Cheng-Ming Chuong

Chickens pattern their feathers in the same way that people find seats in a movie theater. They self-organize, says Cheng-Ming Chuong, a Professor of Pathology at the University of Southern California's USC Keck School of Medicine. Chuong is a pioneer in the use of feather follicles as a model system for organ morphogenesis, patterning, and regeneration.

Embryonic feather buds space themselves out like an audience trickling into a movie theater—politely and hexagonally. Normally, you will not sit down next to a stranger, Chuong explains, unless you are holding a numbered ticket for a numbered seat. That doesn't work with chicken feather buds; there just isn't room in the genome for a molecular coding for each feather, according to Chuong. Instead, chickens spread out their feather buds with a self-organizing system driven by intercellular signaling and basic physical-chemical principles. In humans, similar principles are at work during development to get tissues and organs into the right places.

Chuong calls his feather model a "Rosetta stone," which he can use to decipher the "language" used in a variety of biological systems. Chuong has used his feather model to study everything from how stem cells regenerate to the molecular mechanism behind the "evolution novelty" of skin. Chuong's main studies have focused on epithelial-mesenchymal interactions during skin morphogenesis and on self-organization in pattern formation. Studying how those interactions and patterns occur focuses on basic research questions, but also raises intriguing possibilities for biotechnology and clinical medicine.

Switching On

Consider hen's teeth and snake legs. A postdoc in Chuong's lab is now trying to manipulate chicken embryos genetically into forming teeth. In the evolution of birds from dinosaurs, Chuong says that the chicken's ancestors had teeth but lost them. Embryonic chickens still develop a small tooth bud but then development is arrested. Similarly, embryonic snakes develop leg buds and then switch off further development. "The pure question is, how do they shut it off?" asks Chuong. "But in general terms as a practical issue, if you knew how to turn it off, maybe you might be able to turn it on. And if you can turn it on, you have a regeneration situation." The goal is not a grinning chicken but some understanding of how to regrow a missing digit or a lost head of hair.

Chuong's feather model can take him far afield. As a cell and developmental biologist, he has collaborated with mathematicians, engineers, and paleontologists. He has traveled to northern China to dig "feathered dinosaur" fossils in remote sites and published on how reptile scales were transformed into avian feathers. He remodeled the beaks of embryonic chickens and ducks to model the molecular changes behind the evolution of Darwin's famous Galapagos finches. And Chuong is probably one of the very few members of the ASCB to publish in the journal *Autonomous Robots*. He coauthored a paper with USC information scientist Wei Min Shen on a "digital hormone model" linking stem cell behavior and "robot swarms." All this flows from Chuong's insatiable curiosity about how living things unfold in the natural world. "My research is like a conversation with nature," is Chuong's explanation.

The curiosity began in Taiwan. The chicken feathers came from Manhattan. Both his parents were physicians who practiced in Taipei where "Ming" Chuong was born. His mother encouraged his childhood fascination with natural process—how seeds germinate or how caterpillars morph into butterflies. "That's what probably got me into developmental biology," he believes. Chuong graduated from Taiwan University Medical School in 1978 with one clear ambition. "I'd always wanted to do basic research. In those days if you thought of cell biology, you thought of the Rockefeller [University] and names like Keith Porter and George Palade." Accepted as a graduate student, Chuong landed in the laboratory of Nobel Prize laureate Gerald M. Edelman and in the midst of a worldwide research blitz to identify cell adhesion molecules.

The World in a Feather

Chickens had just yielded up a breakthrough for the Edelman lab. Using immunological methods, the Edelman lab identified the first calcium-independent, neural cell adhesive molecule—or N-CAM—from the embryonic chicken retina. Chuong's first lab assignment was to figure out how retinal neurons form

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patterned connections with the brain. With the cutting-edge technology of the day—monoclonal antibodies—Chuong isolated the mouse homolog of N-CAM. For his thesis, Chuong tried to unravel the role of murine N-CAM in wiring up the embryonic mouse brain. The experiment went well enough but Chuong was frustrated by the sheer tangle of the brain.

He stumbled onto feathers. "We were mapping different adhesion molecules in developing chicken spinal cord with immunofluorescence," he recalls. By mistake, a piece of chicken skin with developing feather buds was stuck to the spinal cord sample. The staining revealed the most exquisite patterns in the feather buds, displaying detailed structures down to the single cell level. "The fluorescence really lit up like stars in the night sky," says Chuong. "This was a defining moment in my life."

Searching the literature, Chuong came upon papers from the 1950s and 60s that used chicken feather buds as a model for embryonic induction. "Observations in the classical literature were insightful, but they didn't have the molecular tools to study the mechanism. In our time, we have these tools," Chuong explains.

The first immunofluorescence images that Chuong photographed in his Rockefeller lab transformed feather follicles "almost into a work of art," recalls Gerald Edelman, who is now Director of the Neurosciences Institute on the Scripps Research Institute campus in La Jolla. "They were staggeringly beautiful. Absolutely gorgeous. You have to see them for yourself. To describe a Picasso or an embryo in words is not sufficient." In sticking with his feather model, "Ming has continued with great intensity and depth to study the process of what I call 'topobiology,' namely place-dependent biology," Edelman declares. "He has pursued this with relentless precision, generalizing the results to other epithelial structures but Ming has always been very rigorous, very much a real scientist. It's been an impressive achievement."

The Beak of the Chicken

In 1987, Chuong took his feather model with him to USC where he set up a tissues development and engineering lab in the medical school's Pathology Department. Today Chuong lives in Irvine with his wife, Violet Shen, a pediatric oncologist at Children's Hospital of Orange County. They have a son, Edward Chuong, 22, who just entered a graduate program in genetics at Stanford. Besides his 10-member lab, Chuong now directs the graduate program in Pathology at USC.

Pradip Roy-Burman, who helped recruit Chuong to USC, says that Chuong has a knack for restating complex scientific problems as simple questions that engage ordinary people. "Too many of us in science are not very good at answering simple questions like, 'Why are beaks formed differently in ducks and chickens?" says Roy-Burman. Chuong uses such "simple" questions as take-off points for research into stem cell differentiation, tissue regeneration, and "Evo-Devo."

Chuong's scientific productivity is no surprise to Roy-Burman. "You know, he was trained by a Nobel laureate," says Roy-Burman, "and I think Ming has some of those traits. I consider him as someone approaching the genius level. "

Caltech's Marianne Bronner-Fraser has known Chuong for 30 years and seen him at so many different meetings that she momentarily loses track of whether she last saw him in Finland or in Cancun. But Chuong is invited to so many different types of meetings precisely because of his broad interests and cross-disciplinary approach, according to Bronner-Fraser. "Besides, Ming gives a really great talk," she adds.

"His feather model is a system that's very amenable to experimental manipulation. Much of what he's been doing is really stem cell biology, but there is also pattern mechanics. So there are all sorts of growth factors involved plus lots of signaling issues. He's been able to plug these things into his feather model and put them into a new context," says Bronner-Fraser.

Chuong's context for Angela Christiano of the Columbia University Medical Center is through the "hair" community, a subspecialty of developmental biologists and geneticists focused on hair disorders. According to Christiano, hair researchers have made limited use of feather models before, and yet the community had seen nothing like Chuong's highly detailed model nor his rigorous comparative approach. "I hate the term [push the envelope] but it's true in his case," Christiano declares. "Ming is one of the few people who consistently does push the envelope. Every time I hear him talk, there's something new or some kernel of genius that floats through. He's so unconventional in how he thinks."

"I try to direct our research to answer questions not easily answerable by conventional models," says Chuong. "Nature is so rich. There are many things we can learn from a million years of evolution." ■

—John Fleischman