

ASCB PROFILE

Barbara J. Meyer

"I felt that I needed to create my own question and my own problem if I was going to be a real scientist," says Barbara Meyer of her arrival 25 years ago at the MRC Laboratory of Sydney Brenner in Cambridge, England. "I needed to start from scratch."



Barbara Ries for HHMI

Barbara Meyer

For Meyer, who has been a Professor of Genetics and Development at UC Berkeley since 1990 and an HHMI Investigator since 1997, starting from scratch began with a new worm. When Meyer first arrived in Cambridge in 1979, Brenner's *C. elegans* was still a scientific

dark horse with a meager literature and a virtually unexplored genome. But the nematode could be grown in petri dishes, frozen in batches, and mutated into all sorts of intriguing phenotypes, which appealed to the new American post-doc who'd done her graduate work at Harvard with Mark Ptashne on lambda phage. Meyer had big questions

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in mind for the little worm to answer: how does the worm count the number of X chromosomes to determine sexual identity, and how does it then compensate for the different doses of X chromosomes in the two sexes?

It was a daring strategy for a young scientist, says Frank Solomon, a former colleague at MIT where Meyer established her first lab after leaving the MRC. "Barbara Meyer started on a brand new and very difficult problem using a model system that at the time wasn't

well known or widely used. Remember this was before [*C. elegans*] won a Nobel Prize. So it took Barbara a relatively long time to get going because she chose to do something new, original and hard. She started fresh in dark, uncharted territory but she made something of it." Continues Solomon, "even a few years ago, I would have said that Barbara was the person largely responsible for working out sex determination in worms. Yet since then, this work has led in a million directions. What started out as the genetics of a fundamental biological problem has in her hands blossomed into this multi-faceted, broad-reaching set of results that take us to lots of fundamental biological processes that would not have been anticipated."

It took Meyer nearly a decade to unravel the puzzle of sex specificity in *C. elegans*, years spent screening for mutations, identifying key genes, characterizing proteins,

sketching pathways and working out the interactive protein complexes that switched sex fate between males (XO) and hermaphrodites (XX) while compensating for differences in X chromosome dosage.

In 1990, Meyer and her husband Tom Cline gave up their tenured positions (she at MIT, he at Princeton) to return to their native Cali-

fornia for new faculty posts at UC Berkeley. By then, it was clear to Meyer that these genes and proteins that could recognize X chromosomes in *C. elegans* were similar to components in the mitotic chromosome condensation and segregation machinery already discovered in yeast and frogs. There are major implications here for evolutionary biology as well as for cell division and replication control, says Meyer. "Some of the genes that are important in the sex-specific dosage compensation machinery have retained their ancient roles in chromosome segregation while being co-opted for their new role in gene expression."

The implications keep growing, Meyer says. "One of our proteins has turned out to be involved in controlling the number of crossovers between homologous chromosomes during meiosis. So now we've gone off in that direction as well." One result is the amazing variety of meetings that Meyer finds on her itinerary. "I go to tons of them—epigenetics, meiosis, chromatin—you name it. I joined the ASCB in 1995 as soon as I realized that components of the dosage compensation machinery are involved in chromosome segregation. Then I started speaking at ASCB and this year I serve on the Program Committee."

Her ability to move easily from field to field in pursuit of her problem doesn't surprise those who've followed Meyer's work. "Barbara has always been fearless about applying any technique or technology available to whatever problem she's working on," says Jasper Rine, a Berkeley colleague. "Recently I've been struck by how Barbara has brought this whole new dimension of cell biology to her work. She's pushed the frontiers of microscopy to complement the molecular genetics and biochemistry in her lab. Now she's pushing dosage compensation, which is intrinsically a somatic or mitotic phenomenon, into an investigation of the roles of these proteins in meiotic chromosomes. She keeps uncovering deeper and deeper levels."

Barbara Meyer is a native Californian, born and raised in Stockton, where her father owned a car dealership and her mother was a housewife. "I'd never really been East until I went to Harvard in graduate school, but everyone there thought I was from the East Coast. But then everyone in California thought I was from the East Coast, too. They still do. I guess I don't fit the stereotypical California mold."

Whatever the mold, Meyer grew up fascinated by numbers, reading, and puzzles.

Biology in high school seemed "too phenomenological for my taste," she recalls, and Meyer entered Stanford undecided between a degree in literature or math. After

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her sophomore year in Germany where she satisfied her Humanities requirements, Meyer returned to Stanford for another look at the sciences. "What changed my thinking," Meyer recalls, "was reading Jim Watson's book, *The Molecular Biology of the Gene*, and realizing that you could ask precise questions in biology and get precise answers." Stanford's David Clayton showed her

how to pose questions in biology. In her senior year, she worked in the Clayton laboratory on a mitochondrial-specific thymidine kinase. By the time Meyer enrolled in graduate school at Berkeley, she was zeroing in on the question of choice. How did a simple organism like a virus "decide" whether to switch on its replication machinery after entering a new host cell or integrate into the host genome and remain quiescent? Her Berkeley advisors thought the question too

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hard for current methods. Soon after, Meyer heard Harvard's Mark Ptashne talk about his work on this very issue in lambda phage. Meyer went East for a summer in the Ptashne lab. There they tried a new approach to analyze the function of lambda repressor, and the experiment went like gang busters. Meyer decided to transfer.

Eventually Meyer published 13 papers as a graduate student with Ptashne, helping him to establish lambda phage as a comprehensive model for gene transcription and regulation. Those papers also established Meyer as a minor celebrity, at least among grad students. Cynthia Kenyon, who is now at UC San Francisco, vividly remembers Meyer in those days. Later Kenyon and Meyer would become friends as overlapping post-docs at the Brenner MRC lab. "But back in Boston, Barbara was already a legend,"

Kenyon recalls. "I remember seeing her first at a discussion of lambda transcription regulation. She was just so amazingly eloquent and clear. Everybody was spellbound by this beautiful young graduate student with long black hair and a stylish wool shirt. Actually, I thought Barbara was almost scary, so I was really glad when we became friends in England."

Meyer recalls that during her early work in *C. elegans*, the only published insights on sex determination genes came from papers written by fly geneticists including one T.W. Cline. "I'd read his papers for years and I always thought he was this old guy at Princeton," Meyer recalls. "Then I finally met Tom Cline and he was this young guy. We talked for a long time after that because we had all these interests in common. Ultimately, I decided that I was interested in more than just Tom's science." They married in 1986, with the idea of eventually returning "home" together to California.

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Life in Berkeley suits them, says Meyer. The Meyer-Cline house is a showplace for the art they collect and the unique art furniture that Meyer designs and then collaborates with craftsman-furniture makers to construct. They garden, raise parrot finches, and are once again back on the High Sierra trails as Meyer has overcome the last lingering effects of a 1999 hiking accident in rural Costa Rica that shattered her ankle. "We're outdoors people," she says. "So we try to hike all the weekends we can."

Friends, colleagues and students who saw Meyer hobble her way through endless months of treatment and therapy after the accident still speak of it in hushed voices. "Oh, it was just awful to watch," says Anne Villeneuve, a former MIT graduate student now at Stanford Medical School. "Frankly, they didn't think that she would get back this much mobility. But Barbara's a person who gathers all possible information and that's what she did after her accident. It's the same way she does her science. She's tough. She's intense. She brings all different approaches to bear on a problem. She was a tremendous mentor for me."

Says Kenyon, "Barbara has this really incisive, clear-thinking mind and you can see that in her science but it extends into her everyday life. If someone in my family is sick or ill, Barbara will research the condition totally. Then she'll tell me who to see, what to do and what not to do. Barbara is the most loyal friend, always ethical and just smart about everything in life." ■

Call for Proposals

Summer Meeting Series

All ASCB members, individually or in teams, are invited to submit proposals to organize an ASCB Summer Meeting in 2006. The three-day meetings will host about 200 participants.

Topics should be novel (e.g., combining fields that don't traditionally meet together, or focusing on an emerging area) and include:

- a one-page summary of the scientific substance of the meeting;
- names of 3-10 potential speakers (confirmation need not be obtained in advance);
- CVs of proposed lead organizers.

Submit proposals to the American Society for Cell Biology, 8120 Woodmont Ave., Suite 750, Bethesda, MD 20814 or ascbinfo@ascb.org.

Application deadline is **December 1**. Some participation in fundraising may be required of organizers. Meeting dates and sites are to be determined by the Society in consultation with the organizer(s).