ASCB PROFILE

Gary Ward

Gary E. Ward was finishing a postdoc in 1989 on a hot topic in a hot lab. The lab was Marc Kirschner's at the University of California, San Francisco, and the topic was the cell cycle. "Connections in cell cycle regulation were being made between yeast and sea urchins and frogs," Ward recalls. "All of a sudden, it was clear that we were all seeing the same thing. It was an amazing time." So it was hardly expected when Ward jumped from the cell cycle to a narrow and entirely different field about which he knew little—parasitology—to study the cell biology of *Plasmodium*, the malaria parasite.

"In some respects, I had to start over," Ward says about his decision to join Lou Miller's malaria research lab at the NIH in 1989. "There was very little being done then on the fundamental cell biology of *Plasmodium* and the related *Apicomplexa* parasites like *Toxoplasma*." But Ward's motivation and the source of his determination were clear: "The cell biology is fascinating, and these are diseases that really matter," Ward says simply. "All of us in basic research argue in our grant applications that what we're doing has medical relevance; but malaria is one of the truly Big Ones. More than 40 percent of the world's population is at risk, 300 million people suffer from the disease, and over a million die annually, mostly young children." After his initial interview with Miller, Ward called home to ask his wife, Zail Berry, who was finishing her medical residency at UCSF, if she could move to Bethesda while he figured out how to become a molecular parasitologist. They stayed seven years.

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Says his former UCSF colleague Tim Mitchison, now at Harvard Medical School, "After a successful postdoc in the Kirschner lab, Gary could have gotten a good job anywhere in cell biology, but he wanted to work on malaria and do something important. You've got to feel good about somebody who's working on an organism like *Toxoplasma* that's a difficult to treat human disease, especially in AIDS patients, and still quite relevant to malaria."

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Today Ward's only regret about going into molecular parasitology is that the work has not gone fast enough or far enough. First, he had to come up to speed on the "Byzantine life cycles" of the *Apicomplexa* parasites. Culturing and manipulating the invasive stages of *Plasmodium* turned out to be excruciatingly difficult. Eventually, Ward turned to *Toxoplasma* for a lab model of parasite-host cell invasion that could still be applied to malaria. The human disease burden from *Toxoplasma* is real if more insidious, says Ward. It is an important cause of congenital birth defects worldwide. Additionally, 20 percent of Americans and as much as 95 percent of the population in other parts of the world are chronically infected, leaving them vulnerable under the immunological strain of AIDS, cancer chemotherapy or an organ transplant to the sudden re-emergence of a life-threatening *Toxoplasma* infection.

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"That's the downside when you go into a field where not a lot has been done," says Ward. "There wasn't a large community of researchers when I started where I could turn to for reagents or methodologies, the way I could in cell cycle. We didn't have the genomes and the knockouts, so we've all had to spend a significant portion of our time

developing some of the tools that every yeast biologist takes for granted."

His peers think Ward has already brought the field a long way. "Gary's been instrumental in changing how we think about parasite invasion and in developing new technologies to apply to these complex biological problems," says David Roos of the University of Pennsylvania. "Gary was the first to apply electrophysical approaches to the process of cell invasion. He gave us our first indication that when the parasite invades and sets up its specialized vacuole, it uses the host cell's own lipids to form the parasilophorius vacuole. That was a critical discovery."

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Roos continues, "Gary's development of novel cell biological screens for looking at interesting cell processes like motility or invasion using the kind of small molecule high-throughput analysis was typically limited to biochemical studies of a particular enzyme. Gary has done a fantastic job developing what are really whole organism screens."

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Like nearly everything else in molecular parasitology, small molecule screening presented both special difficulties and tremendous opportunities, says Ward. Previous studies of host cell invasion had been severely handicapped by the fact that, in a haploid obligate intracellular parasite such as *Toxoplasma*, disruption of a gene essential for invasion is lethal by definition. Ward explains, "In the absence of an inducible promoter or efficient conditional mutagenesis, both forward and reverse genetic approaches suffered from the same problem: the most interesting of the mutants one might generate were likely to be non-viable." Ward and his British collaborator, synthetic chemist Nick Westwood, wondered if they could use libraries of structurally diverse small molecules to screen for compounds that cause a particular biological effect and then to work backwards from "hits" to directly identify the molecular target that was disrupted.

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"This new work by Gary goes beyond revealing some interesting compounds with drug potential," says Tim Mitchison. "It reveals the whole idea of targeting the secretory pathway of the parasite. It's a piece of physiology that no one has considered before as a suitable target. The importance here goes beyond the compounds themselves. The approach shows that the microneme secretion pathway is a plausible, drugable target."

Today, Ward is a Burroughs Wellcome New Investigator in Molecular Parasitology and Associate Professor in the Department of Microbiology and Molecular Genetics at the University of Vermont. In addition to his research, Ward teaches cell biology and parasitology to undergraduates, graduate students and medical students. Zail Berry practices internal medicine in Burlington, specializing in palliative care. Their two children, Zina, 13, and Grady, 9, ski like true Vermonters—as does their Canadian dad—despite their Bethesda roots. Ward plays ice hockey twice a week, including on the Microbiology faculty's intramural squad, "The Geezers." He loves Vermont's mountains and Vermont politics, and has followed with passion "the rise and stall" of their former Governor Howard Dean.

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Ward's research interest makes him acutely aware of Third World health issues, and he is a strong advocate for open access publishing. He serves on the editorial board of the Public Library of Science Biology journal, and has been a major player in the ASCB's contributions to this movement. He has also served the Society as its elected Treasurer since 2002.

Ward was born in Montreal, Canada, the third of four boys. His oldest brother, Bruce, is a dentist and his older brother, Brian, is a physician and tropical disease researcher at McGill. (Brian and Gary have collaborated and are hoping to publish together soon). His younger brother, Glen, is a pediatrician. Gary majored in Biology and Physics at the University of New Brunswick in eastern Canada and chose the Scripps Institute of Oceanography at UC San Diego for graduate school, thinking of a career in oceanography. But he fell under the spell of Vic Vacquier, who convinced him that cell biology was the way to answer almost any question. (Vacquier also convinced Ward that the ASCB was the society for almost everyone in biology.) For his doctoral thesis under Vacquier, Ward worked on sea urchin sperm, analyzing how they sensed and chemotaxed toward sea urchin eggs.

"Vic firmly planted in me the idea that the cell was 'where it was at' and that cell cycle regulation was going to be one of the next Big Things," Ward says. He joined the Kirschner lab in 1985.

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Says David Roos, "Many cell biologists are drawn by the world health implications [of parasitology], but some are still put off by the prospect of working in a small field which they feel lacks a critical mass of investigators. Gary took this as a challenge rather than an impediment. I think what Gary has been able to accomplish shows what an unusually innovative and ingenious cell biologist he is." Says Tim Mitchison, "Gary's the kind of scientist all of us should aspire to be. Plus," Mitchison adds, "he's a super nice guy." ■