Yukiko Yamashita

Supposedly Archimedes cried "Eureka!" at the moment of discovery, but Yukiko Yamashita remembers saying nothing so coherent. "I literally screamed," Yamashita recalls. Fortunately, Yamashita was by herself, closeted in a blacked-out microscope room, when she had her eureka experience. She had been manipulating a green fluorescent protein (GFP) construct to label the asymmetrical division of centrosomes in dividing fruit fly stem cells. When the construct finally worked, "It was one of the best moments of my life," says Yamashita.

It was also an important moment in recent stem cell science, say the ASCB members who nominated Yamashita for the 2009 Women in Cell Biology (WICB) Junior Career Recognition Award. Yamashita, who is now at the University of Michigan Medical School in Ann Arbor, will receive the "Junior WICB Award" this December at the ASCB Annual Meeting in San Diego.

How stem cells manage the tricky business of duplicating while sending daughter cells to asymmetrical fates—one to differentiate and one to preserve the stem cell line—has been intensely investigated in recent years, says Margaret "Minx" Fuller. Fuller was Yamashita's mentor at the Stanford University School of Medicine. It was while working as a postdoc in the Fuller lab in early 2005 that Yamashita made her stem cell breakthrough.

Maintaining stem cell balance is critical, Fuller explains. "Too few stem cells, the pool dries up. Too many differentiating daughters, growth can get out of hand." The key was thought to be in controlling the number of stem cell niches, the microenvironments that regulate stem cells, says Fuller. "As long as the niches are full, you're fine. People had talked about this idea but there was no clear evidence."

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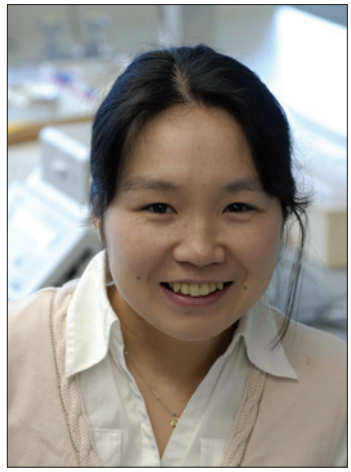
Stick to the Niche

Yamashita provided a key piece of that evidence, using Fuller's model system, the *Drosophila melanogaster* male germline stem cell (GSC). In that system, the "stemness" niche is the junction between a somatic "hub" cell and a germline cell. According to Fuller, Yamashita first demonstrated that the stem cell sticks close to the niche, maintaining a stereotypical position with its centrosome at right angles to the hub. In the G1 phase of the cell cycle, the centrosome duplicates itself, creating two daughter centrosomes. One centrosome copy stays in the niche and remains within a stem cell. The other copy migrates to the opposite pole of the soon-to-divide cell. As Fuller puts it, "The other daughter is going to be sent out of the Garden of Eden to differentiate."

But no one knew which centrosome was which. Was the "mother" centrosome that started in the stem cell niche the same centrosome that ended up there after division? Finding a way to mark mother from daughter became Yamashita's quest, says Fuller. Yamashita zeroed in on the centrioles, the pair of barrel-shaped organelles that are the motive center of the centrosome. If she could label the centrioles at the moment in the G1 phase when new copies assemble, perhaps Yamashita could follow their role in deciding stem cell fate.

As Yamashita tells the story, her first GFP attempts failed. But before she could figure out a solution, mother-daughter issues of another kind intervened. In December 2004, Yamashita gave birth to her daughter, Haruka. "I came back to the lab after two months," she recalls. "My mind had been quite empty in a good sense, and I thought, 'Why don't I try heat shock-inducible promoters?'"

Yamashita tagged a centrosomal protein with GFP in such a way that she could switch on



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expression with a heat-shock pulse, indelibly marking daughter centrosome from mother centrosome. That's what provoked Yamashita's eureka scream in the blacked-out microscope room—she saw the original mother centrosome back home in its niche.

Stay in the Garden

Yamashita's discoveries have shaken up the field, according to Fuller. "No one suspected how the centrosome would be anchored (by orientation to the niche). It was a complete surprise. The other unexpected thing was that it was always the mother centrosome that stays. The centrosome, which contains the centrioles, was made way back in embryogenesis. It's got Eve there. Eve stays in the Garden."

Fuller's description of "centrosomal Eve" is an intriguing echo of "mitochondrial Eve," the nonnuclear genes passed down through maternal descent. But Yamashita offers a critical caveat. "I have to say this is not as old as mitochondrial Eve. An 'Eve' centrosome is only as old as each individual." It's also far too early to know how widely conserved a centrosomal Eve might be beyond *Drosophila* germline cells.

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Yamashita's discoveries are significant, says Allan Spradling, a Howard Hughes Medical Institute investigator and Director of the Department of Embryology at the Carnegie Institute for Science. "Her creativity and ability to make new connections even in a field like this that's been pretty heavily studied for 10 years is really impressive in my opinion." Moreover, Yamashita has gotten off to an impressive start since opening her own lab at Michigan in 2007, according to Spradling. She has followed up on her observation of the stereotypical positioning of germline stem cell centrosomes, using orientation as a way of assessing dysfunction in aging stem cells. Yamashita demonstrated that without proper orientation, the GSCs arrest in the cell cycle. The older the fly, the more GSCs are misoriented. This is one of the first direct explanations of how stem cell aging could affect an organism's fitness.

Spradling expects more surprises from Yamashita. "I just heard Yukiko give a talk at a stem cell meeting in Canada. She had a number of other new things that I found extremely interesting and creative."

By the Inland Sea

Yamashita is from Akashi, a town just west of Kobe on Japan's Inland Sea. Her father works in the Japanese patent office. With his training in physics, he raised Yukiko and her three younger siblings with a passion for all sciences.

Yamashita did undergraduate biology at Kyoto University and, as is traditional in Japan, stayed at Kyoto for her graduate work. There she entered the cell cycle lab of Mitsuhiro Yanagida. Earning her doctorate in 1999, she moved to a postdoc, also at Kyoto, with Shunichi Takeda.

In 2001, her husband, Kentaro Nabeshima, broached the idea of doing postdocs in the U.S., and she jumped at the suggestion. Nabeshima soon had a fellowship offer in the developmental biology lab of Anne Villeneuve at Stanford, while Yamashita began scouring the Internet for interesting labs in the Bay Area. She found Minx Fuller's lab, which turned out to be just down the hall from Villeneuve's.

"I was so lucky to get her," Fuller declares. Yamashita's credentials were fabulous. The Yanagida lab is a world leader in mitotic control, and Takeda's is at the cutting edge in DNA repair research, Fuller explains. "In both labs, she did great work and got really good papers." Having someone from such a rigorous background walk into her lab was a gift. Besides, Fuller found Yamashita "an utter delight" to have around. "Yukiko seems quiet but once you get through that, there's this mischievous sense of humor underneath."

For her part, Yamashita found the visual element of cell biology immediately engaging. "For me, understanding means knowing enough to draw it," she explains, tracing this to her early fascination with nature and art. "When I started my postdoc with Minx Fuller and did my first micrograph with GFP, I felt on fire. I thought, 'This is it.' It all comes from my childhood. I love to see things and only when I can see them do I become convinced."

Visualizing Science

Coming to a cell biology lab in America was liberating in other ways, Yamashita reports. Beyond the appeal of cell imaging, Yamashita felt freed from traditional social expectations. She could throw herself into her scientific life without anyone thinking it unnatural for a woman. "All my free time now became time for me to think about my science. In the first week here, I thought, 'This country is my place.'"

When the couple went on the job market in 2006, their best double offer was from the University of Michigan Medical School where Nabeshima's lab now studies chromosome dynamics in meiosis. Yamashita holds a joint appointment in the medical school and the freestanding Life Sciences Institute's Center for Stem Cell Biology.

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Having survived two Michigan winters, Yamashita claims they are not so bad. "I'm enjoying the change of seasons, but I have to say that I'm not shoveling. My husband is." Their daughter, who is now approaching five, loves to sing and dance, her mother reports, adding, "This is certainly not from me." Haruka is bilingual, although her English is much better than her Japanese, says Yamashita. "Her Japanese is kind of funny/cute. She is okay to communicate with her relatives, but can she be polite enough in Japanese to communicate with strangers? I'd say no. But the grandma, the grandpa, and the aunts and uncles are fine with this, so it's okay."

Parenting usually takes whatever time Yamashita and Nabeshima can spare from their respective labs, but this is the second summer that the whole family has gardened in their Ann Arbor backyard. Yamashita reports that their strawberry beds overwintered in good shape and, as of late June, were promising a bumper crop.

Margaret Fuller predicts a bumper scientific harvest from the Junior WICB winner. It's not just her brains, her background, or her track record, according to Fuller. Yamashita has a wider perspective than many scientists, junior or senior. "Yukiko reads the scientific literature more than anyone I've ever known," says Fuller. "She really thinks about science. That gives her a lot of power." ■

—John Fleischman

Textbooks for Africa

Science textbooks, courtesy of the ASCB and scientific textbook publishers, were donated to Maseno University, Nairobi, Kenya. Left to right: Science Librarian Alice Agoch and Librarian Peter Omondi Otieno accepted the donations from Sheila Weir, Information Resource Officer at the U.S. Embassy.