Profile of Ruth Lehmann

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"The spirit of US science embraces diversity and innovation and fosters the freedom to ask questions," says developmental geneticist and cell biologist Ruth Lehmann, who migrated from Germany to the United States more than three decades ago and is now director and president of the Whitehead Institute in Cambridge, MA. She is also a professor of biology at the Massachusetts Institute of Technology (MIT) and an adjunct professor of cell biology at the New York University (NYU) Grossman School of Medicine and NYU Langone Health. Elected to the National Academy of Sciences in 2005, Lehmann was recently named a Great Immigrant by the Carnegie Corporation for her service to society and was recognized by the Vilcek Foundation, which annually honors contributions of immigrants to the arts and sciences. Lehmann received the 2021 Vilcek Prize in Biomedical Science for her foundational contributions to the understanding of primordial germ cells and the germ cell life cycle and for her institutional leadership.

Ruth Lehmann. Image credit: Vilcek Foundation/Ian Johns Photography.

Progressive Upbringing

Lehmann was born in Cologne, Germany. "My father [an engineer] invented machines and, like me, was dedicated to his work," she says. "The idea of invention fascinates me, whether one is an engineer or in biomedical research." Lehmann's mother strove to raise Lehmann and her brother without gender biases. "My mother was very revolutionary in her educational modes," says Lehmann. "This freed my brother, who is now a psychologist, and me to pursue our own careers."

In high school, Lehmann took a biology class that increased her budding interest in science. She says, "Instead of focusing only on textbooks that were idealized snapshots of present knowledge, we were encouraged to actively participate and raise questions. It showed me how exciting science really is." She chose to major in biology at the University of Tübingen, where she earned her *vordiplom*, which is comparable to a bachelor's degree, in 1976.

Year of Personal and Scientific Discovery

Skilled in math, Lehmann decided to pursue a Fulbright scholarship in ecology with a focus on two areas within the field: biomathematics and population genetics. She traveled, in 1977, to the University of Washington, Seattle, where she learned about the emerging field of developmental genetics under the direction of Gerold Schubiger. He introduced her to the model organism *Drosophila melanogaster*. She says, "Schubiger was a great mentor and teacher, with many of his students going on to successful careers."

The period between 1977 and 1978 was one of self-discovery for Lehmann. During a break from studies, she rebuilt an engine and motorcycled solo down coast-hugging Highway 1 from Seattle to Big Sur, CA. She says, "It was an exhilarating and totally transformative year for me in many ways. I was discovering myself and my love of science."

Research on Early Neurogenesis

At the fellowship's end, Schubiger suggested Lehmann attend the 1978 Society for Developmental Biology meeting in Madison, WI. There, she met developmental biologist Christiane Nüsslein-Volhard and admired her talk on polarity and self-generating gradient reactions in *Drosophila* body plan development. Nüsslein-Volhard was not able to take Lehmann on as a student, but she referred her to neurobiologist José Campos-Ortega at the University of Freiburg. With Campos-Ortega,

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Lehmann earned a diploma degree (equivalent to a master's) in biology in 1981 and helped define the evolutionary conserved Notch signaling pathway, which regulates neural versus epidermal cell fate decisions in the *Drosophila* embryo (1, 2).

Discovery of *oskar*, *nanos*, and *pumilio*

Lehmann returned to the University of Tübingen for doctoral studies in 1982, with Nüsslein-Volhard as her advisor. Using a series of genetic screens, Nüsslein-Volhard and biologist Eric Wieschaus performed systematic mutagenesis in *Drosophila* to identify gene groups with similar developmental defects. These efforts, together with those of biologist Edward Lewis, who was studying homeotic genes, revealed conserved strategies controlling animal development. The research laid the groundwork for understanding molecular principles of animal development and led to Nüsslein-Volhard, Wieschaus, and Lewis winning the Nobel Prize in Physiology or Medicine in 1995.

Lehmann's contributions to this ongoing line of research include discovery, cloning, and characterization of the genes *oskar* (3), *nanos* (4, 5), and *pumilio* (6), and others that are part of a pathway underlying the establishment of oocyte and embryo polarity (7). The gene *oskar*, for example, attracts egg RNA and protein components required for establishing posterior polarity and germ cell fate in the embryo (8). It holds a central germplasm assembly role critical for germ cell specification. At high concentrations, *oskar* undergoes a phase transition to organize into membraneless granules upstream of the other identified genes (9). Using superresolution, single-molecule imaging, Lehmann and colleagues (10) recently determined that these germ granules are highly structured, such that different RNA species self-sort and coexist at defined positions within them.

Leadership Roles

From 1987 to 1988, under the direction of molecular biologists Michael Wilcox and Peter Lawrence and as a postdoctoral associate in the Medical Research Council Laboratory of Molecular Biology in Cambridge, United Kingdom, Lehmann began the molecular characterization of the genes she identified as a graduate student. In 1988, she accepted an associate member position at the Whitehead Institute and an assistant professorship in biology at MIT before advancing to full member and tenured associate professor in 1993.

In 1996, she became cocoordinator of the developmental genetics program at NYU's Skirball Institute and a professor of cell biology. From 2006 to 2020, she served as director of the Skirball Institute and, from 2014 to 2020, was the chair of the department of cell biology at NYU. She held numerous other leadership roles at NYU and was an investigator at the Howard Hughes Medical Institute, first at MIT and then at NYU, prior to accepting her current position at the Whitehead Institute in 2020.

Networks Regulating Stem Cell Behavior

Lehmann continues to deftly balance teaching and administrative work with research. Her laboratory's interests focus broadly on the germline life cycle: from the fusion of egg and sperm, to the specification of primordial germ cells in the embryo and gonad morphogenesis during larval stages, to the critical role of the egg cell in restarting the next generation. She is determining networks that regulate the initial separation of the germline and soma (terminally differentiated nonreproductive cells) in the early embryo and their critical coexistence later, when somatic cells support egg and sperm differentiation (11–14). For example, Lehmann and colleagues (15, 16) recently discovered a transient signal from the soma that times when germ cells begin their differentiation into egg cells.

Mechanisms Controlling Germ Cell Migration

In most organisms, germ cells move from their site of origin to join the somatic part of the gonad. Lehmann and her team used *Drosophila* germ cell migration to study and elucidate this process from start (17) to directional migration (18, 19) to termination (20). They found that the conserved lipid phosphatase Wunen acts in both the soma and the germline to apparently opposite outcomes. Wunen, at its highest level, leads to germ cell death and, at lower levels, to repulsion. Conversely, Wunen expression in germ cells is required for their survival (19).

Lehmann says, "We use large-scale genetic screens that are unbiased with regard to the specific gene function, and choose to focus on genes with specific and severe phenotypes that more likely have a regulatory function." The method led to her team's discovery of previously unknown roles for lipid signaling in germ cell migration (19, 20). The enzyme HMG-CoA reductase, for example, synthesizes cholesterol in humans, among other roles, but is rate limiting for production of a hormone that guides migrating primordial germ cells in *Drosophila*.

Transcriptional Repression in Germline Fate Regulation

"We are ultimately interested in the mechanisms that protect germline integrity and distinguish the germline's potential for totipotency from the restrictive potential of somatic cell fates," says Lehmann. She and her team are therefore interested in the role of transcriptional repression of the somatic program and preservation of DNA integrity in germline fate regulation.

Some of her team's work has centered on Piwi proteins and their bound small RNAs (Piwi-interacting RNAs [piRNAs]), which provide defense against transposable element activity. (Other laboratories initially discovered and studied piRNAs.) Lehmann and colleagues (21) made the surprising observation that piRNAs require heterochromatin, a tightly packed form of DNA, for their transcription. She and her team have also expanded the known roles of piRNA function (22) and recently found evidence that transposable elements, rather than piRNA clusters, may act as a major source for piRNAs (23).

Mechanisms of Mitochondria Germline Transmission

Depending on the sex of an organism, germ cells differentiate into either egg or sperm. In addition to providing genetic information to the next generation, eggs deliver organelles and cytoplasmic structures required for initial development of the embryo before it can synthesize these cellular structures. Of particular interest to Lehmann are mitochondria, which have their own genome and are only passed through the female germline. She and her team showed that mitochondria are enriched in the germplasm, with a long isoform of the protein Oskar controlling mitochondrial inheritance in *Drosophila* (24).

Using a direct imaging technique, Lehmann and colleagues (25) confirmed a theory that egg cells execute mitochondrial selection and found an inroad into the underlying mechanisms. She says, "The findings may set the stage for new approaches to the treatment of mitochondrial diseases, which include myopathies that cause muscle weakness, neurological problems, and forms of diabetes."

Training the Next Generation of Scientists

Lehmann's awards and honors reflect not only the breadth of her achievements but also the multidisciplinary nature of her work as a geneticist who studies developmental processes at cellular to subcellular resolution. She received the Conklin Medal of the Society of Developmental Biology (2011), the Keith R. Porter Award and Lecture of the American Society for Cell Biology (2018), and the Thomas Hunt Morgan Medal of the Genetics Society of America (2021). For contributions to the field of reproductive biology, she and colleague Trudi Schüpbach of Princeton University were recipients of the American Academy of Sciences 2020 Amory Prize.

She extends gratitude to her partner of 30 years, neurobiologist Steven Burden of the Skirball Institute and NYU, and to her colleagues and the more than 60 graduate students and postdoctoral fellows who trained in her laboratory. In a video released upon her winning the 2021 Vilcek Prize in Biomedical Science, she says, "I think I am most proud that I've created an environment that encourages people to look at science with the same joy, enthusiasm, and fearlessness that I do. If we want to include everyone in the scientific process, then we need to make sure that everyone can get mentored, so I consider the impact I've made not only with the research we've conducted but also training the next generation."

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