R. Dyche Mullins, Jr.

Dyche Mullins

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Dyche Mullins felt very much the outsider when he arrived on Cape Cod to take the renowned Physiology course at the Marine Biological Laboratory (MBL) in the summer of 1993. Mullins was from rural Kentucky, an engineer, and no cell biologist. He'd never taken a course in biochemistry. True, Mullins was finishing his doctorate at the University of Kentucky (UK) in Lexington in Biomedical Engineering. His UK mentors—engineer Betty Sisken and her cell biologist husband Jesse Sisken—had urged Mullins to take the MBL course to see if his growing interest in biological control systems extended into cell physiology. He'd seen the list of MBL faculty and speakers—Tom Pollard, Tim Mitchison, Ron Vale, and Roger Svoboda—and their impressive institutional affiliations. But Mullins thought to himself, "I'll be goddamned if I'm going to be intimidated by these guys."

His Physiology instructors had never seen anyone quite like the biomedical engineer from Kentucky. "I was immediately struck by how smart Dyche was," recalls Andrew Murray, now at Harvard Medical School. Mullins seemed to grasp key concepts instantly and gave no hint at the bench that he wasn't an experienced biochemist, according to Murray. "In the [Physiology] course, someone ends up there every year for some random reason who is completely off scale. That year, it was Dyche." Murray remembers, "By the end of the course, both Tom [Pollard] and I were trying furiously to recruit him as a postdoc. Tom won."

Murray consoles himself: "Dyche is one of my closest friends today. He's a wonderful scientist, but he's an even more wonderful person."

Back in 1993, Mullins believed that Pollard stuck out his neck by inviting him to join his Johns Hopkins lab as a postdoc. Pollard, now at Yale, remembers it differently: "I've always felt that Dyche had a clear vision of where to go scientifically. It was my good fortune that he decided to go in our direction and work on our problems, but I'm sure he would have been a great success working on something else."

Pollard's problem was simple. How do cells move? Under the innocent-sounding name of cell motility, the field had been grappling since the 1960s with the mystery of how the actin cytoskeleton assembled and disassembled itself so that cells could advance, surround, or separate themselves.

The Central Dilemma

The problem delighted Mullins, although he winces now when he recalls his rookie enthusiasm at Woods Hole. "I remember coming up to Tom and saying that I'd been reading a lot and it seemed to me that one of the important questions was how actin filaments are actually nucleated. Tom just laughed and said, 'Tell me about it. This has been the main issue in the whole field for the last 30 years.'"

The newest postdoc in Pollard's lab at Johns Hopkins would play a key role in solving the question. Mullins arrived in Baltimore soon after a key discovery by Laura Machesky, a graduate student in the Pollard lab. In 1994, Machesky identified what became known as the Arp2/3 complex in *Acanthamoeba*, a microscopic soil-borne protozoa. What role, if any, the Arp2/3 complex might play in actin nucleation was unknown. Then in 1997, Tim Mitchison and Matt Welch, working at the University of California, San Francisco (UCSF), identified the human homolog of the Arp2/3 complex. Machesky, now working with her husband Robert Insall at the University of Birmingham in the United Kingdom, linked the human Arp2/3 complex to a human protein called WASP already implicated in a genetic disease, Wiskott-Aldrich syndrome. Suddenly, an obscure amoebic protein complex was a player in a known human disorder.

A Model of Parsimony

Pollard had put Mullins on the Arp2/3 complex soon after he joined his lab in 1995. By 1997, they had already published part of their "story," demonstrating that the Arp2/3 complex binds to the sides of actin filaments and can cross-link them into networks. They also had unpublished data demonstrating that the Arp2/3 complex could nucleate new actin filaments. Despite this progress, Mullins recalls that the data didn't tie up into a neat package. "This is my favorite kind of science," Mullins notes, "where you don't just look at it [the data] and the answer is immediately obvious. It's where there are paradoxes or when you have lots of little hints, lots of disparate pieces of data that don't quite fit together. You have to come up with the most parsimonious model that could explain all this data. That suggests another experiment. You do that, and then you see the actual result."

Taken together, Mullins' data suggested that the complex might nucleate new filaments from the sides of pre-existing filaments. This was exciting because it would mean that the processes of filament nucleation and network formation are not just coupled, they are inseparable. The biochemical data pointed the way. However, to pull all the pieces together, Mullins decided that he needed better electron microscopy (EM). He sent protein samples and preparation protocols to John Heuser, a microscopist at Washington University in St. Louis. Mullins remembers Heuser's response to the first EM images. "He e-mailed us, 'Oh, my God, these look like Christmas trees or bottle brushes!'"

The suddenly visible Arp2/3 complex was more precise than any Christmas tree, although it was tree-like enough for Mullins and Pollard to coin the term "dendritic nucleation" to describe it. Mullins moved Heuser's micrographs into PhotoShop®, printed them out and then plotted the angles on paper with an old-fashioned protractor. The Arp2/3 complex produced new filaments at an angle of 70 degrees, ± 2 degrees. It's a finding that recalls science fiction novelist Douglas Adams and his *The Hitchhiker's Guide to the Galaxy.* In that novel, the answer to the meaning of life turns out to be the number 42. But the Arp2/3 complex is strictly nonfiction … and truly fundamental to cell motility. In eukaryotes, the Arp2/3 complex is central to everything, from the way that amoebae hunt for and seize prey, to how the human embryo "wires up" its neurons, to how cancer cells metastasize.

Despite this success at the bench, however, a significant barrier to publication still remained. If the Arp2/3 complex was making all these branched filament networks, why had no one seen them in cells? There were scattered reports in the literature of end-to-side or y-branched filament crosslinks but there was no evidence for the densely branched network predicted by the Pollard-Mullins model. Then, as if on cue, Gary Borisy and Trina Svitkina at the University of Wisconsin developed an improved method for preserving and visualizing actin filaments. They took a close look at the dense latticework of actin filaments on the leading edge of fish keratocytes. In their images, the latticework was built almost exclusively of the rigid y-branch crosslinks suggested by the Pollard-Mullins model. Mullins recalls reading the Svitkina and Borisy paper. "When I saw their images, I sat bolt upright. My heart was pounding. I could barely finish reading the paper, and I ran immediately to show Tom that we were right."

A Diagram to Remember

The resulting Mullins-Heuser-Pollard 1998 *PNAS* paper became a citation classic. "It's the most reproduced piece of information from our lab of all time," Pollard acknowledges. "It was a formative moment in the field." At the time, a lot of people were making predictions about how filaments would be nucleated by comparing them with microtubules. As Mullins recalls, "Most people thought that the nucleation sites had to be fixed at the membrane, and that the filaments were nucleated and then released from the nucleation sites. In our model, the nucleation sites are an integral part of the network and move with it."

To illustrate this point Mullins drew a simple diagram showing their model for the role of the Arp2/3 complex and integrating it with the functions of other fundamental actin regulators. That diagram is still in use, says Pollard. "Every time you go to a meeting about the Arp2/3 complex, someone will show a form of Dyche's diagram." It brought together 30-plus years of research at the molecular and cellular level on how actin contributes to cellular motility, declares Pollard. "Dyche has a real flair for summarizing complexity with approachable, transparent diagrams," Pollard continues. "He's continued to do that with the new work he publishes from his own lab."

The Arp2/3 complex papers launched Mullins into his first faculty position at UCSF. But in Andrew Murray's opinion, Mullins' best science is what he's doing today: "It [the Arp2/3 complex] was a scientifically important piece of work, but … the work that Dyche is doing now on how bacterial actins direct DNA segregation is actually going to be much more important. This work with his students Ethan Garner and Chris Campbell is spectacularly beautiful. It tells us about the potential origins of chromosome segregation. In my mind, Dyche's Arp2/3 complex stuff was sort of a warm-up to this."

The Heartland

Rockcastle County is in eastern Kentucky, almost due south as Interstate 75 flies from Lexington on its way to Florida. It is in the Appalachian heartland—hilly, largely rural, and the center of Dyche Mullins's galaxy. "Every time I go home, I get this weird vibe of being simultaneously incredibly connected and at ease, like nowhere else on earth," Mullins explains. "Everyone knows me. Everyone knows my whole family. At the same time," Mullins continues, "it can feel stifling."

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Mullins is descended on both sides from pioneer families who came into the Kentucky territory in the 1780s. His mother's people came with Daniel Boone. His father's people came in less distinguished company, says Mullins, but they brought the family name Dyche with them. It's pronounced "dike." According to *The Oxford English Dictionary,* it comes from the Old English word for an earthwork or ditch. "It means that I'm named after a long line of ditch diggers," Mullins deadpans.

Leaving the County

That long line is still rooted in Rockcastle County. Mullins' father was a school principal who helped found, and then ran, the regional community mental health agency. His mom taught high school English. One of his sisters became a pediatrician, the other, a lawyer and writer. Both moved back to Rockcastle County to practice their professions and live on farms. "I'm the black sheep professor who moved away," Mullins says. "Still, when I was growing up, I never imagined leaving the county for good."

For college, Mullins never imagined going anywhere but UK in Lexington. Cell biology was the farthest subject from his mind as an undergraduate. Mullins was torn between mathematics and Russian. He studied both and spent a semester at what was then the University of Leningrad before returning to UK. "I was being advised by practical-minded people who said that with my interests I should become an engineer." He listened and graduated in 1988 with separate degrees in Mathematics and Electrical Engineering.

From Farmer to Biomedical Engineer

Then Mullins promptly moved back to Rockcastle County, where he purchased a 250-acre farm and tried to raise cattle. Influenced by the Kentucky writer and environmental philosopher Wendell Berry, Mullins went home to pursue the ethical rural life. Reality convinced him otherwise. "I did not make much of a farmer," Mullins confesses. After a year and a half, he bolted back to Lexington and enrolled as a graduate student in electrical engineering.

That summer, Mullins was hired by a UK biologist to construct some electrical apparatus. Gradually Mullins became intrigued at what was going on around him in the lab: "I started to realize that biology was less purely descriptive and more quantifiable than I'd imagined." In the fall, he switched from electrical to biomedical engineering. That's when he met the Siskens.

At UK, Betty Sisken had never met a student quite like Dyche Mullins. "This character appeared out of nowhere," Betty Sisken remembers. A faculty member told her about an American engineering grad student who was carrying around Russian literature books, which he was apparently reading. "That was Dyche," Sisken laughs. "He's incredible."

Under the guidance of Betty and Jesse Siskens, Mullins developed a thesis proposal. It featured an engineering approach with Betty Sisken and a study of intracellular calcium homeostasis with Jesse Sisken. Says Betty Sisken, "Dyche was the best student we've ever had here. We get lots of good students, especially from these small towns in Kentucky, students who have good preparation or are extremely self-motivated. Most of them go into medicine, but Dyche has always been exceptional."

Cytoskeleton in the Prokaryotic Closet?

Today, the Mullins lab at UCSF presses ahead on three fronts. One section still explores how the Arp2/3 complex collaborates with other cytoskeletal proteins to drive cell motility. The second focuses on a *Drosophila* protein called Spire that seems to be crucial in establishing the very earliest cytoskeletal landmarks in embryos. The third is looking for the roots of the eukaryotic actin cytoskeleton in actin-like filaments that prokaryotes use for DNA segregation.

A Multitude of Interests

This year, Mullins has also served as Program Chair for the 2007 ASCB Annual Meeting. The Committee's work went much more smoothly than he imagined, Mullins reports. "Still, you don't want to do too good a job at this sort of thing or people will never stopping asking you to do it again."

As ever, Mullins continues to pursue an amazing variety of interests, from Russian poetry to building a "city" bike. He also shoots photographic portraits of the leading lights in cytoskeleton research.

Still another Mullins interest is restoring antique microscopes. Mullins says that the old microscopes have opened yet another career track—wading through Bay Area marshes in search of unknown cyanobacteria. "I'm becoming an amateur naturalist," Mullins proudly announces. ■

—John Fleischman