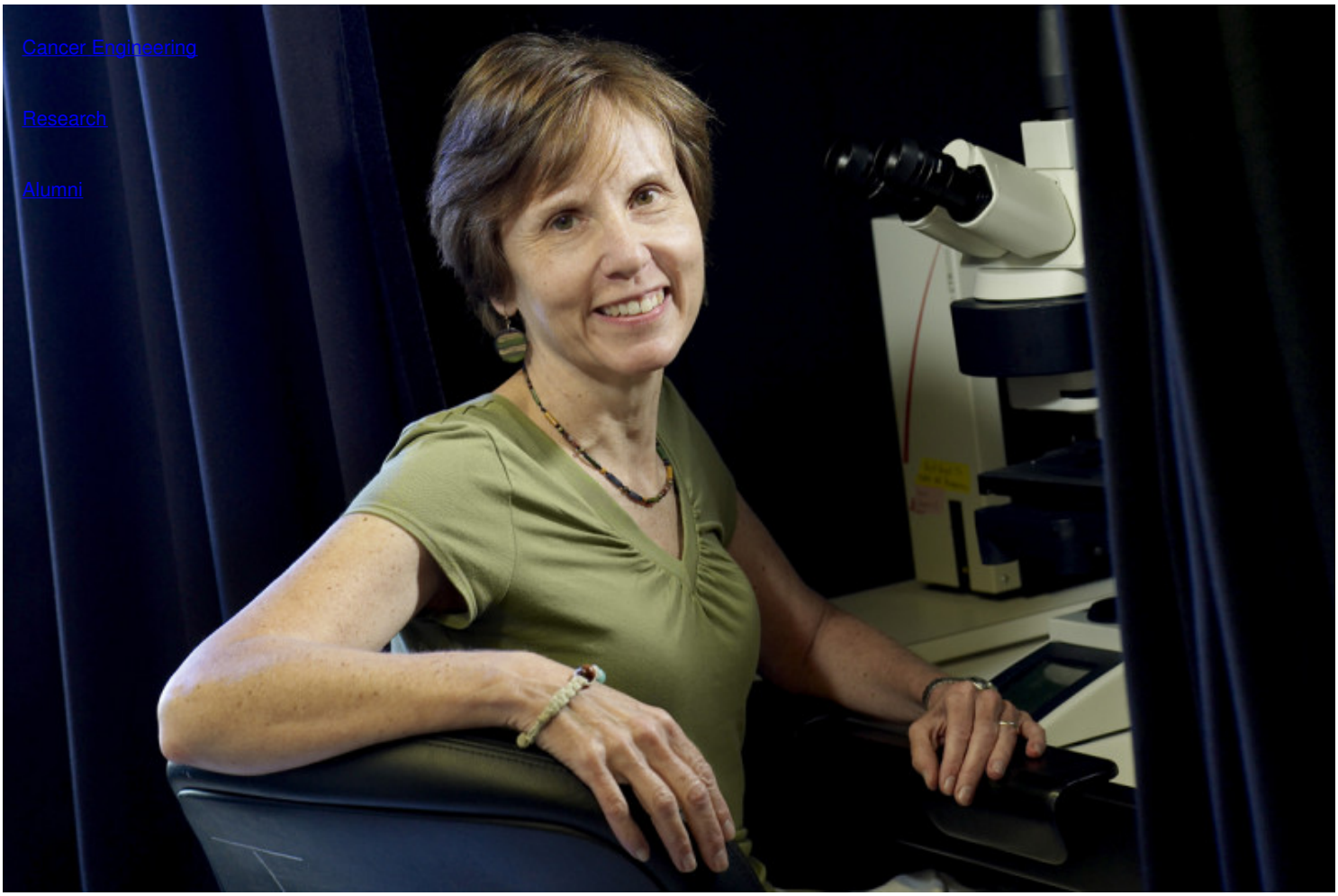
At Work: Developmental Biologist Alexandra Joyner



Alexandra Joyner

Development biologist Alexandra Joyner, a global leader in mouse developmental genetics, studies development of the mammalian brain and how the body's natural stem cells might be harnessed to fight disease. We spoke with her in 2007, soon after she joined the Sloan Kettering Institute as a Member of the Developmental Biology Program.

Like many people, my interest in science began with my love of nature. My early experiences learning about ecosystems piqued my interest in how the diversity of organisms is determined and how the fine balance needed to maintain complex systems is attained.

As an undergraduate at the University of Toronto, I worked with a wonderful mentor, Ellie Larsen, who was studying developmental genetics in *Drosophila* fruit flies. I found it exciting to study genetics in a living organism, though I wasn't thoroughly satisfied working with flies. In my mind, I wanted to do the same type of genetics but in mice — which became my goal for both my doctoral and postdoctoral research. In 1979, I entered the doctoral program at the Ontario Cancer Institute. The institute's research was on the cutting edge of the new wave of molecular genetics. It was also an interesting time for cancer research in general. Scientists were just beginning to get hints that some of the genes responsible for certain cancers might also normally regulate development. This meant that you had to understand their normal developmental role to understand why and how they caused cancer.

There, I began to realize that we would need to develop new technologies in order to use genetics to its fullest potential in mice. As a result, my doctoral research involved making some of the first retroviral vectors and using these to introduce genes into cells in mice. It was an exciting time because a lot of disparate strands were coming together into a new understanding of cancer.

When I began my postdoc, there were only a few labs I could go to in order to combine molecular biology and traditional mouse genetics to study development. One of the few people offering that possibility was developmental biologist Gail Martin of the University of California, San Francisco. My idea at the time was to use embryonic stem cells as a vector for manipulating the mouse genome.

Using Stem Cells as Tools

Working in Gail's lab, I tested if we could develop methods for introducing DNA into embryonic stem cells, with the ultimate goal of changing gene expression. At the same time it became apparent that a number of key developmental fly genes had something now known as a homeobox domain, which is a conserved sequence in transcription factor proteins that binds DNA. A number of people began to wonder if we could use these sequences as probes to find similar genes in mice, and whether the genes would be key developmental genes in mammals. I began to test the general idea that developmental genes are conserved between fly and mouse by using a fly gene thought not to have a standard homeobox (the *Engrailed* gene). With the help of Thomas Kornberg, a fly developmental biologist, I was able to locate the equivalent genes in mice. Now that I had these genes that we thought were probably important for mouse development, we needed to have a tool to study what role they actually play in mice. To do this, we required a method to induce mutations in particular genes and to observe the resulting effects on embryonic development.

> "I had started to wonder if I was going to put myself out of business. The infrastructure and expertise I need for my research are rare in academic institutes."
>
> Alexandra Joyner
> Developmental Biologist

With an interesting research project in hand, it was time to find a place to set up my own lab. At this time, in 1986, I had just had a baby, and my husband and I decided to limit our job search to Toronto, where our families lived. Mount Sinai Hospital in Toronto had just created the Samuel Lunenfeld Research Institute, and I started a lab there that was one of five at the institute doing mouse developmental genetics. Using embryonic stem cells, my colleague Janet Rossant and I created mice with a mutation in one of the *Engrailed* genes in order to learn its roles in development. It was an exciting time to be involved with the development of these and other genetic methods in mice. We could now begin to study mouse genetics with precision.

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A Focus on the Brain

In 1994, I was invited to create a program in developmental genetics at New York University's newly created Skirball Institute of Biomolecular Medicine. I liked the idea of having the opportunity to bring together developmental geneticists working in mouse, fly, worm, and fish, and have them all on one floor. I decided that the cerebellum would be an ideal system to study how a region of the brain is transformed from a simple embryonic structure to eventually become a complex adult brain structure with billions of cells working in unison. In my 12 years at the Skirball Institute, we were able to develop the basic ground rules for how we think that developmental system works. In addition to our studies of the cerebellum, we analyzed the Sonic hedgehog signaling pathway and its implications for brain development, cancer, and most recently stem cell biology. While we initially studied stem cells in the brain, we now realize that this hedgehog pathway probably regulates stem cells in many different adult tissues.

As I was trying to decide where next to take my two-pronged cerebellum/adult stem cell work, the one institution that continued to rise to the top of the list was Sloan Kettering Institute. It is rare in a center's leadership to have someone like [then President] Harold Varmus, who truly understands the importance of mouse genetics and mouse *in vivo* studies. The excellent core facilities at Sloan Kettering Institute also made this one of the few places where I could easily expand my research. In addition, I knew that [Program Chair] Kathryn Anderson was building a very exciting Developmental Biology Program, which had the kind of interactive and complementary feel that my past research environments had offered.

With the excellent team I have at Sloan Kettering Institute, our research goals are twofold. First, we will continue to analyze how genetic decisions made in the early embryo affect the final structure and function of the cerebellum. As one way of helping to understand this process, we are studying a childhood cancer of the cerebellum called medulloblastoma. We are also beginning to develop new genetic tools to allow us to study the physiology of

cells in mice. The second focus will be on adult stem cells, in order to understand how our body's natural stem cells could combat disease or injury. With both goals in mind, I feel this is the perfect place for me to make significant progress.

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