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People & Ideas

Daniel Colón-Ramos: Observing and making connections

Colón-Ramos studies neurodevelopment in *C. elegans*.

The nematode *C. elegans* has exactly 302 neurons, and we know the developmental lineage and physical position of each of these cells within the organism. We also have the "connectome": a wiring diagram of the *C. elegans* nervous system that tells us exactly which neurons are connected to each other. We know a lot about the nervous system of this organism, yet we don't know how its neuronal connections are achieved during development.

Daniel Colón-Ramos is fascinated by connectivity. As a postdoc (1) and in his own lab (2–5) he has investigated where and how sites of neuronal connection are designated. He also has been a vocal advocate for science, seeking to nurture connections between the scientific community and the public, especially in his native Puerto Rico. He kindly took the time to give us the big picture on how everything is connected when we called him at his lab at Yale University.

CONTEXT DEPENDENT

Where did you grow up?

My family's from a small town in the center of Puerto Rico called Barranquitas. The climate there is tropical rainforest, so there's a lot of biodiversity, which fostered my deep interest in biology and nature. But I didn't seriously think of pursuing science as a career because I didn't know any scientists. I didn't have the ability to visualize myself as a scientist or as a person capable of doing science. That's something that later inspired my efforts in science advocacy.

> "The experience inspired me to visualize myself as a scientist."

What are you focusing these efforts on?

When I was growing up, it seemed to me that science was something done by other people in other places. I was not sure how science had anything to do with my reality as a kid growing up in Puerto Rico.

When I was in graduate school I decided I wanted to help expose Puerto Rican kids to research done by other Hispanic scientists and to explain to them why science is universally important and very relevant to them. I started CienciaPR.org, an organization that uses social networking tools to bring together a geographically dispersed but emotionally connected community of Hispanic scientists. We organize formal science education projects in Puerto Rico and publish articles in newspapers that are used as teaching aids in classrooms.

It's been very rewarding to see the reception this has gotten, but doing this has also made me realize that science education needs to be contextualized. The best way to teach science is to use examples that will be meaningful to the student. If the curriculum focuses only on organisms and examples from other parts of the world, it sends a message to a child that science is not relevant to him or her.

How did you break free of that message?

For one thing, my parents really encouraged my interest in science. My dad was the director of a newspaper while I was growing up, and as a treat he would bring me newspaper clippings about scientific advances. Then I got a scholarship to participate in a now defunct NSF-funded Young Scholars Program. We met university scientists and got to do some experiments with them. The first person I worked with was a Hispanic female scientist, and that quickly changed my perception of scientists. The experience inspired me to visualize myself as a scientist and to understand that people who looked like me could do science.

Later, my high school college counselor encouraged me to apply to all the famous colleges we had heard about. I chose to go to Harvard because it was the only one I had ever visited—I had been there once with my dad when I was a child.

PHOTO COURTESY OF MICHELLE MCLOUGHLIN/MCLOUGHLIN PHOTOGRAPHY

Daniel Colón-Ramos

REACHING OUT

What did you do after college?

After college, I applied for a Fulbright scholarship to continue some work on ethnopharmacology that I had begun independently as an undergrad. It involved visiting indigenous groups living in remote rainforest communities in Panama, learning which plants they used and trying to identify them, with the idea of eventually identifying the pharmacological basis for indigenous medicines. The indigenous people taught me an amazing amount about rainforest biology, but, as the project progressed, I became increasingly interested in molecular questions. How are these bioactive compounds executing their function? I realized that, to understand those questions, I needed formal training in molecular biology. However, I was concerned about whether a career in basic research would be compatible with my interests in education and outreach. I sought advice from a mentor at Duke University, Mariano García-Blanco.

He listened to me, and he was very frank. He told me, "Look, I don't have the answers to any of those questions—they're very personal questions. But what I do have is a spot in my lab if you want to come and work and figure it out for yourself." So I declined the opportunity to go back to Panama and decided to work in Mariano's lab for a year instead—and I loved it. I got to develop my own project but with more resources and better support than I'd had as an undergrad. Mariano was the right mentor for me at the right time.

When I later enrolled at Duke for my PhD, I chose Sally Kornbluth's lab. She was

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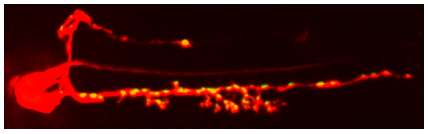

IMAGE COURTESY OF JESSICA NELSON

Synapses (green) formed by the main serotonergic neuron in *C. elegans* (cytoplasmic staining in red).

also a great mentor. She was very committed to developing scientific skills in her students. I try to emulate her mentoring style in my own lab now.

But it was as a postdoc that you first encountered the subject you work on now…

By that time, I had decided that I wanted to study developmental neurobiology as a postdoc. My girlfriend—who's now my wife—had completed her medical degree and matched in the Bay Area, so I started looking at labs there. During my interviews, I had really great conversations with Kang Shen at Stanford and Cori Bargmann at UCSF about *C. elegans*. From these conversations I could see that the *C. elegans* connectome would allow us to take what are traditionally systems-level questions—for example, developmental or behavioral questions—and turn those into cell biological questions. That just blew my mind. I knew immediately that this was what I wanted to do. One of the central questions that my lab is interested in is: What are the cell biological decisions that individual neurons make during development that result in a correctly wired circuit? I am particularly interested in how the brain of the worm, called the nerve ring, forms. Essentially nothing is known about it.

> "We [want] to build what we're calling 'the living connectome.'"

HIGHLY CONNECTED

Can you tell me about some of these decisions?

I had assumed—and I think a lot of people assume—that the postsynaptic partner is critical in dictating where the presynaptic specializations of the presynaptic partner will form. And one of the surprising results of our work is that, in the neurons we studied, the postsynaptic cell is not necessary for indicating to the presynaptic cell where to position its presynaptic specializations. Instead, a nearby glial cell secretes a protein called netrin which acts as the orchestrator by simultaneously talking to both the postsynaptic partner and the presynaptic partner. Netrin tells the postsynaptic cell to project towards the glia while telling the presynaptic cell to form presynaptic specializations at a pre-specified area. The glial cell is, therefore, a matchmaker.

That is what I showed as a postdoc, and since then my lab has been digging further to understand the molecular mechanisms of orchestrated circuit assembly in vivo. We came up with the surprising discovery that there are similar mechanisms that are acting in both the pre- and the postsynaptic cells to guide presynaptic assembly; both cells detect netrin using the same receptor, for example. But the presynaptic cell expresses a particular isoform of an adaptor molecule that instructs it to form presynaptic structures in response to netrin. We also recently discovered a new role for glia in maintaining synaptic positions during growth.

Where are you taking this work now?

We have continued our genetic screens and identified new netrin-independent pathways that regulate synaptic assembly. But these genetic approaches, while productive, have led me to the realization that even if we knew all the genes involved in circuit formation—which we don't—we still would not understand how precise circuit connectivity comes about in vivo. In the human brain there are over 100 trillion synapses but only about 25,000 genes. So genes are necessary, but not sufficient, to understand the organizing principles of the connectome.

We have recently set up a collaboration with Hari Shroff at NIBIB, Zhirong Bao at Sloan-Kettering, and Bill Mohler at the University of Connecticut to build what we're calling "the living connectome," which will detail the decisions of every single neuron in the nematode as they're coming together. We'll be using new microscopy and single-cell tracking technologies to image and record the decisions of all 222 embryonic neurons and to examine how different genes affect the connections these cells make with each other. It's going to be a very challenging project, but it will create a lot of research opportunities.

I hear you have an interesting and ambitious experiment going on at home, too…

[Laughs] Yes, my wife and I have triplets, three-and-a-half-year-old girls. My life is very rich. It's wonderful to watch them experimenting and learning about the world. I really do believe that kids are born scientists, and I see a lot of analogies between the way they learn and the way that scientists learn.

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PHOTO COURTESY OF DANIEL COLÓN-RAMOS

The grand experiment: Colón-Ramos exploring the world with the help of his daughters.