BIOGRAPHICAL MEMOIRS

Mary-Lou Pardue

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A Biographical Memoir by Susan A. Gerbi, Allan C. Spradling, and Terry L. Orr-Weaver

Figure 1 MIT Professor Emerita Mary-Lou Pardue. *Photo courtesy of Linda Earle/MIT Department of Biology.*

Mary-Lou Pardue was an influential biologist who co-developed in situ hybridization that helped usher in the genomics era. She was a leader in chromosome research and was a highly respected role model and advocate for women in science. Mary-Lou was noted for her love of science, scientific rigor, kindness, and outdoor adventures.

Early Life and Education

Mary-Lou Pardue was born in Lexington, Kentucky, on September 15, 1933. Later in life, she added a hyphen to her first name to indicate that she should be called "Mary-Lou" and not simply "Mary." She had always been fascinated by plants and animals and emulated her father in becoming a scientist with an academic career and settled on biology for her major. During summer research after high school, she worked in the corn fields and discovered the wonders of genetics. After obtaining her undergraduate degree in biology at the College of William and Mary in 1955, she declined opportunities to pursue a Ph.D. because she had no female role models in the research career she wanted. She had recently married Peter Rekemeyer, an engineer trained at the Massachusetts Institute of Technology (MIT), and believed that going to graduate school was not appropriate for a wife; her marriage lasted only a few years. Following this, she continued her science education as a research assistant at Oak Ridge National Laboratory, working with Robert C. "Jack" von Borstel and Dan Lindsley. At the time, Lindsley was organizing the first annual *Drosophila* Research Conference, and *Drosophila* would become Mary-Lou's preferred model system throughout her career. As the limitations of classical and radiation genetics for understanding genes became clearer, she moved to Purdue University to work with Seymour Benzer and expand her biochemical repertoire. At that point, Mary-Lou decided that it was time for a Ph.D. and matriculated in graduate school at Yale University in 1965 (her father also had a Ph.D. from Yale). She was ten years older than her classmates, had already co-authored papers in *Nature* and *Genetics*, and had acquired the knowledge and judgment of an experienced scientist.

NATIONAL ACADEMY OF SCIENCES

Figure 2 Mary-Lou Pardue (left) and Joe Gall (right). *Photo courtesy of Allan Spradling.*

Research Career and the Development of In Situ Hybridization

At Yale, Mary-Lou joined Joseph Gall's laboratory to study chromosomes at the molecular level. Gall had recently co-discovered that the genes for ribosomal RNA (rRNA) amplify in oocytes of the frog *Xenopus*. Mary-Lou's initial thesis project was to determine whether the first rRNA genes to begin amplification are copied from the chromosome or excised from the chromosome to form extrachromosomal DNA. Progress stalled, however, despite elegant experiments using BrdU labeling and CsCl density gradients, and the question remains unanswered today.

Co-developing in situ hybridization (ISH), for which Mary-Lou became well-known, arose as a pivot in her thesis research. Molecular hybridization had recently been developed. The logical sequitur was to denature DNA in fixed chromosomes on a microscope slide, hybridize the DNA with a radioactive (H^3-labeled) RNA probe, and use autoradiography to visualize where the radioactive probe was bound. Gall already had promising preliminary results, and Mary-Lou joined the effort. They reported successful development of an ISH technique in 1969, visualizing H^3 ribosomal RNA bound to amplified rRNA genes in the multiple nucleoli of *Xenopus* oocytes.[1,2] A major factor in their success was choice of a biological system in which the expected localization was distinctive and could be predicted. The next step was to demonstrate that ISH could be used to map genes directly on chromosomes, and this proved possible using insect polytene chromosomes in which the aligned endoreduplicated chromatids helped to amplify the radioactive signal from the rRNA probe at the tandem array of repeated rRNA genes.[3] Following that, the quest was to do ISH using a probe other than rRNA. They chose satellite DNA because it is highly repetitive in the genome, and they could make highly radioactive RNA transcripts using a newly developed method. The race was on, as Ken Jones at the University of Edinburgh was attempting the same thing. He submitted his paper in January 1970 to *Nature,* and Pardue and Gall independently submitted their paper[4] in February 1970 to *Science*; both papers showed that highly repetitive mouse satellite DNA localized to centromeres.

After receiving her Ph.D. in 1970, Mary-Lou undertook postdoctoral research with Max Birnstiel at the University of Edinburgh, who had independently co-developed ISH. There, she localized the repeated genes for 5S RNA to *Xenopus* telomeres[5] and the repeated genes encoding histone mRNA in *Drosophila* polytene chromosomes.[6] A year after her arrival in Edinburgh, Birnstiel announced that he was moving to Zurich, but Mary-Lou declined the offer to move with him.

Through her observations at Yale of women with doctoral degrees, Mary-Lou presumed that, like them, she would have a career as a non-faculty senior scientist. She wrote to Don Brown asking if she could continue her postdoctoral studies in his lab. He replied that she should look for an independent faculty position and that he would circulate her CV. Times were changing for women in academia. For example, the U.S. Department of Labor revised its Order No. 4, which called for increased efforts to hire minorities, to include women in 1971. Mary-Lou was eminently qualified for a faculty position regardless of her gender, had many interviews, and ultimately joined the MIT Department of Biology as an associate professor (bypassing the rank of assistant professor), despite their initial pro forma rejection of her application in a letter from Boris Magasanik. Her appointment to Associate Professor was only two years after completion of her Ph.D.

At MIT, Mary-Lou used *Drosophila* polytene chromosome ISH as the read-out for expressed RNAs; this was a primitive DNA microarray experiment two decades before chips were developed. ISH of RNA from cells subjected to heat shock no longer labeled chromosomal sites identified using control RNA but instead strongly labeled six new loci corresponding to sites of the six largest heat-induced puffs.[7] These findings implied that cells undergo a "heat shock response" that involves the induction of a common set of new genes at high levels. The field rapidly developed, and *Drosophila* heat shock genes became some of the first genes to be cloned and to have their regulation characterized. Mary-Lou's contributions to helping launch the heat shock field led MIT to grant her tenure. She continued her work on heat shock for several years. In addition to visualizing transcriptional repression that turns gene expression off for most of the genome after heat shock, her group also found a block to translation elongation, which was one of the early examples

of control at this level.[8] Her subsequent studies on heat shock puff 93D revealed that it encoded one of the first examples of a long non-coding RNA (lncRNA) that she named hsr-omega.[9] Discovery of hsr-omega proved to be the forerunner of the recognition of many lncRNAs in the genome.

Mary-Lou had experienced the negative effects of competition on researchers when developing ISH, and she strove for a different approach. The heat shock discovery became competitive when Mary-Lou learned that Matt Meselson's group at Harvard University had also identified heat shock proteins and RNAs. Eschewing competition, Mary-Lou organized a meeting with his students, Susan Lindquist and Steve Henikoff, and promised cooperation. She believed that rival groups should still provide mutual assistance and taught the Harvard researchers her in situ hybridization technique. Another proud accomplishment was to bring together as co-authors Brown and Birnstiel, who had raced to purify the first gene.[10]

Mary-Lou's contributions played a significant role in bringing about the genomic era. David Finnegan from David Hogness's laboratory at Stanford University visited Mary-Lou at MIT to learn polytene chromosome ISH and used it to localize individual cloned fragments from the first animal (*Drosophila*) genomic library to their chromosomal sites of origin. Subsequently, thousands of ISH experiments by *Drosophila* researchers worldwide provided a common genomic reference point for all *Drosophila* gene studies, beginning two decades before similar genomic anchors based on sequencing were possible in other systems. The sensitivity of ISH was eventually improved by others using fluorescent probes and signal amplification, advancing genetics, genomics, and cancer genetics.

In the last part of her career, the lure of heterochromatin led her to study a repetitive element she named HeT-A.[11] After looking in vain for short telomeric sequences known from other organisms, she collaborated with Harald Biesmann and Jim Mason to show that HeT-A heals the ends of broken chromosomes.[12] Further work showed that, surprisingly, *Drosophila* telomeres are formed by retrotransposable elements rather than by the telomerase mechanism that maintains telomeres of most organisms.[13] The telomere community believed her results, but how maintenance mechanisms distinct from telomerase evolved is not yet understood.

Mary-Lou greatly valued the freedom to follow her curiosity in research. She did not feel compelled to join the bandwagon, but rather she explored topics that were of interest to her. Instead of pursuing the protein-encoding heat shock genes, she studied the heat shock puff 93D that encoded a lncRNA. Similarly, she worked on retrotransposons at *Drosophila* telomeres that were an outlier to the more common telomerase-based mechanism.

MIT Women's Faculty Study

Despite her scientific achievements, Mary-Lou believed that she was becoming marginalized over time at MIT. Initially, she did not publicly complain about inequalities faced by women, both because she was a very private person and because she believed that providing an example of female faculty success would be the best way to encourage younger women to pursue faculty careers. When fellow biologist Nancy Hopkins sought her advice about a draft letter to Dean Robert J. Birgeneau of the School of Science detailing the discrimination she experienced, Mary-Lou, the most senior woman in the Department of Biology, unexpectedly said she would sign it as well. She could respond decisively when it mattered most.

Mary-Lou's decision to sign the letter led to a 1994 outreach to all of the senior female faculty in the School of Science and revealed common shared experiences. Prior to the letter, each woman on the faculty viewed her experiences as unique. Thus, Mary-Lou was instrumental in bringing the women faculty together. Hopkins notes that Mary-Lou's incisive wisdom, derived from her personal and professional experiences, was crucial to the success of the effort. One example of her importance was her input about setting up a committee in the School of Science to gather and review data on lab space, teaching assignments, resources, and compensation. The conclusions based on these data were sent to MIT's president, Charles Vest, in 1996. With his support, further studies resulted in the MIT Report on the Status of Women Faculty, which was publicly released in 1999 and had an impact that reverberated internationally.

Mary-Lou's development as an advocate for women in science reflects her own evolution during changing times in American society. As noted above, initially she felt that it was inappropriate for a woman to get a Ph.D.; she later changed her mind on this, but then did not expect to hold a faculty position in her career. While still a postdoc and attending the 1971 annual meeting of the American Society for Cell Biology, Mary-Lou spotted a sign advertising an organizational meeting of women cell biologists. She told one of us (S.A.G.) that is was important for both of us to attend this meeting so that our voices as moderates could balance any extreme views of radical feminism. It was at that 1971 meeting that Women in Cell Biology (WICB) was formed. Some years later, Mary-Lou spoke against a proposal for WICB awards, because she thought that special awards for women would suggest to some that women were second-rate and could not compete on an equal footing with men. As a role model for women in science, Mary-Lou held high standards and did not expect special treatment based on her gender.

Mary-Lou as a Mentor

Mary-Lou has an enviable record of the trainees that she mentored as graduate students and postdoctoral fellows, including Tom Cech, Joan Ruderman, Matthew Scott, and Allan Spradling. She attracted MIT graduate students and postdocs through the lab culture she created. Her enthusiasm for science was infectious. Mary-Lou was rigorous in her science and critical of conclusions not adequately supported by data, experiments of poor quality, or work lacking in creativity. Any criticisms always were modulated by her ready smile.

Lab members had independent projects, and this included Mary-Lou herself: she liked working in the lab on her own projects and did so throughout her career. Her presence in the lab provided daily access to her knowledge and skills. She hit an ideal intersection between hands-on advice and allowing lab members to define their own research projects. This included her technicians, who also had independent projects and designed their own experiments. Karen Traverse, a longtime technician in the lab described one project thus:

> This was a true collaboration. It is difficult to express how much it meant to me that Mary-Lou had valued my thoughts about this and other projects.

The foundation of Mary-Lou's genuine interest in science and in moving research forward, combined with her mentorship, generated a collaborative environment in the lab and fostered friendships among lab members. Birthdays were celebrated, there were lab outings to hike or canoe, and Mary-Lou hosted evening gatherings at her home. She remained in contact with former lab members and covered a door in the lab with photos sent by trainees updating her on their lives. Mary-Lou cared about the lives of her mentees and understood when personal issues affected time in the lab. Her nephew, Todd Pardue, remembers that she often spoke about her trainees, taking pride in their accomplishments while in her lab and in their subsequent careers. She wanted her trainees to succeed.

In addition to the trainees in her laboratory, Mary-Lou recruited and mentored young faculty in the Department of Biology at MIT. One of the authors (T.O.-W.) had first-hand experience of this as Mary-Lou's mentee.

> She was key to my acceptance of the job offer from MIT and the Whitehead Institute, and she regularly took me to lunch to hear about my teaching and research progress, offering sage advice in both areas. A vivid memory is the lunch when she told me about the growing women's initiative in the School of Science and spoke about her own experiences, their impact on her professionally and personally. This was startling, given what a private person she was, so focused on her research, and led me to sign the report. I also benefitted from her skills and joy in teaching techniques, particularly chromosome in situ hybridization, as it was new to me. I took slides over to her, we sat together at her microscope while she taught me the landmarks of the *Drosophila* polytene chromosomes.

Mary-Lou also served as a role model and mentor for scientists beyond MIT. As a beginning graduate student at Harvard in 1980, Chao-Ting Wu took the Cold Spring Harbor Laboratory course on molecular biology and developmental genetics of *Drosophila* co-organized by Mary-Lou and recalls:

> I was in awe of Mary-Lou, her research on in situ hybridization, ribosomal genes, transcription, heat shock puffs, mobile elements, and so much more. I was in awe of the breadth of what she knew, the details she had in her head, and the speed with which she could draw disparate information together.

At the conclusion of the course, Mary-Lou offered to drive her back to Boston, and Chao-Ting continued her recollections:

> All the way to Boston, Mary-Lou took care of me, making sure I was aware of what lay ahead if I continued in science, what I would have to be careful about/watch out for, what to avoid, how to gain footholds and, by her example, the importance of taking care of each other.

Awards and Honors

Mary-Lou's scientific contributions were recognized by multiple honors. In 1983, she became the first woman in the MIT School of Science to be inducted into the National Academy of Sciences. She was appointed as a Fellow of the American Academy of Arts and Sciences in 1985, served as president of the Genetics Society of America from 1982 to 1983, and was president of the American Society for Cell Biology from 1985 to 1986. In 1995, she became the first Boris Magasanik Professor of Biology at MIT.

Mary-Lou's Love of Family, the Outdoors, and Other Cultures

Mary-Lou loved outdoor activities. She could be found at dawn in a single-person scull on the Charles River. She walked from her home in Cambridge to the lab daily. When it snowed, she would cross-country ski around Boston. Mary-Lou was an avid hiker who trekked and backpacked in Nepal, India, Japan, and the Sierra Nevadas. Hiking in New England made for social interactions with colleagues.

Figure 3 Mary-Lou Pardue (left) and Susan Gerbi (right) climbing the White Mountains of New Hampshire at a Gordon conference. *Photo courtesy of Susan Gerbi.*

Mary-Lou was close to her parents, her brother William, and his son and daughter. Her father, Louis Arthur Pardue, was a physicist who had worked on the Manhattan Project at Oak Ridge National Laboratory to develop the atomic bomb. Later in his academic career he was dean of the Graduate School of the University of Kentucky and then at Virginia Polytechnic Institute. Her mother, Mary Allie Marshall Pardue, was a teacher. Nephew Todd Pardue recounts that in her fifties Mary-Lou joined his Boy Scout Explorer post 12 group on ski trips. She was able to relate to young people and was interested in their future plans and ideas.

Mary-Lou had a broad range of interests and enjoyed talking to people from all walks of life, from street vendors in India to Nobel laureate scientists. Todd Pardue sums up Mary-Lou's attributes:

> She was a loving person who cared a lot about people both in her personal and professional life, being interested in what made them up, their backgrounds, and their cultures.

Just as she climbed mountains throughout the world, Mary-Lou moved mountains for women in science. She had a great sense of humor, and it was delightful to hear her imitation of a Scots accent, projected with her Kentucky twang. She is remembered as a quietly spoken, wise, and experienced person. With her love of biology, she was enthusiastic and knowledgeable. Her eyes sparkled when talking about science. She has given much to the scientific community and we will miss her. She passed away on June 1, 2024, at age ninety.

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