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At Work: Molecular Biologist Scott Keeney

Scott Keeney

Molecular biologist Scott Keeney studies the mechanisms by which cells make and repair breaks in their DNA, especially during meiosis (the cell-division process that gives rise to reproductive cells, such as egg and sperm).We spoke with him about his work in 2004, when he was the recipient of MSKCC's Louise and Allston Boyer Young Investigator Award.

I was the kind of kid who liked turning over rocks to see what was underneath. I've always been fascinated with biology, observing nature and learning from it. Thanks to this inclination, I gravitated towards science and engineering during high school in Baltimore, where I grew up. Also, my mom was a secretary in the Biochemistry Department at Johns Hopkins School of Public Health, giving me a chance to hang out in the labs there, which was my indoctrination into being a lab rat.

I went to Virginia Tech. for college. I had the opportunity to do some real laboratory research, and it didn't take me long to decide that this was what I

really wanted to do. The hands-on stuff in the lab was what I enjoyed doing most. When you look at what we do day to day in the lab, most of it is very tedious, so if you don't get some kind of aesthetic pleasure out of doing those tasks, then you're out of luck.

I knew I wanted to do academic research, so my career path, after graduating from Virginia Tech., was pretty obvious. At the same time, I wanted to move to California for various ill-defined reasons; so I applied to a number of grad schools there and ended up choosing the University of California, Berkeley, where I studied biochemistry.

My mentor at Berkeley, Dr. Stuart Linn, Professor of Biochemistry and Molecular Biology, pushed me toward studying DNA repair in mammalian cells. It was kind of a watershed time in the field because a more modern era was taking over. A lot of the genes encoding proteins involved in repair were being discovered, and in that 10-year-period, a year or so before I started, the field just completely opened up. It was exciting to be around in this period.

Yeast Envy

After receiving my PhD from Berkeley in 1993, I decided that I was going to switch fields to a very different kind of DNA repair, and change my focus from mammalian cells to yeast. I was always frustrated working with human proteins because it was more difficult using genetics to verify the relevance of one's work in living organisms. I wanted to switch to an organism where we could do both genetics and biochemistry, so I'd had serious "yeast envy" for a number of years.

A few years before finishing my PhD, I had given a presentation in our weekly journal club on a paper by Nancy Kleckner, a renowned molecular biologist at Harvard University. A comment by Stu stuck with me, to the effect that she might be interesting to be a postdoc with. When the time came, I applied to her lab and got in.

Nancy is one of the real intellectual movers and shakers in the field of meiosis and recombination. She's intellectually aggressive and working with her was a great challenge for me. As a member of her lab, I went to work on a system where a lot of genetics had been done. This meant that the framework was in place, but what was lacking was an understanding of the role of these genes and the proteins that were encoded by them. Eleven years later we still haven't made much progress on the biochemistry. My joke is I went to make it biochemically accessible, but the system turned me into a geneticist instead.

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My research there (and now) focused on homologous recombination during meiosis. Homologous recombination is essential for the proper segregation of chromosomes when cells divide to produce gametes (sperm or eggs in humans, spores in yeast). Through studies in yeast, several groups, including Nancy's, found that the introduction of double-stand breaks into chromosomes is needed to promote homologous recombination.

In essence, the cell deliberately damages its own DNA every time a reproductive cell is made. What was not known was how the cell made these breaks. My work in Nancy's lab culminated in the identification of Spo11 as the protein that cuts the DNA during meiosis in yeast. Subsequent work in my lab and others has shown that Spo11 is evolutionarily conserved, and that essentially every sexually reproducing organism uses a Spo11-related protein to start homologous recombination during meiosis.

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Starting at SKI

In 1997, after completing my postdoctoral fellowship at Harvard, I started my own lab, the Laboratory of Meiotic Recombination, at Sloan Kettering-Institute, where I am a member of the Molecular Biology Program. At first, it was both overwhelming and exciting. The first six months to a year was a baptism by fire, but I'm glad that I did it here because this place is very supportive of junior faculty. I've had some great mentoring relationships which have really helped me make the transition from postdoc to independent investigator. Ken Marians and Jerry Hurwitz were particularly helpful.

I started my lab to build on the work that I'd done at Harvard, continuing to study how meiotic recombination works in yeast. Taking this one step further,

we are also taking what we are learning in yeast, and, with the collaborative efforts of Dr. Maria Jasin, we are trying to understand how the meiotic process works in mammals. To accomplish this, we have cloned a mouse homolog of Spo11, using it to create mice with Spo11 knocked out. Our ultimate goal is to further understand the meiotic recombination pathway in mammals and the cell-cycle checkpoints that respond to defects in meiotic recombination.

The details in yeast and mice are different enough that by comparing and contrasting two organisms you get a more complete picture of what's going on. Sometimes you are sure things work one way, and it's not until you look at it in another organism where things are so obviously different, that you then say, 'Oh, that's how it works…I completely misinterpreted what was happening.'

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A Twist of Fate

More recently my lab started a new project in germ cell tumor biology. The reasons we gravitated in this new direction are two-fold. First, Memorial Sloan Kettering has tremendous resources related to this cancer. Second, and more personally, in 2001 I was diagnosed with a germ cell tumor.

Dr. George Bosl, Chairman of the Department of Medicine at Memorial Sloan Kettering, and Dr. Robert Motzer, a medical oncologist at the Center, were the clinical oncologists who were responsible for my treatment. I remember conversations with them in which they said that while much is known about the treatment and management of the disease, not a lot is known about its biology. George and I joked that once my treatment was done, we'd start collaborating. Then, about a year later, after my treatment was complete, we were actually able to come up with some research ideas, which I found quite satisfying.

It was almost as if I was fated to do this sort of research. My lab works on normal germ cell biology, so it was ironic that that's the kind of tumor I got. And the chemotherapy for germ cell tumors is all based on DNA damaging agents, which had long been of interest in my studies. In fact, during the course of treatment we actually were writing a paper that involved using one of the drugs I was taking.

Since my treatment concluded, I've been collaborating with George and Dr. Raju Chaganti, Head of the Cancer Genetics Laboratory at SKI. I'm still on the very steep part of the learning curve, but the resources here are helping me climb that curve.

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Potential Implications

I'm a basic scientist, which means that I'm interested in how things work. There is the hope that once you learn how things work, you can use that information to aid diagnosis or treatment. But that's down the road. First we would like to know the biological mechanisms that underlie the sensitivity of these germ cell tumors to DNA damaging agents.

Most of the tumors are susceptible to chemotherapy, though a small subset turn out to be resistant, so we'd like to understand the molecular mechanisms that underlie those differences between sensitivity and resistance. That might allow us to identify ahead of time patients that might be resistant to standard chemotherapy.

It's quite an honor to receive this year's Boyer Award for Basic Science Research. You're always pleased when your work is recognized by your peers. Those kinds of pats on your back are special. It's one thing when your mom is proud of you for getting a PhD. It's something else entirely when people who have been through the same process appreciate your work.

All of the science that goes on in my lab is a collaborative effort. Everyone has a different role, but everyone brings in ideas. I've been fortunate in having some terrific people choose to join me in my lab. My job is to bounce crazy ideas off of them. And eventually things get done, either because my crazy idea was right, or it was wrong but challenged somebody else to come up with a better idea.

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