Mariana Wolfner: 2018 Genetics Society of America Medal

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The Genetics Society of America (GSA) Medal recognizes researchers who have made outstanding contributions to the field of genetics in the past 15 years. The 2018 GSA Medal has been awarded to Mariana Wolfner of Cornell University for her work on reproductive processes that occur around the time of fertilization. This includes characterization of seminal proteins in *Drosophila melanogaster*, which has uncovered a wealth of information about sexual conflict in evolution.

ACCORDING to her colleagues, Mariana Wolfner's fruitful research career is a testament to her great creativity and skill, not to mention her exceptionally effective approach to mentoring trainees. But her career path also exemplifies the benefits of following the questions that drive you—even when they lead in unanticipated directions.

Wolfner never imagined she would study seminal proteins; she simply followed her lifelong interest in biology through the twists and turns of science. Biology caught her interest as a child, and, when she applied to college—a time when many students are not sure what major or even field they want to study—Wolfner specifically sought admission to schools that were strong in genetics. Her choice, Cornell University, was home to many prominent genetics laboratories—and now Wolfner's group is among them.

Wolfner got her start in research in Gerry Fink's laboratory at Cornell, working on general amino acid control in yeast. Then, as a graduate student with Dave Hogness at Stanford University, she was part of the early wave of molecular biologists to use recombinant DNA to isolate and study *Drosophila* genes. Specifically, Wolfner and colleagues developed and used differential cDNA hybridization screening to isolate genes whose expression responded to the steroid ecdysone during metamorphosis. After completing her graduate training, Wolfner began investigating the genes that control sex determination in *Drosophila* as a postdoctoral fellow with Bruce Baker, then at the University of California, San Diego. Wolfner and Baker cloned the gene for Doublesex, a conserved transcription factor that regulates sex-specific genes. When she left to form her own laboratory at Cornell, Wolfner continued to pursue the mechanisms behind sex determination and development, setting out to study genes that are expressed in one sex but not the other.

Some of the first of the genes she identified encoded seminal proteins. At the time, Wolfner had no idea what these proteins did, but she and her group quickly became fascinated with them. By that time, it was known that mating produced profound behavioral changes in female flies, triggering them to lay eggs and to avoid mating again, but the mechanisms behind these and other mating-induced changes were murky. Wolfner's genetic ablation experiments established that seminal proteins made in males' accessory glands and transferred to females during mating caused those postmating changes (Kalb *et al.* 1993). "How does a male make a protein that acts in another animal and influences her?" Wolfner remembers wondering. "The second question is, how do you evolve that?"

Pursuing these questions led to Wolfner's career-long, multidisciplinary exploration of the >200 *Drosophila* seminal proteins and how they influence female behavior and physiology (*e.g.*, Heifetz and Wolfner 2004; Avila and Wolfner 2009; Rubinstein and Wolfner 2013; Findlay *et al.* 2014; LaFlamme *et al.* 2014; Mattei *et al.* 2015). While fruit fly seminal proteins may seem an esoteric subject, the group's sustained effort to identify and characterize them has produced a trove of information that has proved insightful far beyond the topic of *Drosophila* reproduction.

The genes that encode these proteins are among the most quickly evolving in the *Drosophila* genome and have provided a powerful illustration of the effects of sexual conflict in evolution (Swanson *et al.* 2001; Mueller *et al.* 2005; Haerty *et al.* 2007; Sirot *et al.* 2011). In one example of this conflict, seminal proteins that temporarily increase the rate at which females lay eggs after mating provide an obvious

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reproductive benefit for the male. But postmating changes such as producing more eggs shorten the lifespan of the female (Chapman *et al.* 1995), meaning that selective pressures acting on this trait partially oppose each other. The ensuing coevolutionary tug-of-war can drive rapid evolutionary changes. Seminal proteins have become an empirical goldmine for evolutionary biologists looking for rich sources of data to help explore these phenomena.

These discoveries have also captured the attention of those who see the potential for practical applications. Wolfner's group is now collaborating with Laura Harrington's group, also based at Cornell, to find seminal proteins in the mosquitoes that transmit the Zika and dengue viruses (Degner *et al.* 2018). Better understanding the reproductive biology of disease vectors could one day open up options for controlling the spread of such global diseases. Moreover, mechanisms that Wolfner's laboratory identified—such as seminal proteins acting as switches to activate poised physiology in females—likely generalize to mammals, whose seminal proteins also cause physiological changes.

Another major area of inquiry in Wolfner's laboratory is the egg-to-embryo transition, which occurs when the oocyte is released from meiotic arrest and activated for its transformation into a developing organism. This activation process is highly conserved, but one distinction between mammals and fruit flies has proven instructive. In mammals, the fertilizing sperm triggers the transition, but Wolfner's group showed that in *Drosophila*, the key event is the mechanical pressure experienced by the oocyte as it is squeezed into the oviduct during ovulation (Heifetz *et al.* 2001). This separation of the fertilization and activation processes has allowed Wolfner and her colleagues to home in on the specific events that follow the trigger (Krauchunas *et al.* 2012). They found that egg activation in *Drosophila* involves a spike in calcium concentration that activates downstream signaling pathways (Kaneuchi *et al.* 2015)—very similar to what happens in mammals.

Wolfner's great success in leading these two distinct yet complementary projects reveals much about the type of scientist she is. "She's fearless in being able to move from one discipline to another when it's necessary to answer a question," says fellow *Drosophila* geneticist Marla Sokolowski of the University of Toronto. "She's always using fantastic state-of-the-art techniques. Her experimental design is impeccable," adds Sokolowski, who has known Wolfner for over 30 years, and says she has always had great admiration for her as a scientist.

These characteristics are not all that underlies Wolfner's success; she attributes much to those with whom she has worked, including both her many collaborators and the members of her own laboratory. The fact that the talented, motivated individuals Wolfner attracts thrive in her laboratory is no accident, though. Sokolowski calls Wolfner an "unbelievably wonderful mentor" and a great role model—statements echoed by one of Wolfner's former postdocs, Geoff Findlay of the College of the Holy Cross.

In fact, Findlay says Wolfner's mentorship of him began long before he joined the laboratory, and continues even now that he is an assistant professor. Findlay says the way Wolfner treated him when he met her as an undergraduate made an impression on him. "She was happy to meet with me and answer my questions even though I had no scientific track record yet," he says. "She treated me very seriously and gave very thoughtful answers to questions." Sokolowski says Wolfner is known for being the person at conferences who approaches students at their posters, asking questions, providing suggestions, and even following up with them later.

When asked what in her scientific career has made her proudest, Wolfner cites her students and postdocs—but adds that she does not like to use the word "proud" because she does not want to take credit for their accomplishments. Wolfner's career so far highlights the rewards of pursuing a truly collaborative model of science in which time and expertise are shared widely—and of following wherever curiosity may lead.

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