

Timothy J. Mitchison



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Once upon a time in cell biology, the cytoskeleton with all its mysterious moving parts was considered a backwater. The time was the early 1980s. The place was the University of California, San Francisco (UCSF). And the career advice being offered to new UCSF graduate students was to follow the DNA. “That was really the big news then,” recalls Tim Mitchison, who’d just come to UCSF with a biochemistry degree from Oxford University. “Everything to do with the DNA molecule, its transcription and regulation. Basic cell biology was sort of off to one side.”

Also off to one side was a young associate professor, Marc Kirschner, a respected but not yet “big name” researcher at UCSF, who gave a special topics seminar for the incoming grad students on microtubule nucleation and growth. It was a problem not just of polymerization biochemistry, Kirschner told them, but also of space and time. Kirschner’s approach was “quirky,” Mitchison remembers. “I was electrified.”

Microtubule Formation

Kirschner recalls, “Tim was so articulate and so bright that I kind of worried that he would be one of those people who could never settle down to actually do anything. I was completely wrong about that.” Joining the Kirschner lab, Mitchison tackled the formidable technical task of purifying centrosome proteins. It took him two long years to produce a reliable and abundant tubulin supply. Along with the tubulin came growing doubts about the widely accepted “treadmilling” theory of microtubule formation.

In the treadmilling model, microtubules ran like tractor treads, adding tubulin subunits at the front end and shedding them at the back. But in the characteristic “asters” that microtubules form *in vitro*, Kirschner and Mitchison realized that they had a visible, empirical assay for microtubule growth.

Treadmilling could not explain what they were observing—microtubules sprouting from a nucleation site in all directions, growing at different speeds and to unpredictable lengths. The process looked nearly random, except that by hit and miss in living cells, some microtubules managed to extend themselves to the cell membrane. There they stabilized, laying down the tracks of the cytoskeleton.

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Dynamic Instability

Mitchison and Kirschner proceeded to discover an alternate mechanism of microtubule growth that they called “dynamic instability.” It combined stochastic unpredictability with molecular precision. The driving force behind microtubule growth and catastrophic collapse was the difference between the populations of GTP- and GDP-capped tubulins. A

microtubule grows through polymerization only as long as its end is securely capped by GTP-tubulin. Inside the column though, hydrolysis is constantly working its way up, destabilizing GDP-tubulin. Once undercut, the GTP-tubulin cap is displaced and the microtubule enters catastrophic free fall, unless a random passing GTP-tubulin can bump in for the rescue. Beyond its far-reaching implications for cytoskeletal structure, dynamic instability suggested an evolutionary solution to the old problem of how an “unguided” cytoskeleton could navigate the cell interior.

Dynamic instability launched Mitchison’s career. “I very much remember giving my first talk at ASCB at the meeting in San Antonio where I announced dynamic instability to a skeptical audience. I was very nervous, and it all went by in a blur. But after that, I always thought of myself as an ASCB scientist.”

Two years after leaving UCSF as a newly minted PhD, Mitchison returned as a junior faculty member in pharmacology. At 28, Mitchison had his first R01 grant funded by the National Institutes of Health. At 39, Mitchison

left UCSF for Harvard Medical School (HMS) at the invitation of his old mentor, Kirschner, who had become chair of cell biology. When Kirschner created a systems biology department at HMS in 2004, Mitchison was one of the founding faculty.

There is another connection between Kirschner and Mitchison. In 1991, Kirschner became president of the ASCB. In 2010, Mitchison took up the ASCB gavel himself.

Influence and Education

Tim Mitchison was born in 1958 in Edinburgh, Scotland, but grew up in north London where his father, Avrion Mitchison, was a renowned immunologist at the National Institute for Medical Research in Mill Hill. His grandfather, Dick Mitchison, was a leading Labour Party politician, and his grandmother, Naomi Haldane Mitchison, a prolific novelist. His grandmother's elder brother was the legendary population biologist J.B.S. Haldane. (It was he who when asked by a theologian what characteristics Haldane could ascribe to a divine Creator, supposedly replied, "An inordinate fondness for beetles.")

The family luminary who had the greatest personal influence on Mitchison was his novelist grandmother. "I was very close to her," he explains. "I had a troubled youth in the best British tradition. I used to go hang out at her house in (western) Scotland and do gardening. She was a free spirit and quite a strong influence."

For high school in London, Mitchison went to the wonderfully named (and wonderfully punctuated) Haberdashers' Aske's School. "The key scientific influence in all my life was my high school chemistry teacher, Mr. Carleton," Mitchison declares. "He probably did have a first name, but in those days we didn't know them. It was an all-boys school. I had no social life at all but everything I ever learned, I learned at that school."

Mr. Carleton's chemistry carried him to Oxford where Mitchison was distinctly underwhelmed by undergraduate biochemistry, especially after a nine-month internship in the UCSF lab of Bruce Alberts between high school and university. At Oxford, Mitchison was determined to join a working research lab, only to be told that such a thing was against the rules. "I begged and pleaded but they said I had to wait until my fourth year." A second research internship in America—this time a summer in the Cold Spring Harbor lab of Michael Botchan—convinced Mitchison to seek his

graduate training in the U.S., preferably in San Francisco.

Doc of the Bay... and Boston

His return to the Bay Area in 1988 as UCSF junior faculty was the beginning of an incredibly creative period when Mitchison carried his breakthrough work on microtubule dynamics into kinetochores, mitotic spindles, polymer motor systems, and cell division. Tony Hyman was Mitchison's first postdoc in his new lab in 1988. "It was chaotic but fun," Hyman remembers. "There was this incredibly dynamic atmosphere. Anybody could come forward with a new idea or approach because Tim was always looking for new and creative directions." A decade later when Hyman helped found the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany, he used the Mitchison lab as part of his model. "I wanted to try to create within the new institute a sense of labs as family units that could interact with each other and avoid the 'tribal' system of rival departments that breaks up academic institutions."

Today in Boston, the Mitchison lab at HMS presses ahead with an array of projects on basic cytoskeleton dynamics, chemical biology, and cancer pharmacology. Mitchison's interest in cancer drugs came out of his collaboration with Harvard University chemist Stuart Schreiber on their Institute of Chemistry and Cellular Biology (ICCB). The ICCB was a daring attempt to borrow the concept of high-throughput, small molecule compound screening from the pharmaceutical industry and scale it up in an academic setting. It ran full blast for five years before it morphed into separate institutions, but Mitchison remains fascinated—and frustrated—by pharmacological applications of basic biological discoveries. He has concentrated on potential "mitotic spindle poisons" turned up in the ICCB screenings. He followed derivatives of one compound, the kinesin-5 inhibitor monastrol, all the way to clinical trials. So far, they have performed no better against cancers than already available taxol-derived compounds.

The kinesin-5 inhibitor experience has left him wiser but no less curious. "Cancer pharmacology can be brutal. Either the drug works or it doesn't," Mitchison says. "We have to get beyond that, to generate the kind of understanding we need to predict which drugs will work and which won't."

Yet Mitchison still believes, "You have to be an optimist. You have to believe that when

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something odd happens, it’s Mother Nature trying to tell you something and that it’s not just you screwing up. Nine times out of ten, it is you screwing up but you’ve got to be an optimist to get up the next morning and do the experiment again.”

Boston’s Worst Lawn

With his wife and longtime lab member Christine Field, Mitchison adopted two children, Lorna, who is now 13, from China and Duncan, who is now 10, from Cambodia. The family lives in Brookline, a leafy, upscale city just west of Harvard’s Longwood campus. They have a large, wonderful house, Mitchison declares, with “the most neglected lawn in Boston.” Between school, youth soccer, and dogs, they lead “a very privileged but very typical suburban life,” he says.

The family decamps for the entire summer to Woods Hole on Cape Cod where Mitchison co-taught the physiology course at the Marine Biological Lab (MBL) with Ron Vale for seven years. Mitchison says he is invigorated by the contrast between high-stakes academic science at Harvard and his small-scale lab work at MBL. Plus the kids love the Cape.

Family Central

“Did Tim tell you about his family?” asks Kirschner. “Tim’s a wonderful father. Christine is a wonderful mother.... They’ve really built a life with these children that is central. Yeah, Christine does the soccer. That’s always been her thing, but Tim is very involved as well. Did he tell you he’s very good at woodworking? Or that he knows the forest and is always taking the kids on hikes? He used to fish a lot when he was younger and he loves showing his kids that kind of stuff.”

ASCB Community and Outreach

Says Kirschner, “I think Tim’s image is of a brilliant and effective scientist. But there’s this

other side of him that was always there but is coming out more now.” Mitchison has always been extremely serious about his obligations to colleagues and to the next generation of scientists, according to Kirschner.

Taking up the presidency, Mitchison is diffident about the changes he’d like to bring to ASCB in his term. “It’s always easier to talk about these things than to do them,” he admits. “But I’ve made a lot of fuss about the need to broaden the scope of the Society, for example, to include more people using cell biology in the pharmaceutical industry, or teaching it to undergraduates.” But this has to happen without alienating the core membership who attend the Annual Meeting year after year, Mitchison believes.

The importance of ASCB goes beyond its once-a-year meeting, Mitchison says. “The ASCB is not just the Annual Meeting. It’s help for your career. It’s spreading the word on the importance of basic science in Washington, and perhaps most of all, it’s a way to participate in the world-wide community of cell biologists.”

Science as Transformative

Mitchison also thinks that science can be personally transformative. It rescued him, he says. He winces at the memory of his first arrival in San Francisco for his summer internship. “I was such a different person then. I was a typical pimply British youth who loved science and was utterly clueless.” When he came back to San Francisco four years later as a graduate student, Mitchison plunged into microtubule dynamics and San Francisco punk rock. Both were amazing scenes, says Mitchison, recalling late-night science and even-later-night punk music clubs.

Does he still listen to punk rock? “I do when it comes on the radio,” Mitchison confesses, “but then my children tell me to turn it off. I guess it’s one of those things where you had to have been there.” ■

—John Fleischman