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## 2001

### Laura Machesky

It would have been one of those neat little discoveries, even if it had led nowhere, and for a long time, the discovery of the Arp2/3 complex seemed to lead exactly there. In 1993, Laura Machesky was a graduate student in the Johns Hopkins laboratory of Thomas Pollard when she isolated and characterized a group of seven previously unknown proteins that became the Arp2/3 complex. She found the protein complex in *Acanthamoeba*, an organism much beloved in labs because it is about as simple as life can be and still be a eukaryote, a creature with a nucleus, chromosomes, and its own DNA. Amoebas, fruit flies, mice and humans are all eukaryotes. The problem with finding novel eukaryotic proteins is figuring out what they might do. Of the seven in Arp2/3, five remained "novel," that is, of unknown purpose, but Machesky discovered that two of them were actin related. That was big news, at least in the small circle of those who worked with actin assembly and disassembly. Actin filaments are key elements in the cytoskeleton, the cell's internal matrix that provides structure, delivers bioactive molecules, and enables the cell to move about, doing its business. A 1994 paper announcing Arp2/3 by Machesky and Pollard in the *Journal of Cell Biology* caused a significant ripple in cytoskeleton labs. The rest of the world went on unruffled. Arp2/3 was the subject of Machesky's doctoral thesis.

The newly minted PhD left the U.S. with a Damon Runyon-Walter Winchell Cancer Research Fellowship that supported a post doc in Britain at the MRC Laboratory in Cambridge with Rob Kay. "When I left Tom's lab in '93, I thought that was the end of Arp 2/3," Machesky recalls. "It was a little unsolved mystery that I thought I might come back to someday." Instead, she went to Cambridge to learn about *Dictyostelium*, another beloved lab model animal, a lowly soil amoeba with great possibilities for genetic and molecular manipulation.

Machesky concedes that her decision to do a post-doc in the UK was not entirely unrelated to her deepening relationship with Robert Insall, an English researcher who was doing his post-doc in another Hopkins lab. Ironically, Insall's work kept him in Baltimore until 1996 while Machesky's career was blossoming in Britain. They were married in 1995. Today, they hold separate appointments but adjacent laboratories at the University of Birmingham, living "round the clock, more or less, in each other's pockets," says Machesky. "I don't know how we dealt with it before, but we can't stand to be apart now."

In 1997, Arp2/3 suddenly reappeared in her life. Machesky was making a successful transition from post-doc in Alan Hall's lab to independent researcher by winning an MRC Career Development grant. The British title is "Group Leader" and she set up her lab in the Gower Street Laboratories of the MRC in London. Then word came that the Arp2/3 complex had been found in human cells by Matthew Welch, a post-doc in the University of California, San Francisco lab of Tim Mitchison.

The jump from amoeba to human raised the stakes enormously. Any cellular mechanism that can be traced from the genome of the simple but ancient amoeba to the complex but relatively recent human is said to be "highly conserved" by evolution. That meant that Arp2/3 probably plays a fundamental role in human cells. New proteins that play ancient roles don't turn up every day, and Machesky had to find out what went wrong in humans when Arp2/3 is defective.

She found the link through a rare but devastating genetic condition called Wiskott-Aldrich Syndrome (or WAS) that disrupts the immune system and blood clotting and causes terrible skin rashes. It is X-linked—that is, largely confined to males—and usually fatal by age seven unless a bone marrow transplant is successful. Wiskott-Aldrich Syndrome had been linked to defects in the WASP/Scar family of proteins.

"Using a two hybrid screen, Laura identified an interaction between one of the proteins in the Arp2/3 complex and the WASP/ Scar family," says Hall, her former lab chief in Cambridge. "Thus her work has come full circle and the complex that Laura first discovered in *Acanthamoeba* is now linked to molecules involved in GTPase regulated signal transduction pathways in mammalian cells. This, in my opinion, is one of the most significant steps forward in understand the connection between signaling pathways and the actin cytoskeleton." Hall nominated Machesky for the Women in Cell Biology Junior Career Achievement Award, which she will receive this year at the ASCB's Annual Meeting in Washington.

"Arp2/3 started a whole new field and set the cell motility community in an entirely new direction," says Tom Pollard, Machesky's PhD advisor and former ASCB President who is now at Yale. "There are whole lot of people working on it. At the cell motility Gordon conference this summer, there were so many people making reports about it that the people who weren't got up and proudly announced that they were not going to talk about the Arp2/3 complex."

To have a Senior Lectureship, a British husband, and a world reputation in cell motility at age 36 is not bad for a girl from the small Detroit suburb of Walled Lake. Machesky says she was always interested in science and math and went off to her state's Alma College (the University of Michigan only had football

scholarships, she recalls) with the firm intention of becoming a physician. A summer internship at Henry Ford Hospital near Detroit changed her mind. She rotated through various hospital departments including the Emergency Room, Surgery and General Practice. She felt most at ease in the Cytogenetics Lab where a friendly technician, Jim Zabowski, showed her how to draw her own blood and to prepare and stain a karyotype. "I still have it somewhere," she says. "I thought the cytogenetics were the really fun part. All the MDs were really down on medicine. They told me how they were under a lot of stress and lots of debt. When I went back to college that fall, I told my advisor, Larry Wittle, that I wanted to go into research. It was the brain and hand work that appealed to me."

She entered the cell biology grad program at the Johns Hopkins School of Medicine in 1987. Tom Pollard's lab was her third rotation and her home for the next six years. Machesky was the ideal graduate student, says Pollard, doing excellent work on the lab's major projects while pursuing her own experiments that led to the Arp2/3 complex. "People always have good ideas but Laura was one who had more good ideas than most," he says. With a laugh, Machesky remembers the Arp2/3 experiments differently. "Tom told me, 'Don't do it. It's a waste of time.' I went ahead with it anyway."

Pollard also notes Machesky's boundless energy, her antic sense of fun, and her fondness for elaborate practical jokes, the details of which he will not reveal for fear of retribution.

Today, Machesky is a Senior Research Fellow at the University of Birmingham in the English Midlands. Having worked in both the American and British research systems, Machesky is diplomatically neutral when comparing. The American system of extended doctorate education is probably better preparation, she says. The British system of shorter, limited term post-docs that lead to independent Group Leader positions is probably better for career productivity, she observes. British researchers are more laid-back and less desperate, she says, but much more hand-off. "That means I can still work my seven-and-a-half-day week. Everyone can think I'm mad but nobody would think of interfering. On the other hand, my chairman isn't going to call me in to say that if I don't get a paper into Cell this month, I am out of a job."

Machesky contends that she and Insall have few interests outside the lab beyond their home, their cat Delilah ("Samson ran off," she explains), and "rambling," a British outdoor pastime that she and her husband have perfected as "rambling up a not very large mountain and then going for a huge meal at a very nice B&B. I guess you'd call us luxury ramblers."