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ESSAY

A conversation with Mariana Wolfner, newly inducted member of the National Academy of Sciences

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Abstract

Molecular Reproduction and Development is delighted to announce that editorial board member Mariana F. Wolfner has been elected to the National Academy of Sciences. Here, Dr Wolfner is interviewed by two of her former postdocs. She discusses her path to studying reproduction and her career as a researcher and mentor.

KEYWORDS

Drosophila, egg activation, Mariana Wolfner, reproduction, seminal fluid

Molecular Reproduction and Development (*MRD*) is delighted to announce that editorial board member Mariana F. Wolfner has been elected to the National Academy of Sciences. Mariana's work has used genetic, biochemical and evolutionary approaches in *Drosophila* to study the functions of seminal fluid proteins and the process of egg activation. Perhaps Mariana's best-known work is on the function of *Drosophila* seminal fluid proteins, known for their rapid divergence likely driven by sexual conflict. Upon mating, these proteins have a variety of effects on females, including inducing ovulation, reducing remating rate, and affecting sperm competition outcomes. Her functional studies have been critical to the understanding of rapidly evolving reproductive proteins and provided keen insight into other systems with clear connections relating to human health, such as her work with Dr Laura Harrington's lab on mosquito seminal fluid. Indeed, her seminal *Drosophila* work has spawned numerous studies of reproductive proteins in a wide variety of animals including bed bugs, butterflies, primates, crickets, chickens, and medflies, just to name a few. Mariana has always been a fantastic colleague and wonderful mentor, and her election to the NAS is a well-deserved honor for a stellar scientist and educator. As two of Mariana's previous postdoctoral fellows who have benefitted from her mentoring, we were thrilled to interview Mariana for *MRD*. Mariana's answers have been edited for length and clarity.

1 | HOW DID YOU BECOME INTERESTED IN STUDYING *DROSOPHILA* SEMINAL FLUID?

It was a lot of "evolution" of scientific interest, and some serendipity too. As an undergraduate I was interested in gene regulation and worked with Gerry Fink at Cornell, on the regulation of genes in the amino acid biosynthesis pathway in yeast; in summers I worked with Ray Gesteland, at Cold Spring Harbor, on the mechanisms of translation. As a graduate student I became interested in development, because this process involves changes in gene expression, and in *Drosophila* as a great model system for genetically dissecting development. In Dave Hogness' lab at Stanford, I identified and studied the genes that were ecdysone-regulated during the larval to pupal transition. My colleagues and I worked out methods for cloning complementary DNAs (cDNAs) on material from tiny tissues and using differential cDNA hybridization to identify developmentally regulated genes. We found genes that were turned off during this developmental transition (like the salivary gland glue proteins) and genes that were turned on by the steroid ecdysone. When deciding on an area for my postdoc, I chose sex determination, because it mediated a developmental decision between two normal states, female and male (as opposed to other developmental processes, where the choice was essentially alive vs. dead). So I joined Bruce Baker's lab at UCSD. Bruce had genetically dissected the *Drosophila* sex determination pathway, but nothing was known about how its genes worked. At that time, the Hogness lab was one of only a few labs in the world that knew how to do cloning/molecular biology in *Drosophila*. As each of us left the Hogness lab, we fanned out to different places, bringing the technology with us. I brought it to Bruce's lab, and Bruce and I cloned the Drosophila *doublesex* gene, a major regulator of sex determination, that has since been shown to have this function across animals. *Doublesex* was the first sex determination gene to be cloned, but I moved on to my own lab at Cornell, before figuring out how it worked; that was done by Bruce

with his subsequent postdoc Ken Burtis, who identified the sex-specific splice isoforms that mediate *doublesex'* activity.

Since analysis of *doublesex* was going to continue in Bruce's lab after my departure, it was prudent for me to find something else to study in my own lab. So, in the waning months of my postdoc, I combined my old and new areas and used differential cDNA hybridization to screen for sex-specific genes that would be the targets of *doublesex*. My colleagues and I then used mutants in various sex determination genes to discern which of these genes were expressed in the soma (controlled by *doublesex*) or the germline. In my new lab at Cornell, we found that the first male-soma genes from that screen were expressed in the male accessory gland. This was initially disappointing to me because since the accessory gland is a male tissue, I figured that *doublesex* regulation of these genes would be indirect, just specifying the formation of the tissue only in males; the gland would then just make its own products (we later showed this to be true). But when I presented the results at a meeting in Crete, noting that the screen had worked but "unfortunately" the first few male genes we'd found were expressed in the male accessory gland, Antonio Garcia-Bellido told me "You need to read the entomology literature! That is a really important tissue!" (Embarrassingly, I was unaware that he had done some of the foundational work on it.) And, he was right. The male accessory gland, determined by *doublesex*, makes components of the seminal fluid that are transferred to females during mating and dramatically change the female's physiology and behavior: They convert an unmated female to a very different creature—the mated female fly. I was fascinated. So, my lab switched to studying seminal proteins. It was serendipity. Later, my student John Kalb genetically ablated the accessory gland, allowing the discovery of many additional functions for its products. We looked directly for more seminal proteins by differential cDNA hybridization (and, later, by "-omics" methods). Early on, we found an important one, ovulin, by screening a chromosomal walk in the 26A region, from the lab of my Cornell colleague Ross MacIntyre. Ovulin's sequence prompted us to probe its function. Laura Herndon in my lab generated a null mutant and showed that ovulin affected egg output in mated female flies. Yet at about that time, Chuck Langley's and Montse Aguade's labs reported that ovulin is rapidly evolving. I believed their results but could not understand them because important developmental genes like the Hox genes, *doublesex*, and so forth were usually highly conserved. How could an important gene be rapidly evolving? Fortunately, another Cornell colleague, Chip Aquadro, set me straight, explaining how phenomena like sexual conflict could drive the rapid evolution of critical molecules. That was fascinating, too. So, Chip, and Andy Clark and I began to collaborate on the interesting evolutionary dynamics of seminal protein genes (a general phenomenon), something that both of you contributed to, greatly.

2 | WHAT CAREER ADVICE WOULD YOU GIVE TO POSTDOCS OR GRADUATE STUDENTS?

There are many things, but here are three. First, you certainly need to work on something that *you* think is interesting and important. Other people may not realize that at the time (but of course funding agencies, or your advisor, have to recognize it at some level), but if it is interesting to you, go for it! You will find something important and exciting. Second, things don't always go in the direction that you expect. You have to be careful that you don't assume you know how something is going to work and get disappointed if it doesn't go your way, because maybe it shouldn't go that way. Maybe the answers are somewhere else—and they may even be more interesting than what you originally anticipated. Keep your focus, but let serendipity in. Third, it's important to work well with others, to collaborate. Certainly, my lab and its research would never have gotten to the things we study, nor to what we have found, without collaborations within our lab and with many other labs. Science is much more fun and interesting when you work and talk with others—people outside of your area, as well as in it—and try to find areas of cross talk. Relatedly, find good mentors (informal as well as formal).

3 | WHAT MENTORING ADVICE WOULD YOU GIVE TO NEW FACULTY?

As exciting and fun as the science itself is, it is also a human endeavor (more on that, later). Each person you work with is unique and has different strengths, different knowledge-bases, different ways of thinking or viewing things. It is very energizing, fun, fascinating, and productive to work with others. I've learned so much about science (and other things) from my mentees and colleagues, it's really been such a pleasure.

A big part of your job is helping others excel in science. I think it's important to be encouraging. And I know this sounds trite, but everyone is unique: Each person in your lab needs to be mentored in the best way for them individually. Some need a lot of guidance at first and then just take off. Others prefer to be more independent from Day 1, and but with collegial guidance along the way. Some people work better with encouragement and others work better with challenges. (Once in a while, you have to get a little tough. That has happened to me, and it is not easy, but you have to be able to do it.) Finally, I suspect that people who didn't want to be mentored with your style will probably not end up joining your lab. So, eventually, it becomes self-fulfilling. One thing I was told as an assistant professor, and read again in Mohammed Noor's book (*You're Hired: Now What?*), is not to underestimate the power of your words because you are in a very powerful position. Something that you say, even if you don't think it's that big a deal, could have a very big effect on the person you're mentoring, with positive or negative consequences.

I think it is also important to formally meet with everybody in your lab regularly, at least once a week. These meetings ensure that you don't fall behind on what's going on, and your lab members know that they have time with you every week. It is also important to let people in your lab realize that you're also clueless at times; they might be the expert, not you. For me, whenever statistics come into

the mix, I need my lab members to guide me. That's certainly better for our science because my lab members know what they're doing, but I think something like this can also make a principal investigator (PI) more approachable.

Finally, get a mentor or several, for yourself. These can be formal mentors from your department or informal mentors, people whose professional progression you respect and with whom you are comfortable speaking about science, teaching, mentoring, and so forth.

4 | WHAT IS YOUR FAVORITE *DROSOPHILA* GENE NAME?

That's impossible to answer; there are so many that I like. Cute phenotype-descriptive names like *armadillo* and *hedgehog*, *Indy* ("I'm not dead yet") or *foi* ("fear of intimacy"). Cute, cute names. (Of course, what have I come up with? "*Ovulin*" for an ovulation regulator! Really?!? I have to start getting more creative with gene names…) When I was a graduate student, Elliot Meyerowitz, a postdoc in the lab, said he had set up crosses to make multiple mutants just because of the final name: "*black tuxedo pink carnation*."

5 | WHAT IS YOUR FAVORITE BOOK, SCIENCE OR OTHERWISE?

I've always liked Barbara Kingsolver's books. I like that her fiction includes biology. *Prodigal Summer* is probably my favorite of her books. Audrey Niffenegger also integrates biology into her fiction books; for example, *The Time Traveler's Wife* is about a person with a *period* gene mutation that lets him go back and forth in time. Other favorite fiction authors include Margaret Atwood, Michael Chabon, Anne Patchett. And I am from the generation where books like *Arrowsmith* caused us to consider going into science.

6 | WHAT WERE SOME INFLUENTIAL SCIENTIFIC PAPERS IN YOUR CAREER?

There are too many to list. Bruce Baker's paper in 1980 called "Sex and the Single Cell" was influential and elegant (and it made me choose to postdoc with him). Another was Hotta and Benzer's paper using genetic mosaics to map the neural loci for behaviors in *Drosophila*. Lee Hartwell's cell cycle genes papers were also amazing to me, as were Gerry Fink's gene regulation papers. There are so many others, such as the classical *Drosophila* papers that we postdocs discussed with our PIs, during weekly sessions at UCSD, and many new papers. Finally, I always enjoy the cleverness in cool new techniques papers, like CRISPR (obviously), MARCM, brainbow, and so forth.

7 | WHAT ASPECT OF SCIENCE DO YOU WISH WERE BETTER APPRECIATED BY THE GENERAL PUBLIC?

Basic science. That by studying things that may sound completely esoteric we understand how the world works, and that is super important. Sometimes, the results of studies may have important applications, but this can often be totally unanticipated (e.g., who could have guessed that studies of bacterial immunity would lead to the CRISPR/Cas9 method that has revolutionized how we do biology, and has many other applications?). But sometimes they don't have direct applications, yet it is still important to know the information. It's funny because it is often the latter kind of information that motivates kids to get excited about science. Kids aren't looking into applications per se; they are seeking to understand why our world is the way it is. Basic science provides those answers. (And then, as a bonus, it sometimes can be applied.)

Another thing that I wish were better appreciated is that science is an incremental process and is not often fast. Each discovery builds on lots of prior research done by lots of other scientists. And experiments don't always work, or not in the way you expect, and usually not as quickly as you think they will. I think the public hears a beautiful, completed story, but they don't always realize what it took to get there, or even some of its limitations.

Finally, I wish it were better appreciated that science is really a human enterprise. Not simply that research provides education, jobs, and so forth although that's certainly true. But also, most of my day involves working with people. And honestly, we would never get any research done if not for working with people and learning from them. It is not like the image (from the movies) that I had when I decided to be a scientist: That you put on a lab coat, go into your little lab, and discover something important all by yourself.

8 | OUTSIDE OF SCIENCE, WHAT DO YOU ENJOY?

Hiking and being outside in nature. Hanging out with my family and my kids, and our friends. Puns, much to everyone's chagrin. Puzzles; I am a crossword (and other puzzles)-fiend. Visiting new places, especially unusual museums.

9 | WHAT KIND OF UNUSUAL MUSEUMS?

Oslo has a miniature bottle museum. Fifty thousand miniature bottles of all shapes and sizes. Very cool. The Postal Museum in Washington, DC. It is part of the Smithsonian. It's all about stamps and mail delivery. The first time I went there, they had a special exhibit that let you print and send a card. I did so, and it took 6 months to arrive. My family remains convinced that I put the card into a display mailbox. The Key Museum, near Rocky Mountain National Park. A former

exhibit on model staircases at the Cooper-Hewitt Museum. The model staircases were lovely (or, weird) wood constructions to scale; I had not previously realized that this is a major art form. And, of course, natural history museums anywhere. I practically grew up in the one in New York City, but I also love the ones in DC, Chicago, San Francisco, San Diego, Oxford, and so forth. And getting to see the *real* Darwin's finches in Cambridge's Zoology Museum was amazing. I use some Galapagos finches from the Lab of Ornithology here when I teach Evo Devo to show different beaks, but seeing the actual ones collected by Darwin—and also birds collected by Wallace—was incredibly special.

10 | WHAT IS IT LIKE BEING A FEMALE SCIENTIST AND HOW HAVE THINGS CHANGED OVER THE COURSE OF YOUR CAREER?

I'm always aware that I am and have always been a female scientist, but professionally I put the boldface on **scientist,** not female.

The situation for women in the profession has certainly changed, some, over the course of my career. There are more women in science now, which is fantastic, and I think/hope it is becoming easier for all genders, which is also fantastic. It's not as unusual to be a female in science as it used to be (I was the first female grad student or postdoc in my respective labs, and the first female faculty member in my department; it always felt a little "interesting"). My husband Jim Rothenberg and I waited to have kids until I was tenured, which thankfully, people don't have to do anymore.

Some more subtle issues are definitely still there, but more overt issues are far less common, in part because of changes in institutional policies (e.g., family leave and tenure-clock stoppages). Speaking of kids, I couldn't have had kids without Jim. Obviously for the biological reasons, but also because he was a great and equal (or more) partner in raising them; we could not otherwise have had raised our family, keeping both of our careers going, including my lab's science.

There were gender issues that I was probably oblivious to as a student or postdoc but certainly others that I wasn't; you just kind of deal with them and go on. There were people whose own journeys inspired me to just push on, like Barbara McClintock, with whom I interacted when I was a student, postdoc and junior faculty, and who was an informal mentor (as well as inspiration) to me. And I had a "secret weapon" in Jim, because more than just being a good guy he is also a sociologist. If I told him about something odd that happened at work, he almost always would say, "Oh, that's what happens when someone is different. Don't worry about it. It's the institution/environment, not you." And he would quote some sociological study to me to back this up. That was always very helpful—to me, and years later as I mentored and advised others.

As I said, some issues are still there. Organizations want representation from nonmajority people. So, I tended to be asked to be on lots of committees at Cornell and other places, more so than my equivalent-stage male colleagues. I think that sort of thing continues, for all who are minorities in their profession or unit. It comes from a good place: There should be people with different perspectives, lived experiences, and so forth on these committees, and to some extent it gave me additional opportunities to be patched-in to what was going on, but there is a risk that this study can take too much of your time. We need to be sure it's not penalizing the people who are asked to serve; if someone is on lots of committees, bringing a certain perspective, then maybe some other job responsibility should be reduced to make up for the time.

11 | ANY FINAL THOUGHTS?

When I started in science I didn't realize that people are one of the most important things in science. The science that you and your lab discover is certainly extremely important. But at least as important are the mentees and colleagues with whom you work and the friends you make within the profession. I didn't realize the former until I was a PI. I am so proud of my mentees. It's been wonderful and such an honor to have the opportunity and privilege to work with each of them, learn from them, and so forth. But it is also amazing to watch what they do, not just while they are in my lab but for the rest of their lives. And beyond that to see it ripple out to the people whom they go on to train or work with (whatever their career choices), and the lives that they influence. It is really special. I am realizing that it is something that I should tell my students and postdocs more; I think mentees may not know how important they are to their mentors (not just to their mentors' research). I certainly didn't know that when I was a mentee. That said, it can be a bit of a shock when a student comes up to you at a meeting and says "I'm your scientific grandchild". I'm, like, "No, I can't possibly be that old." But after a moment you regain your equilibrium and realize how exciting it is to see all these threads connect—between people, between their science, and in what we thus learn about the world.

CONFLICT OF INTERESTS

W. J. S. and G. D. F. were postdoctoral fellows with Dr Wolfner. They have no conflict of interests.

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