Meiosis Maven

Fueled by her love of visual data and addicted to chromosomes, Abby Dernburg continues to study how homologous chromosomes find each other during gamete formation.

By Anna Azvolinsky | February 1, 2014

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When I was a kid, I always felt stupid, in the sense that I didn't understand how the world worked," says Abby Dernburg. Although she can't explain why her twelve-year-old self homed in on biology rather than physics or economics, Dernburg says she already sensed that understanding biology was the best way to understand the world she lived in. The teenage Dernburg would tell people she wanted to be a neuroscientist, to study how the brain worked. "I knew what the term meant, but I didn't really understand what research was until I went to graduate school," she says.

As a high school student in the 1980s, Dernburg happened upon an old computer in her school. "It was already an antique—it had a teletype instead of a screen," she says. Dernburg decided to see if she could, without any help, program a blackjack game on the computer. "I became obsessed with it. I would skip meals, I would go early to school and stay late."

For more than 15 years, Dernburg has aimed that laserlike focus on meiosis—the two-part cell division process that reduces diploid germline cells to haploid gametes (such as ova and sperm)—using C. elegans as a model system. She studies how the jumble of chromosomes in the nucleus transitions to orderly pairs before the first division. More recently, she has been investigating meiotic recombination—the exchange of DNA between paired homologous chromosomes that is necessary for the genetic variation of progeny.

"But with a family, I now need to be able to confine the obsession to just parts of the day," Dernburg says. Here she discusses her fruit fly "coitus interruptus" experiments, how she conquered her fear of public speaking, and initial apprehensions about running her own laboratory.

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Dernburg's Direction

Chemistry to crystallography. As an undergraduate at the University of California, Berkeley, where she is now a professor of cell and developmental biology, Dernburg so relished the intellectual challenge of organic chemistry that she spent a semester and a summer working in an organic synthesis laboratory. "It was this really hard-core environment where the researchers spent five years synthesizing an infinitesimally small amount of a compound and then characterizing it. I couldn't grasp what was interesting or intellectually stimulating about that," she says. "Plus, it was smelly. I really didn't enjoy it." Dernburg spent the rest of her undergrad years working in Dan Koshland's biochemistry laboratory on bacterial chemotaxis "based on nothing except that I knew he had other undergraduates in his lab and that he said yes to my request to work in his lab."

Crystallography to chromosomes. After college and an additional year working as a technician in the Koshland lab, Dernburg entered graduate school at the University of California, San Francisco (UCSF), thinking she wanted to do crystallography. After a year of the PhD program, she realized the crystallography lab she wanted to join was not particularly enthusiastic about her. She then considered joining John Sedat's laboratory, where she would end up essentially doing three separate, successful thesis projects which resulted in three major 1996 publications: a *Cell* paper showing that condensed heterochromatin regions function to ensure chromosome segregation during meiosis; another *Cell* paper on how chromosomal positioning affects transcription and nuclear organization; and an article in *Genetics* showing how sperm dysfunction can lead to non-Mendelian segregation. "I did the rotation in the Sedat lab as a sort of afterthought. I didn't think I was going to join John's lab. It was a big turnaround from what I thought I was interested in."

Visual thinker. "I wouldn't have been able to verbalize this during my early graduate school days, but structural biology, in the sense that it's biology you can look at, appealed strongly to me. I like having a visual context in which to put biology." In journal club during her first year at UCSF, Dernburg's presentation of a paper showing that chromosomes can walk along a single microtubule made her understand that she was drawn to very visual data. "This was really an important revelation I had as a first-year graduate student. Visual-type data became something I looked for in my own work—an ability to show people what I do and bring them into my world."

Big ball of wax. In *Drosophila* compound chromosomes are fusions of either two entire copies of the same chromosome or two chromosome arms fused by a centromere. Most compound chromosomes segregate normally, but a few are often not transmitted to offspring from male flies. Dernburg set off on a quest to find out where, during the processes of sperm generation and fertilization, one such chromosome was getting lost. "I did an experiment that I called the 'coitus interruptus' experiment. I was trying to figure out if the sperm carrying that chromosome could be transferred to the female, so I would mate a male and female fly and then pull them apart, taking out this big ball of waxy stuff that was the sperm. I would then genotype the sperm to look for this chromosome. It seemed sort of cruel but was also a lot of fun to figure out and taught me a lot about fly biology." Dernburg found that the loss occurred after coitus but before sperm storage by the female.

Dernburg Dominates

A meeting of the minds. In 1996, Dernburg went to Stanford as a postdoc, joining the laboratory of Anne Villeneuve, then a new faculty member in the midst of setting up her lab. "I met Anne at a meeting, and I realized that we cared about the same types of questions and that *C. elegans* was a really powerful model to explore these questions. I felt that it was such a good match and was not worried that the lab was only just getting going or that I had never really seen or touched a worm."

To each her own. During her postdoc, Dernburg developed cell biology tools for visualizing *C. elegans* chromosomes at high resolution. She discovered that meiotic mechanisms in the worm diverged from those of other eukaryotic organisms when she showed that double-strand breaks, which lead to recombination during meiosis, are not always necessary for pairing and synapsis, the physical binding of chromosome pairs, to occur. The work was published in *Cell* in 1998. "The frustrating thing was that I wanted to work on how chromosomes pair and synapse. Instead, I wound up showing how they *don't* pair and synapse. Although my postdoc was great—I developed tools and assays that enabled me to start working on what I really cared about—I hadn't really set up a way to study pairing or to characterize pairing centers, the sections of chromosomes that enable homologous chromosomes to pair, before I started my own lab."

Pushing ahead. In her own lab at Berkeley, Dernburg has pursued a still-unanswered and fundamental question in biology: How do chromosomes recognize their homologs? In 2006 Dernburg's lab reported that in *C. elegans* pairing centers are bound by zinc-finger proteins, which allows an interaction of chromosomes with cytoplasmic microtubules and a motor protein called dynein. Her lab team has also found that dynein-mediated motion promotes the correct pairing of chromosomes. Influenced by the work of colleagues on the physical forces at play in living cells, Dernburg says she now has a better appreciation that "everything in a cell is in an aqueous environment."

"Rather than thinking about chromosomes as pipe cleaners, I want to understand the nature of physical interactions of proteins and DNA in water, in the gelatinous media inside the cell." As a result of recent advances in understanding biophysical forces inside cells, Dernburg says she is now thinking differently about how chromosomes organize inside the nucleus. "I would like to understand the forces that bind cell components together, creating different types of materials inside the cell—that is where I see our work going."

Beyond *C. elegans*. Dernburg's laboratory recently branched out beyond the nematode *C. elegans* to study meiosis in planarians, which are nonparasitic flatworms. "Working with planarians taught me that, just like Mendel said, you need to choose your model organism very carefully. There are so many advantages of *C. elegans* that I am used to that have just not been developed for planarians." Dernburg's lab is currently also doing work on another nematode, Pristionchus pacificus. "This work is really exciting because many people think that some unusual features of *C. elegans* meiosis are just a 'weird worm thing,' but comparing the process in *C. elegans* to that of *P. pacificus*, which has a meiosis that is more like that in mammals and in budding yeast, is allowing us to understand the basis for some of the quirky features of the process in *C. elegans*."

A trained eye. Dernburg will occasionally get her hands wet just for the sake of remaining engaged in the lab. "I do experiments if I have some wacky idea that I don't think I can ask someone else to spend time on," she says. At a lab management course at the Howard Hughes Medical Institute headquarters, Dernburg heard Thomas Cech's advice to new faculty: work in the lab and don't become siloed in an office. "He told us that if you are not in the lab, there is no way for your expertise and experience to be

transferred to the people doing the experiments. At the microscope, I try to get my students to pick up subtle visual cues that may not be apparent to them, and to help them avoid mistakes. But there is not enough time to do this often."

Dernburg Digresses

Stage fright. "In graduate school, we had these journal clubs where the graduate students gave presentations to the entire department. This was a new thing for me—public speaking—and it was really terrifying. I think I was more nervous for those than anything I have ever done," says Dernburg. "It's an important part of the training, to learn the skill of public speaking, and probably everyone goes through some initial stress when giving presentations. Eventually, I learned to turn the adrenaline into something that looked like excitement rather than nervousness."

Principal-investigator stress. Dernburg was in graduate school for seven and a half years. Only toward the end did she think she might have what it takes to become a research professor. "I loved doing bench research, but the idea of running a lab—being a manager and having to guide people—did not appeal to me at all. It scared me. I couldn't see myself in that role. Being a teacher, the managerial and organizational parts of running a lab, it's daunting." Dernburg has grown into the role but says that she still doesn't like telling people what to do. "I much prefer that my students have good ideas, and I just help to refine or prioritize them and help them work out technical issues."

What if? "I quickly became addicted to chromosomes. I often think about what I would be doing if I was not doing research on chromosomes, and it's very hard for me to imagine not working on chromosomes. I may wind up doing something not related to meiosis in the future, but I still think chromosomes are really intriguing. There is so much we still don't know about them."

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For the love of research. "I am often astounded when I hear people say, 'If I don't get into medical school, maybe I will go to graduate school.' I think you have to really enjoy the process of doing research. Graduate training is not a good means to an end. It's a really long time to be doing something if you are not enjoying it."

Embracing the quirky. "I felt very lucky in graduate school at UCSF. It was a very lively place and valued quirkiness. I was in a particularly quirky lab and was doing something off the beaten track. Probably no one else would have done it if I hadn't. Now I think that kind of niche is hard to find. The research moves so quickly. "

Data processing. "I think early in your science career, you really need to think about the type of data you like. At what level you want to understand a problem? It's not the same for everybody. Some people don't enjoy doing the kind of work I do because it is hard to quantify; there are not really binary decisions when you're dealing primarily with images. Image processing in the brain is something that is hard for many people to enjoy and it's something that you either really like or you don't. I think many people choose their field by a random process, but it's good to think about what kind of computer processor you are—what kind of data you are best at processing."

The ultimate recombination experiment. Dernburg has a 6-year-old son and 3-year-old twin boys with her husband, Gary Karpen, who also studies chromosome structure at Lawrence Berkeley National Laboratory. "Partly because both of us are geneticists, we see our kids as a product of our genes, which helps us to not be helicopter parents. We just enjoy watching their genetic program unfold. Our twins are monozygotic. Seeing how they are different despite being genetically identical is really fun and interesting."

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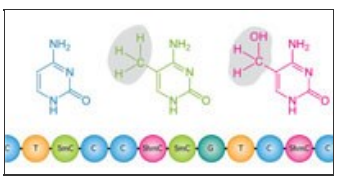

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