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OBITUARY

Kathryn Virginia Anderson (1952-2020)

Tamara Caspary

As an eighth grader in Southern California, Kathryn Anderson was captivated by a photograph of an 18-week-old human fetus on the cover of *Life* magazine (see http://www.lennartnilsson.com/en/a-life-of-stories/the-drama-of-life-before-birth/). The photo is striking in its realism and its recognizable form. I suspect Kathryn wondered how a single cell could transform so. That 1965 cover story, 'Drama of Life before Birth', could also be the title for Kathryn's scientific oeuvre. Understanding what regulates a cell's identity and position across developmental time became her life's work. While she followed the phenotypes to disparate biological processes, her heart clearly lay in understanding the fundamental decisions that define the major body axes to the recognizable form of the embryo.

Kathryn died at home early on 30 November 2020, leaving an unparalleled breadth of scientific discoveries along with a tremendous legacy of trainees. She was principled and uncompromising, a woman of deep intellect and thought. Kathryn spent her career carefully observing embryos. Her knack for 'listening' to the embryos led her to make numerous important discoveries such as learning how the embryo distinguishes its back from its belly. She worked first in fly and then in mouse, always suspecting that the regulatory genes and molecules in those species would be relevant to human biology.

As remarkable as her discoveries was how she went about doing science – with focus, flexibility and efficiency that lay the foundation for her own success and that of her trainees. Kathryn was as pure a scientist as I know – a scientist's scientist. She only asked compelling questions. Genetics always guided her approach and she used molecular, biochemical or imaging techniques as needed. Her effectiveness as a scientist, a leader and a mentor stemmed from her unwavering focus on the signal, and her eschewal of the noise. When doing experiments, she directed her attention to the outcome. 'Just because you can do something, doesn't mean you should,' she gently reminded us. When mentoring, she would suddenly appear at the adjacent dissection scope, available if I needed her to listen or help me solve a puzzle. But once I had an independent position, she gave me space; Kathryn never competed with her former trainees. 'There's enough for everyone,' she always said.

Kathryn led unobtrusively. She did what was important. She became the inaugural chair of the Developmental Biology Program at the Sloan Kettering Institute in 2002 and embarked on a decade of hiring extraordinary scientists. She provided them a fertile and well-funded environment in which to develop their science organically and, in doing so, built an exceptional department. I saw Kathryn one October just after a reception for the promotion of two members and she was flush with excitement for them. Notably, Kathryn hired many excellent female scientists; this was part of an important generational shift and a marked contrast to her earlier encounters with sexism in science. She was unwavering in supporting and encouraging all her hires.

Photo courtesy of Timothy H. Bestor

I first met Kathryn, as many of us did, through her manuscripts. She loved writing and said that had she not become a scientist, she might have been a writer. She wrote as elegantly and directly as she designed experiments, always with clear purpose. 'Say something!' Kathryn would instruct us when we set out to write a review, shunning any efforts that simply summarized or cataloged information. Intention to say something comes close to describing Kathryn's relationship with words. She spoke when it added to the conversation, not to echo others.

As part of a project for the Society of Developmental Biology, I asked all former society Presidents to explain why each chose to be a developmental biologist. Kathryn sent me this haiku, capturing her enchantment with embryos, her allegiance to Viktor Hamburger's maxim to learn from the embryo, and her belief in her trainees:

'Beautiful embryos
Full of life and mysteries
You and I can solve'

Kathryn's career focused on how the early body plan is established in the embryo. During her graduate training with Judith Lengyel at the University of California, Los Angeles, Kathryn defined the relative contribution of maternal and zygotic histone mRNA to DNA replication during early *Drosophila* development. The crucial role of maternal RNA to fly embryo

Department of Human Genetics, Emory University School of Medicine, 615 Michael St. Suite 301, Atlanta, GA 30322, USA.

*Author for correspondence (tcaspar@emory.edu)

T.C., 0000-0002-6579-7589

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development grabbed her attention, as did the superb genetic tools available in *Drosophila*. She moved to the Max Planck Institute in Tübingen, Germany, for a postdoc position in the newly established lab of Christiane Nüsslein-Volhard, who was one of the few people at the time using genetics to identify actual molecules essential for development. Kathryn focused on identifying maternal mRNAs that directed the fruit fly embryo to define its dorso-ventral axis. She succeeded in identifying the genes and relevant protein molecules for several mutants, including the Toll receptor and several Toll pathway components, while in the Nüsslein-Volhard lab.

In 1982, Kathryn returned to the US to start her own lab at the University of California, Berkeley, where she focused on the many mutant lines from the maternal-effect screens. Her group systematically worked through the lines, identified the relevant genetic lesions and combined molecular and biochemical approaches as they ordered many of the components of the Toll pathway, which establishes the *Drosophila* dorso-ventral axis. Kathryn thought about biology broadly, and this enabled her to recognize similarities between Toll pathway components and immunity factors: the Toll receptor and the transcription factor Dorsal resembled the interleukin-1 receptor and NF-κB, respectively. As researchers implicated Toll signaling components in the *Drosophila* immune response, Kathryn's work provided the regulatory logic at play. Kathryn started studying *Drosophila* innate immunity, correctly reasoning that by performing genetic screens assaying a distinct phenotype, she would uncover additional Toll regulators, along with proteins important for immunity.

Meanwhile, Kathryn still wanted to know whether Toll signaling also determined the early body plan of the mammalian embryo. So she went on a sabbatical to Rosa Beddington's lab in the UK to learn mouse embryology. Kathryn cherished her time learning from Rosa at the National Institute for Medical Research on the outskirts of London. Being on sabbatical gave her time to read and think, which led Kathryn to recognize that the polymorphic markers being developed at the Massachusetts Institute of Technology (MIT) mouse genome project would enable small labs to map mouse mutants. Kathryn realized it would be straightforward to screen directly for mutants that disrupt the mammalian body plan.

Kathryn returned to Berkeley motivated by the conviction that mouse forward genetic screens would be facilitated with the imminent availability of the genome sequence. Despite Kathryn's vision and understanding that the logistical barriers that had challenged mouse positional cloning projects were disappearing, her initial proposals to screen in mouse were not well received by grant-giving entities. Kathryn was not deterred and performed a pilot screen showing that interesting phenotypes could be recovered and causative mutations mapped. About that time, other groups cloned the mammalian Toll receptors and implicated them in mammalian innate immunity with no developmental roles – answering the question that had motivated Kathryn's shift into mouse embryology. By this time, though, she had a set of interesting mutant phenotypes to analyze. Kathryn moved her lab to the Sloan Kettering Institute in 1996 and continued to screen. Thus, as the mouse genome sequence emerged, Kathryn's mouse room was full of mutant lines and her freezers packed with DNAs from informative recombination events. While I was a postdoc in her lab, the sequence was released and we regularly celebrated the identification of causative mutations with champagne. Her screens were extraordinarily successful and contributed significantly to a general acceptance of forward genetic screens in mouse as a viable and valuable approach.

More important than the ability to clone the genes disrupted in the mutant lines was the incredible biology uncovered through analysis of the mutants. Through identifying novel genes and analyzing the loss of their function in combination with other mutations, Kathryn pinpointed some of the fundamental features of mammalian development. Most famously, she identified the first mutants revealing that the primary cilium is essential for vertebrate Hedgehog signaling. This led to an explosion of interest in primary cilia over the past two decades and an acceptance that the primary cilium is a fundamental cell organelle.

Kathryn's many achievements earned her substantial recognition. In 2002, she was inducted into the National Academies of Science for her contributions to understanding the Toll pathway in dorso-ventral patterning and innate immunity in fly; meanwhile, her career as a mouse geneticist was just taking off. That same year, she delivered the Rosa Beddington Memorial Lecture at Cold Spring Harbor, an honor that left Kathryn overcome with emotion. After this, other awards followed, including the Thomas Hunt Morgan Medal from the Genetics Society of America, the Edwin G. Conklin Medal from the Society for Developmental Biology and the FASEB Excellence in Science award. As she accepted the latter, she showed the mouse mutants she planned to prioritize next – what she termed 'the coming attractions' – and shared perfectly photographed, improperly gastrulating embryos that she had described as 'cute' at the dissection scope; among Kathryn's talents was discriminating interesting phenotypes from general developmental delay.

Kathryn had many habits I try to follow. She limited her travel so that she could be present for her lab. She helped trainees discover for themselves so they could learn how to be scientists. Sometimes she understood my data before I did and she'd often ask seemingly simple questions to push my thinking in the right direction. In the moment, this made me feel incredibly clever, but the larger lesson was to be patient as ideas need time to percolate and develop. She also taught me to sleep on any important decision, and this has benefited me countless times.

So many of us are inspired by Kathryn's transformative discoveries and her generous spirit. Any one of the topics – dorso-ventral polarity in the fruit fly, innate immunity or the link between cilia and Hedgehog – could define a career. What we have lost is her wonder – beyond curiosity, rapt and always full of delight. Anyone in her world knows the pitch as she exclaimed, 'Oh!' when we shared a stimulating result. Her hop – or was it a bounce? – was legendary in her lab. When excited, she literally couldn't keep her heels on the ground. She never lost the sense of wonder she felt as an eighth grader looking at a photo of a human embryo and contemplating the mysteries of human development. A lifelong fascination with the embryo.