At Work: Molecular Biologist Dirk Remus

Molecular biologist Dirk Remus is a leader in the study of DNA replication in eukaryotic cells. We spoke with him shortly after he began working at Memorial Sloan Kettering in late 2010.

As with many biologists, my love of science started with a fascination about the natural world. My mother told me that when I was in daycare, I would come home with earthworms from the playground stuffed in my pockets. Growing up in Cologne, Germany, I had limited exposure to nature, but I avidly read and watched documentaries.

Near the end of high school, I was accepted into a marine biology program at the University of Kiel on Germany's northern coast. Jacques Cousteau was my role model, so I imagined myself exploring the Baltic Sea in a submarine. But before I got too caught up in this dream, I had to complete a required year of service to the country.

In lieu of serving in the armed forces, I chose 15 months of social service at University Hospital of Cologne, which gave me the opportunity to observe surgeries and participate in laboratory research. It was a career-forming experience; the world of the laboratory drew me in.

When I finished, I was torn between the professions of medicine and research. I liked the thought of curing patients by being a surgeon, but I also enjoyed the idea of helping others by getting to the root of biological problems as a scientist.

Ultimately, I put aside my original dream of becoming Jacques Cousteau and enrolled in a molecular biology program at the University of Heidelberg.

The Magic of Molecular Machines

While at Heidelberg, I interned in the laboratory of Hermann Bujard, who was well known for developing a system that can switch genes on and off in cells. Through his teaching and other seminars, I found myself captivated by the interactions between nucleic acids (such as DNA and RNA) and proteins.

A large number of proteins and groups of proteins, known as complexes, are involved in copying and expressing genes. Protein complexes act like little molecular machines in cells. They swirl around and can bind to particular DNA sequences in chromosomes. In the case of DNA replication, binding triggers a chain of reactions that results in the copying of chromosomal DNA. It seemed like magic to me.

Around that time — and before I began my thesis project — I wanted to spend a few months abroad to experience everyday life in another country. I knew the United States had a great reputation for molecular biology research, and I was fortunately accepted into Michael Botchan's lab at the University of California, Berkeley, where I intended to intern for three months.

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Making Sense of a Complex Situation

DNA replication takes place in two general steps. First, protein complexes gather at a particular location where replication will begin, known as the origin site. Next, during the activation step, additional proteins kick into action to activate the complexes and start replication.

The origin recognition complex is the first protein complex to bind to DNA at the origin site. In the lab at Berkeley, we managed to build the origin recognition complex of a fruit fly, which was a first for a multicellular organism. My research progressed so well that Dr. Botchan suggested that I stay for a few extra months to turn the internship into my thesis. When two of my mentors from Heidelberg said they would serve as my official thesis supervisors, I agreed to stay on.

A few months later, molecular biologist Renato Paro — one of my Heidelberg mentors and an incredible supporter of my work — helped me arrange to continue working at Berkeley, with my PhD awarded from Heidelberg. So the three months that had turned into six months actually evolved into my entire PhD.

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>
> Dirk Remus
> Molecular Biologist

After purifying the origin recognition complex, I was intent on figuring out where this complex assembles on the chromosome. In bacteria, viruses, and budding yeast, replication begins at very specific DNA sequences. When we examined the fruit fly complex, we were surprised to find that it would bind to almost any DNA, not one particular sequence. It is quite promiscuous, actually.

To this day, we can't find a specific DNA sequence where the origin recognition complex assembles in humans either. Nonetheless, the replication process is highly regulated in humans, in order to prevent errors that can lead to DNA damage, such as breaks, incorrect numbers of gene copies, or changes in DNA sequence. Such errors can potentially lead to cancer or other diseases.

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Keeping the Genome Intact

When I finished my PhD in 2003, I wanted to create a system in the lab to study the complete DNA replication process. This would allow us to analyze how various complexes cooperate at a molecular level to copy the DNA contained in chromosomes. An early version of such a system had been

developed in budding yeast in the lab of John Diffley, a prominent DNA replication researcher at Clare Hall laboratories, part of the Cancer Research UK London Research Institute.

Moving to England was an interesting transition. I switched from fruit flies to budding yeast, in which the replication process (and my research) progressed more quickly. I also went from the diverse Berkeley campus to the fields at the edge of London, where scientists are highly specialized in research involving genome integrity — maintaining a healthy, properly functioning genome. DNA replication is an important part of keeping the genome intact.

I spent three years assembling all of the complexes involved in the first step of replication. Our most significant finding involved the enzyme helicase, which unwinds the two strands of DNA to ready them for replication. In cells with a nucleus, called eukaryotes, the helicase is made up of six distinct protein units, known as Mcm2-7.

Under an electron microscope, we saw that the Mcm2-7 helicase is actually made of two rings that encircle the DNA in opposite directions — revealing how replication can move in two different directions along the two strands at the same time.

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’The Best Place for What I Want to Accomplish’

I came to the Sloan Kettering Institute after my postdoctoral work to contribute to the rich tradition of DNA replication research. The institute is a mixture of my past lives, with a great concentration of labs working on aspects of genome integrity as well as a wide spectrum of other programs.

My lab is expanding on the system I established while in England. We’re adding additional components that are required to activate the complex involved in the first step of DNA replication. Scientifically speaking, this is the best place for me to accomplish my goals, surrounded by immense expertise and support.

Once we finally have a complete system to study DNA replication outside of cells, we can gain more insight into how DNA is accurately copied within the cells. When we understand that, we can begin to identify targets for stopping the out-of-control replication process involved in diseases like cancer.

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