications in the field, but there's one theme that's run through a lot of discoveries that we've made. We're interested in looking at diverse species, and we realized that even species as different as rats and humans can have really similar decision-making strategies. To me, that's really exciting. It suggests that, even though there are many very different kinds of animals in the world—rats and humans are pretty different—our brains might be more alike than we realize.

What are your next steps?

I would like to be able to record more neural activity. The field has changed in that we're able to measure the responses of many, many more neurons than in the past. That has transformed the way we think about how the brain works. I'm really excited that as technologies get better, we'll get an even more complete picture of what's happening all across the brain during decision-making.

I would also like to be able to find a more holistic way of characterizing behavior. In the field of decision-making in the past, we've been really thoughtful about how we measured and analyzed behavior. But we were limited, measuring the choices and reaction times of decisions that humans or animals made. There are also individual choices that are part of a much bigger picture. An individual human or animal is making many movements and thinking about many things during a decision. And I think that if we can start to characterize behavior in a more holistic way, we'd be able to make a lot more sense of decision-making and the neural activity that goes with it.

Additionally, as a founding member of the International Brain Laboratory, I'm part of a group of 21 researchers who are collectively working to tackle big problems in neuroscience. We're trying to generate brain-wide recordings during decision-making tasks. It's part of a growing movement in science as we're starting to recognize that some problems are beyond the scope of a single laboratory. These necessitate people teaming up and figuring out how to work collectively to solve problems.

Interviewed by Kathryn Loydall, PhD

New Solutions for Old Problems

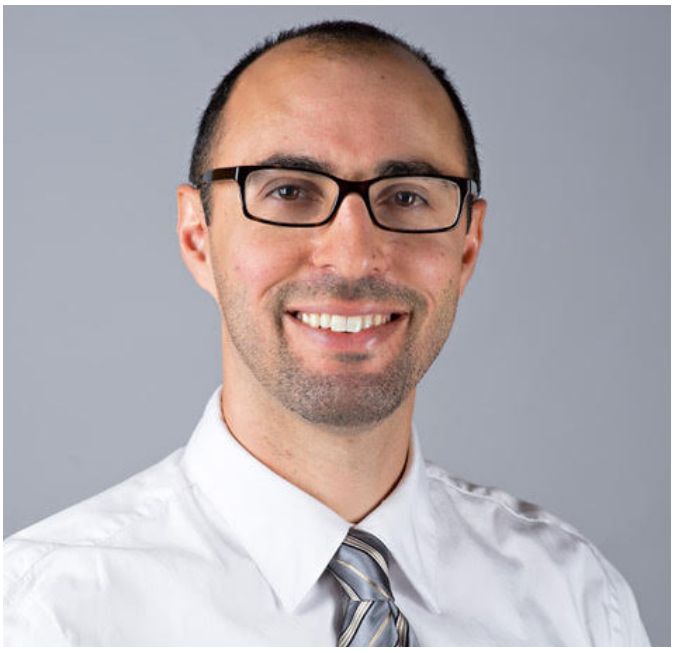
TODD COHEN

Assistant Professor

Department of Neurology

Department of Biochemistry and Biophysics
UNC Neuroscience Center

University of North Carolina at Chapel Hill



Todd Cohen's fascination with the brain and his family experiences with Alzheimer's disease led him to pursue a research career in neuroscience. In his lab at the University of North Carolina at Chapel Hill, he works to understand protein quality control in neurodegenerative diseases. Suppressing abnormal protein aggregation may be a promising avenue for age-related disease treatments.

Where did your interest in neurodegenerative diseases begin?

About 12 years ago, I watched my grandmother pass away from Alzheimer's disease. That was a big thing for me because I didn't understand at the time why we couldn't do anything for such an obvious disease. When she passed away, I thought, maybe there's something that I can contribute to that field. I've always felt that Alzheimer's disease is a very tractable problem because there are two major hallmarks of pathology: tau tangles and amyloid-beta plaques.

Why do you find proteins that aggregate in the brain so interesting?

We want to understand neurodegeneration as a whole, so we study proteins that are involved in a lot of disorders. The implications are obvious—if you understand the proteins, then you can find drugs and therapies for many diseases.

TDP-43 is a protein implicated in Amyotrophic lateral sclerosis, frontotemporal dementia, and Alzheimer's disease, among other disorders. Tau is interesting because it is implicated in 30 or more disorders. Most people know about Alzheimer's disease, but there are a lot of rare neurodegenerative disorders that are exclusively due to tau accumulation in the brain, such as progressive supranuclear palsy and corticobasal degeneration. If we could figure out how tau works, we could potentially find therapies for a lot of different disorders, including traumatic brain injuries which are also influenced by tau.

What's the most surprising thing you have learned about these proteins?

It never ceases to amaze me that every few weeks we find something that we didn't know before. When these moments happen, we sit back and ask, "How did nobody else see this before?"

After all these years, we don't really understand why tau misbehaves. In the diseased brain, hyperphosphorylated tau is the marker for pathology. There are ELISA approaches for studying phospho-tau biomarkers and diagnostic stains used in pathology centers. We used mass spectrometry and found tau modified by acetylation on lysine residues in the microtubule binding region[1]. These acetylation sites probably do things that are perhaps more potent than phosphorylation.

That tau finding prompted us to look at TDP-43, and, lo and behold, it is acetylated in regions that control its binding to RNA[2]. Here you have two proteins that are regulated by acetylation, which can potentially repel or induce binding.

We proposed that when proteins are acetylated, they tend to aggregate because their solubility changes. I wouldn't be surprised if lots and lots of proteins were acetylated and that caused them to aggregate. I think we shouldn't be focused just on our favorite phosphorylation site; we may want to look to other things that could drive aggregation so that we can have multiple targets when trying to suppress these pathologies.

How do you apply your interactions with patients at the UNC Neurology Clinic to your research?

I am fortunate to be a PhD in a neurology department full of MDs; I've been able to make my research more translational by collaborating with the neurologists. I collect post-mortem brain tissue and cerebrospinal fluid from patients to look for biomarkers of brain degeneration.

All of the research we do is pointed towards the clinic. I want to generate tools and models that will help people. When I feel that our research is getting too basic, we reorient and come up with a new path forward based on a potential drug or therapy. Overall, the goal is to identify drugs that we could move into a phase I human clinical trial. Our department has a strong interest in drug development, so once we identify a potential candidate, we start a trajectory towards clinical trials with patients seen locally.

What kind of drugs or treatments do you envision for these neurodegenerative diseases?

We recently published a study where we used a drug to activate chaperone signaling by targeting a transcription factor[3]. This chaperone response might be effective at suppressing TDP-43 aggregative pathology. We are continuing those studies to see what drugs could get into the brain or spinal cord.

The future of treatment is testing all of our resources—gene therapies delivered by viral or CRISPR methods, immunotherapy, and drug compounds.

Interviewed by Niki Spahich, PhD

Riding Scientific Waves

STEPHEN LIBERLES

HHMI Investigator
Professor of Cell Biology
Harvard Medical School

From an early age, Stephen Liberles mapped a careful course for becoming a scientist. But even well-laid plans come with unexpected rises and falls. With creativity and tenacity, he navigated change to become head of a research group studying some of the most fundamental functions of life.

Why did you decide to become a scientist?

Science has always been part of who I am. My dad was a theoretical physicist, so we were constantly talking about science while I was growing up. When I got older, my dad smoothed the road for me to work in a lab. From the first day, I loved it! It was like a big puzzle. I fell in love with the process of doing science.

Near the end of my undergraduate years, my friends were thinking about medical school, but that never even crossed my mind after my experience with research. I went on to earn my PhD in chemistry from Harvard University.

How did you move from chemistry into neuroscience?

Initially, I was fascinated by the work of Richard Axel and Linda Buck, who won the 2004 Nobel Prize for their studies of the olfactory system and its receptors. I was drawn to the beauty of the olfactory system. It has this incredible ability to detect and discriminate between so many different odors with similar chemical structures and then generate divergent perceptions. The system seems to be a great way to tease apart how the brain works. I moved into this field when I began my postdoctoral fellowship with Linda Buck.

Now that you have started your own lab, what are you working on?

One of our major interests is how the vagus nerve—the structure that innervates many of the major organs in the body—detects a variety of stimuli, such as blood pressure changes, the stretch of the lungs while breathing, or nutrient acquisition from eating. In contrast to the classical external senses like smell, taste, vision, or touch, we do not understand the internal senses of the vagus nerve at a molecular or higher level. We are trying to identify the different types of sensory receptors in internal organs that detect these stimuli. What we learn may one day be relevant for controlling autonomic physiology and understanding it in terms of both health and disease. Our goal is to understand the sensory transduction pathways and the diversity of neurons that detect internal organ inputs. We want to know how they're organized and what physiology and behaviors they control.

What has been your biggest challenge with this work?

So far, we have charted the cell types involved using transcriptomics profiling, but understanding which of those cells are relevant for signaling is challenging. We are now trying to identify key signaling proteins and receptors in these sensory neurons. One difficulty in working with the vagus nerve is that the structures are tiny. There are fewer than 5000 neurons in the mouse that control all of these vitally important functions. Because the number of neurons we work with is incredibly small, we cannot use traditional biochemical approaches. We rely heavily on genetics and state of the art genetic techniques for our analyses.

Funding was another major challenge. I studied olfactory and pheromone receptors during my postdoctoral fellowship, but switched to studying the vagus nerve when opening my lab. This was a new system for us, so my grants were declined because we lacked sufficient experience to do the work I proposed. I was running off the fumes of my startup package while launching the project. It was frustrating because there was so much we could learn; it was just a matter of getting that first paper out. I put everyone in the lab on the same project and hoped that would be enough to publish something before my funding ran out. I searched for other options to keep us going and found some industry funding from Roche. They were very

generous, funding me for the early days of the project without any strings attached. Once that first paper came out, other funders also believed that I could produce results.

Science moves in waves. There are times when things are going really well and then there are other times when results are not coming. Those are the gut checks; if things aren't going well, but you still love it, you know you're doing the right thing.

Interviewed by Kristie Nybo, PhD

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Article 1: Peering Into the Brain

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