



The symphony of cells

Cassandra Extavour almost chose a career as a soprano. Instead, she set out to learn how single cells create the rich soundtrack of evolution.

BY GIORGIA GUGLIELMI

By the spring of 1998, Cassandra Extavour had spent more than two years failing to get her PhD off the ground. She had moved from her native Toronto in Canada to a pioneering laboratory in Madrid, where she was trying to engineer the eggs of fruit flies to have two different genetic make-ups. But she hit hurdle after hurdle, and nobody in the lab could help. If she couldn't make the flies within the next few months, she would have to quit the project.

As she sat with her adviser and went through the dozens of unsuccessful tests she had done, they came up with one last strategy to make the flies using a different gene variant. Her adviser reassured her that it wouldn't have any unwanted effects, but couldn't point to any hard data. Even with time running out, Extavour was unwilling to take his word for it. She embarked on a months-long series of experiments to prove to herself that the gene did what he said. In the process, she built her own tools to ask a question that nobody had addressed before. "That's the kind of project that I really love," she says.

Two decades later, Extavour is still pursuing original research questions and overturning convention as she investigates some of the most fundamental aspects of animal development. In her lab at Harvard University in

Cambridge, Massachusetts, Extavour wants to understand how single-celled entities blossomed into multicellular organisms during evolution, and how the intricate bodies of such organisms can develop from cells that all have the same genetic blueprint. “I have never heard of a problem that I thought was more interesting than that,” she says.

Extavour’s curiosity and rigorous thinking have led her to test, and in some cases disprove, widely accepted hypotheses about development and evolution. She upended the leading theory of how most animals generate the precursors of eggs and sperm¹, and in a *Nature* paper this week, she and her team have cracked a long-standing question about the astonishing diversity of insect eggs².

Just as an orchestra produces a sublime concerto, a suite of meticulously balanced genes controls an organism’s form and function. Extavour appreciates this better than most: she juggles science alongside a side career as a soprano. Even while rewriting scientific doctrine, she performs with professional ensembles in Boston and has appeared in operas and choirs from Canada to Spain.

Whereas most researchers work with only a handful of well-studied animals, such as fruit flies and mice, Extavour’s success comes from her penchant for less-ubiquitous lab critters, such as sand fleas and crickets. Typical model organisms harbour just a fraction of the diversity found in nature, so alongside the usual suspects, she examines a wide range of animals that help to reveal which genetic tools evolution most commonly uses.

She has also emerged as a champion for diversity and inclusivity, having experienced racism and prejudice as a gay black woman in science. Even after becoming a tenured professor, she still encounters people who assume she doesn’t belong. She spends time mentoring students from under-represented groups and helped to found the Pan-American Society of Evolutionary Developmental Biology, which unites hundreds of researchers across the Americas.

It’s a demanding schedule, but for Extavour, everything seems to be possible, says Johannes Jäger, an evolutionary systems biologist at the Complexity Science Hub in Vienna who worked with Extavour during her postdoc. “Nothing about her trajectory is typical: her background, how she got into science,” he says. And her approach to research is paying dividends. “She took a bunch of very unusual organisms, she broke traditions and she succeeded.”

HARMONIOUS BEGINNINGS

Music has been in Extavour’s life since she was in the cradle. Science came much later, almost by accident.

Her father, who moved to Canada from Trinidad and Tobago in the 1960s, was a broadcast technician and percussionist. He played in concerts and used to practise in the basement of their three-bedroom house in downtown Toronto with his four kids. The first instrument Extavour played was a steel drum. In elementary school, she learnt to read music and taught herself to play the flute, borrowing music scores from the library. At university, Extavour played in orchestras and duos, and took up classical singing. “The only clear career goal I ever had was to be a musician,” she says.

A high-school friend got her interested in the workings of the brain, and by the end of her undergraduate studies, she had found her way to molecular genetics. At the University of Toronto, Extavour traded off science and music, landing her first professional singing gig with a baroque orchestra and working a summer job as an administrative assistant for developmental biologist Joseph Culotti. There, Extavour heard for the first time about the problem that became the common thread of her research — how genes control the growth and development of organisms.

The following summer, she went back to Culotti’s laboratory, this time as a research intern. Fascinated by the work and talented at the bench, she decided to continue with graduate work and sing on the side.

During her PhD in Madrid, Extavour struggled with the technical feat of engineering flies. But that wasn’t the only challenge she faced.

Although her adviser didn’t treat her any differently from other students, she felt isolated as the first and only female student in the lab.

It was a familiar feeling, being an outsider. “I was not what a scientist usually looked like,” she says. Extavour’s father, who had experienced discrimination as one of the few black employees at his workplace in Toronto, helped to foster her resilience. Every time someone made a racist or discriminatory comment about her, she would phone him. “He would remind me that I had to not let those things stop me from doing what I wanted to do,” she says.

But what she wanted to do was still in flux. Towards the end of her PhD, Extavour considered putting research aside and singing full time. “At the end of the day, the feeling that I get performing for people is maybe better than the feeling that I get when I’m discovering something new,” she says.

But she eventually decided to do a postdoc with Michael Akam, a zoologist and embryologist at the University of Cambridge, UK. There, she set out to study how the mechanisms that specify germ cells — the precursors of eggs and sperm — evolved across animals. But first, Akam says, she organized his lab space and created exhaustive lists of reagents. “She made things work better for everybody,” he says. She was a fiercely rigorous thinker, too. During meetings, “she wouldn’t let people get away with making claims from data that were not really rigorous,” Akam says.

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While in Cambridge, Extavour wrote a paper¹ that upended a widely accepted hypothesis in developmental biology. The prevailing theory held that most animals formed their germ cells early in development, thanks to molecules inherited from the mother. Popular model organisms, including flies and roundworms, all generate their germ cells that way. One notable exception is the mouse, in which those cells form later during development, when signals coax some of the embryo’s cells to take the first step towards becoming eggs in females and sperm in males.

Keen to understand the wider picture, Extavour embarked on a first-of-its-kind review of existing data on the mechanisms that specify germ cells in a wide range of organisms, from jellyfish to turtles. She read more than 1,000 academic papers on germ cells, and in nearly 300 of them, she found relevant information on the cells’ origins, which led her to conclude that the most common method of formation — and probably the oldest in evolutionary terms — is the process seen in mice.

The paper spurred interest in how germ cells evolved in a variety of animals, and helped to give impetus to the ‘evo-devo’ community — a network of scientists interested in the rules governing evolution and development, says Ehab Abouheif, an evolutionary biologist at McGill University in Montreal, Canada. From then on, Extavour cultivated an array of unusual model organisms such as sea anemones and sea urchins — a comparative approach that became central to her research.

EVO-DEVO SUPREMO

Extavour moved to Harvard in 2007, to run her own lab studying the evolution and development of reproductive systems. Over the past 12 years, she has analysed the genetic mechanisms that guide the formation of germ cells in a wide variety of animals, using them to work out how cells assume different identities given the same starting material.

In 2014 and 2016, her team looked at the origins of germ cells in crickets, and found that the molecular messengers that trigger the development of cells that become eggs or sperm are the same as those observed



Cassandra Extavour at the lab bench in the 1990s.

in mice^{3,4}. This finding supports the idea that the signalling system is ancient, inherited from the last common ancestor of both mice and crickets, which existed more than 500 million years ago.

Extavour is studying the cricket *Gryllus bimaculatus* to work out how its genes contribute to development and change over time. One of her graduate students found that the cricket's genome contains the equivalent of a fruit-fly gene called *oskar*, which is crucial to the production of germ cells and is considered to be an evolutionarily 'young' gene⁵.

Finding an *oskar* equivalent in the cricket's genome suggests that the gene is actually rather ancient because, during evolution, crickets split from most other insects earlier than flies did. She suspects that *oskar* was probably doing something completely different in its earlier guise, related to the development of insects' brains and nervous systems, only later becoming important for developing germ cells.

"That's an impactful discovery," Abouheif says. Understanding how the *oskar* gene was repurposed could reveal how genes evolve and contribute to new developmental processes, he says.

Extavour has also re-examined evolutionary tenets using her trademark approach: mounds of new and existing data. In a study published in this issue of *Nature*², her team challenges a long-standing assumption about how the shape and size of insect eggs changed over time.

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All insect eggs have the same function — to protect and provide energy for the developing bug — but their huge variety of shapes and sizes has puzzled biologists for centuries. Some thought that these features are linked to how big the adult animal is, or to how long the embryo takes to develop. But no comprehensive studies had ever tested these ideas, Extavour says.

So she and her team scoured the scientific literature and created a database of more than 10,000 descriptions of insect eggs, with shapes ranging from almost perfectly spherical to banana-shaped, and wide size variations too: one smaller than a speck of dust, one the size of a blueberry.

The researchers looked for connections between egg shapes and sizes and many insect features, including where the insects lay their eggs and the time it takes for a fertilized egg to turn into a larva. The analysis revealed a surprise: the evolution of egg shape and size depends largely on where the eggs are laid. Eggs laid in water are often small and spherical; those deposited into the body of another animal are also small, but tend to be oddly shaped.

The findings challenge old assumptions that relate egg size to adult body size, says Laura Lavine, an insect physiologist and evolutionary biologist at Washington State University in Pullman. Many scientists assumed that those size relations were the "end of the story", Lavine says. "Now the story starts from this study," she says. Understanding how eggs change depending on the environment could reveal some of the major constraints on how animals grow and evolve, Lavine says.

Ultimately, Extavour hopes that her mission to scrutinize the eggs, embryos and reproductive systems of insects will help her to understand the rules governing the evolution of the first multicellular organisms. Working out why cells with the same DNA do different things in different environments — which programs create a sperm cell, or what governs the size of an egg — could help to solve the puzzle, she says. Such questions are the driving force behind a new, US\$10-million research centre at Harvard, which Extavour co-leads.

Many wait in anticipation for Extavour's next breakthrough. "She's a deep evolutionary thinker," says Casey Dunn, an evolutionary biologist at Yale University in New Haven, Connecticut. "But she also addresses really detailed developmental questions."

DIVERSITY DEFENDER

In November 2013, Extavour had to give an important seminar — the final hurdle in her application for tenure at Harvard. Before presenting her scientific achievements, Extavour reminded the audience that women couldn't receive teaching from Harvard scholars until the late 1870s, and that more than 100 years passed before they could be awarded the same Harvard degrees as men. "If this hadn't happened, I wouldn't be here today," she said.

Few people would draw attention to the troubled history of their own institution, says Didem Sarikaya, a biologist at the University of California, Davis, who at the time was a PhD student in Extavour's group. But Extavour has long stood up to represent and support people who have historically been excluded from science. Black scientists and engineers often feel that they do not belong, says Rahel Imru, an undergraduate and incoming president of the Harvard Society of Black Scientists and Engineers, whose members Extavour often advises and mentors.

Extavour says that interacting with black students is also important for her own well-being. In her life, racism is constant, she says. At conferences, people have asked her to refill the coffee, and when she showed up at the door of a Harvard building to attend a business dinner recently, a security guard, who assumed she was there to serve dinner, pointed her towards the service entrance.

Music provides some solace, Extavour says, but her friends and family are absolutely crucial. Extavour's wife, who is also a black woman, is an invaluable source of support. "We can understand a lot of what we're each going through," Extavour says.

Extavour, who didn't tell colleagues about her sexual orientation until her postdoc years, says that she can appreciate how students who come out as lesbian, gay, bisexual, transgender or queer might feel isolated. Rainbow-flag stickers on the doors of her office and laboratory spaces signal to students that everyone is welcome. "Being out at work is important, because it allows young people to see that it's possible to be gay and out and alive and have a job," she says.

Extavour learnt from her family that she should not let other people's prejudices define what she could and could not do; they also inspired her to set her own standards for how well she should do it. And those who know her say that Extavour aims high. "She's motivated by big questions," Dunn says. "She has her eyes on the horizon." ■

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