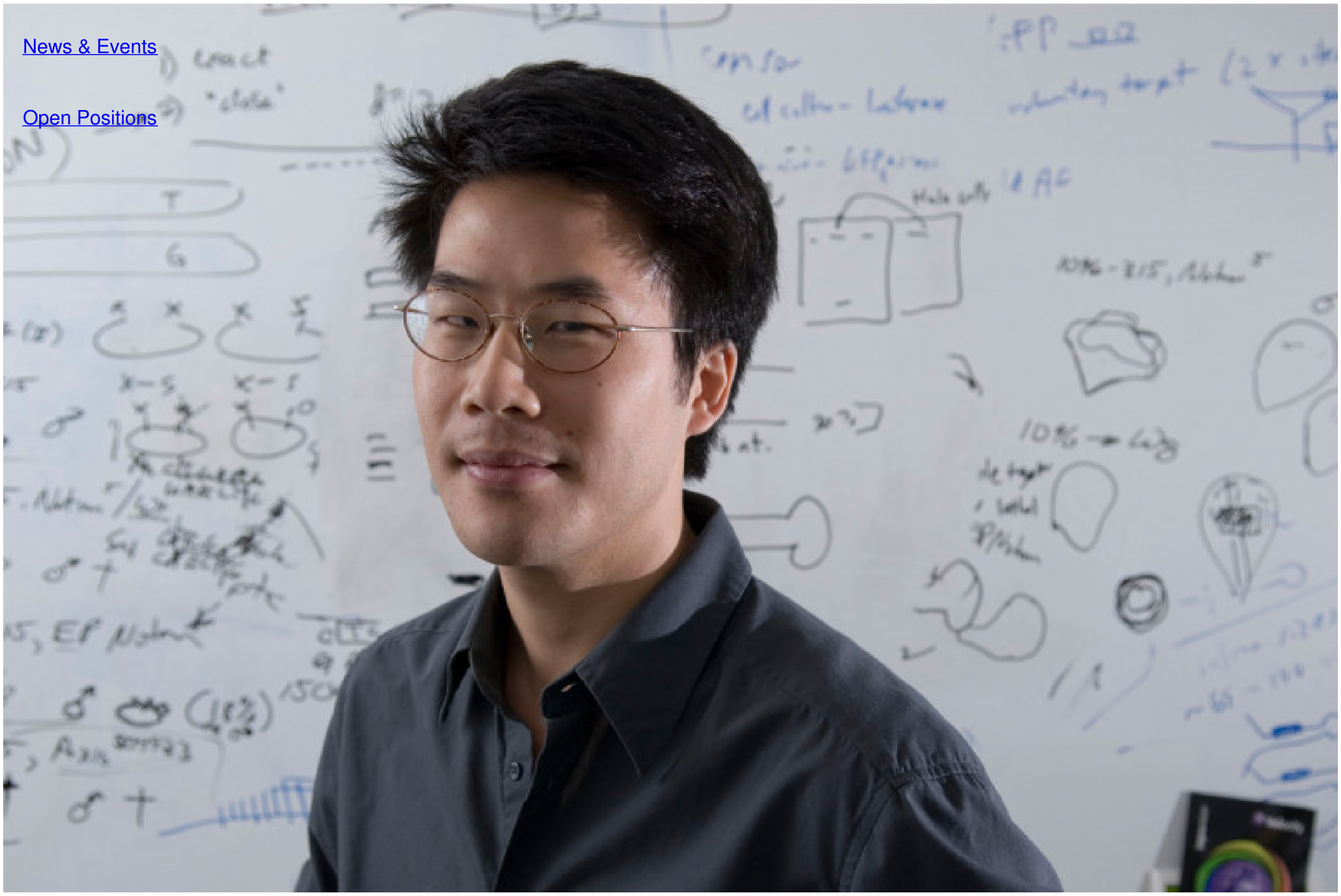
Memorial Sloan Kettering Cancer Center

At Work: Developmental Biologist Eric Lai



Eric Lai

Developmental biologist Eric Lai focuses on comprehending how complex biological patterns can be assembled with exquisite precision. We spoke to him about his research in 2007, two years after he set up his laboratory at the Sloan Kettering Institute.

There are two distinct paths that have shaped me as a scientist. The first involves my father, who studies wood chemistry. Visiting his laboratory as a child, I was fascinated by the jungles of reaction vessels and industrially-sized paper-making machines he used. My dad instilled in me an interest in math and science. A second trajectory influencing my work has been music. I trained as a classical violinist from the age of four, the start of a lifelong interest in performing and writing music.

Although they might seem unconnected, science and music are related systems whose underlying logic is manifest in pattern and beauty. The human eye is drawn to patterns — the spiral of a sunflower, the stripes on a zebra, the crystalline lattice of an insect eye. Unfortunately, many diseases and cancers result from inappropriate activity of biological pathways that control patterning, so there is also a clinical need to understand how patterning works at the molecular and cellular level.

My training in music theory and composition provides a parallel foundation to my interest in how patterns are put together. In fact, my knowledge of musical chord progressions directly influenced some of my key inquiries into DNA-based sequence patterns. So science and music are really point and counterpoint to who I am.

As a student at Harvard in the early 1990s, I became interested in developmental biology. Essentially, this field is the study of how living patterns are created from scratch. I did my thesis work with Gary Ruvkun at Harvard Medical School.

Dr. Ruvkun used the nematode worm as a model system to study questions about complex developmental processes — How did each portion of the worm "know" how, where, and when to create specific cell types? The work I did in his lab was my practical introduction to developmental molecular genetics.

Punk Rock in New Zealand vs. Graduate School in the States

College also brought with it a textbook teenage rebellion. I grew out my hair, immersed myself in punk and indie rock, DJ'ed a weekly Boston radio show, went to shows, and taught myself guitar. By my senior year, I was seriously considering moving to New Zealand. I solicited several foundations to support ethnomusicological research on how the geographical isolation of this tiny island country fostered its amazing indie rock scene. The Bats, the Clean, the Tall Dwarfs, Peter Jefferies, the 3Ds, the Xpressway and Flying Nun record labels — so much great music!

Alas, the funding to study Kiwi punk did not come through. Instead I followed the competing option: to attend graduate school and further my interest in developmental biology. In 1993, I moved to the University of California, San Diego, where I studied fruit flies in the lab of James Posakony.

My graduate work defined many of the questions and techniques that remain the basis of my research to this day. During my PhD, I analyzed DNA codes that regulate genes responsible for building the exquisite pattern of sensory organs that decorate the fly.

Unexpectedly, it was my training in music theory that guided me to notice, in reams of genome sequence data, myriad classes of sequence motifs that connected functional gene batteries. To me, that's proof of the value of a liberal arts education — you never know when disparate knowledge bases are going to unite in fantastic and unpredictable ways.

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Pluses and Minuses of Research Freedom

For the next stage of my training, I decided to pursue a postdoctoral fellowship that would afford me the freedom to investigate a diversity of topics. In 1999, I moved to the University of California, Berkeley, to work with Gerald Rubin, a leader in fly developmental biology.

Quite unexpectedly, the day before I was scheduled to arrive, Dr. Rubin announced he was leaving UC Berkeley to become Vice-President of the Howard Hughes Medical Institute on the other side of the country. I was to get all the freedom I had hoped for, and more.

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There were definite plusses and minuses about such freedom. I could do pretty much whatever I wanted, which included writing lots of music, forming the indie-pop band Highwire, and playing around the Bay Area whenever possible. In the lab, a small core of smart and dedicated colleagues remained, and we continued sans advisor.

However, we were also isolated and undermanned, since each of us worked on a completely different, and usually quite competitive, research topic. We were not really so much of a lab as we were an emotional support group. But I worked alongside some great scientists and made lasting connections, as I built my independent research program on neural patterning and small RNA function.

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New Patterns Form at SKI

As I approached completion of my postdoc in 2005, I became very interested in what I was hearing about the Developmental Biology Program at Sloan Kettering Institute. It was a relatively new department with a large faction of young researchers, and the prospect of becoming an integral part of a growing program was tantalizing.

Equally important was the presence of Kathryn Anderson at the program's helm. I was familiar with her work — some of the hand-me-down labware at Berkeley still bore her "KVA" monogram from when she was a Cal faculty across the hall — and I knew that she would be an excellent chairperson to work with.

Besides the incredible research resources offered at SKI, I was sold on the rich cultural life that New York City has to offer. The art and music offerings are unmatched, and it was important to me to live in a place where I could do great science and enjoy a full life outside the laboratory.

As I pass my two-year anniversary at SKI, I now have some terrific people working with me and we are beginning to make some real discoveries…it's getting exciting! We recently published our first work in *Cell*, about a new class of small RNA gene called the "mirtron" that plugs into the microRNA pathway. More generally, my lab is interested in the biochemistry and the biology of microRNAs, a recently characterized family of tiny gene products that control the activity of a vast proportion of the genome.

In a truly serendipitous turn of events, the DNA sequence patterns that I uncovered as a graduate student, and later studied during my postdoc, turned out to be among the first manifestations of the microRNA universe known. Who knew that I would eventually be competing with hundreds of labs on a corner of biology that as a graduate student I had had largely to myself!

Last year's Nobel Prize went to Drs. Fire and Mello for their groundbreaking work on a related small RNA pathway, the RNA interference (RNAi) pathway, which can be used to control gene activity almost at will. There is a lot of hope now riding on the therapeutic potential of microRNAs and RNAi, but there is still much to do to figure out how they work, what they do, and how they can be best applied.

My lab at SKI exploits the fly as a powerful experimental system with elegant genetic tools and a trove of genomic resources at its disposal. We use computational and experimental methods to discover novel small RNA genes and to expose their functional imprint on the genome via DNA motif patterns. We also use biochemistry to probe the molecular machines that drive small RNA production and function. Finally, we use genetics to figure out what small RNAs actually do in an animal.

We're finding that many small RNAs control key regulatory genes responsible for tissue patterning, data that suggests new avenues for disease mechanisms in humans. In addition, our knowledge of fly RNA genes recently led us to discover a new class of RNA genes in the human genome. It's pretty satisfying when we see that our insect studies lead directly to a better understanding of human biology.

Now is a great time to be a scientist, and recent advances in several technological arenas enable us to do experiments that I could not have dreamed about as a student. I'm very much looking forward to what the next few years has to bring in terms of the growth of my lab and the SKI Developmental Biology program. And keep an eye out for the occasional Manhattan or Brooklyn club gig by "the new milo greene" — that's me!

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