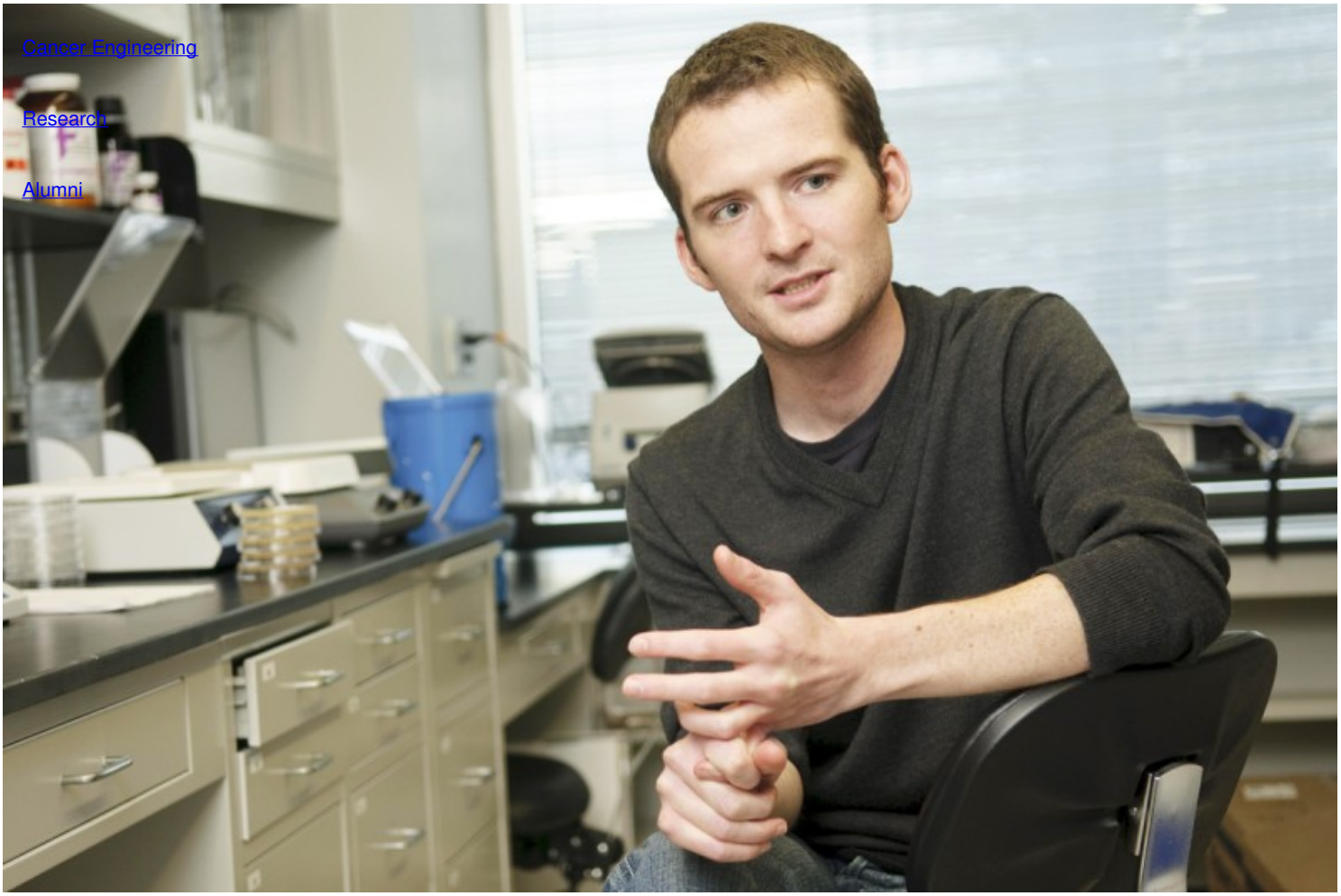
At Work: Molecular Biologist Iestyn Whitehouse



Molecular biologist Iestyn Whitehouse investigates chromatin structure and the function of ATP-dependent chromatin remodelling enzymes. We spoke with him soon after he joined Memorial Sloan Kettering in 2007.

I was born in a little town in the middle of England called Lichfield. At the time, my mother was a school teacher and my father was a cabinet-making carpenter. Like many people who become scientists, I have always been interested in how things work.

As a child, this meant that I was always taking things to pieces, which would frequently get me into trouble. In fact, my father has yet to forgive me for a couple of things I broke back then, including a much-cherished spring-loaded motor.

As I grew older, my father allowed me to help him with some of his work, which taught me the practical skills of wood and metal working. Pulling things apart and putting things together led to my interest in science.

With my interests growing, in 1995, I enrolled at the University of Lancaster, where I studied biochemistry with a secondary focus on genetics. I was fascinated by gene transcription, the process by which DNA passes genetic information to RNA — the first step in gene expression. By my third year I had my first laboratory experience, working in the lab of Alexander Gann. Alex inspired me with his enthusiasm and his ability to describe very complex phenomena in simple terms.

At the time, it was important for me to start to learn some of the basic concepts and practices of laboratory life. We were doing interesting work, studying the regenerative ability of newts, which can regrow lost limbs. I discovered that what had interested me as a child, pulling things apart and putting them back together to understand how they worked, was very similar, in a rewarding way, to what goes on in a lab.

An Introduction to Chromatin

When I completed my degree in 1998, I decided to study for a PhD, working with Tom Owen Hughes at the University of Dundee in Scotland. Tom was studying chromatin, which is the substance, together with DNA, RNA, and protein, that makes up a cell's nucleus.

If you take the DNA from just one cell and unravel it, it would stretch to more than two meters long. The cell uses chromatin to compact all of that material into its nucleus. It does so using hundreds of thousands of small protein discs around which small segments of the DNA is wrapped. The discs (called nucleosomes) are tightly packed together so that the entire genome can be squeezed into the nucleus.

Many cellular processes require access to this package. For example, when a gene needs to be "turned on," the cell needs to unravel chromatin so that the DNA can be accessed and transcribed. For some years many people thought that chromatin was a sort of irrelevant packing of material and when important processes needed to occur, the chromatin would be blown out of the way.

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Chromatin's Role in Accessing the Genome

Then, about ten years before I started to work in Tom's lab, it was discovered that chromatin actually plays an important role in regulating this process. It turns out that there are co-activator and co-repressor complexes, which work by altering chromatin structure. This alteration allows access to the genome.

When I started in Dundee, we were actually working on one of these co-activator complexes, which is called the SWI/SNF complex. We knew from previous studies in yeast that this complex, in association with chromatin, could influence transcription, but no one knew exactly how it was working.

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>
> Iestyn Whitehouse
> Molecular Biologist

Tom was an incredibly bright guy and a very creative thinker. He encouraged us to think creatively, which, in my opinion, is such an essential aspect of science. With his encouragement, I set out to try and understand how SWI/SNF complex works. And what we found was that this enzyme is able to shift the nucleosome discs along the DNA. By shifting them, the enzyme is able to alter the structure of chromatin and, in doing so, regulate access to the genome.

Knowing that I wanted to go on to do a postdoctoral fellowship, I decided to try to find a lab in the States. I didn't know much about the US, especially everything in the middle, so I applied to programs on both coasts, in Boston, Seattle, and San Francisco.

Luckily I ended up working with Toshi Tsukiyama in his lab at the Fred Hutchinson Cancer Research Center in Seattle. He was another young, smart principle investigator with a great deal of enthusiasm for science, which, for me, was great motivation.

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Budding Awareness in Budding Yeast

In Toshi's lab, I wanted to understand how enzymes like SWI/SNF worked in vivo, or within the organism. Fortunately, we had success studying them in budding yeast, which is a very simple organism. Budding yeast is great to work with: it is very amenable to genetic manipulation, and it has a relatively small genome that consists of only about 6,000 genes, many of which are very similar to ones found in humans.

My first success came studying a chromatin remodeling protein in budding yeast called ISW-2, which stands for "imitation switch-2." Like SWI/SNF, ISW-2 also repositions nucleosomes along DNA, but we had little idea of why and how frequently this happens within the cell. To address this difficult

question we needed to develop new genomic approaches.

We used high-resolution microarrays (tools used for profiling gene and protein expression in cells and tissues) to map where every nucleosome is located in a Wild-Type yeast cell. We then made a knock-out of Isw2 and looked to see how this pattern was changed.

From this analysis, we made several interesting findings. For example, we were able to show that Isw2 works at many thousands of places across the genome, where it repositions nucleosomes to prevent inappropriate transcription of the DNA.

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Sorting the Good Ideas from the Bad

When you are a postdoc, you have all these ideas — some that could prove to be good, some that might not work out. You know you can't work on all of them because you don't have the money, resources, or time to sort them out. These kinds of things eat away at you until you realize that if you had your own lab then you could do these projects. With these thoughts in mind, in 2007, I began to look for a place to start my own lab.

I considered more than 20 institutions, some in the UK and some in the US. Sloan Kettering Institute started at the top of the list because of the reputation of its Molecular Biology Program, and its work with genomic integrity.

I liked the fact that SKI was a big institution. I liked that there were lots of scientists working on a whole host of different projects that are not immediately related to what I was working on. And I liked the fact that there is a good retention rate here and there are lots of very knowledgeable young investigators. Ultimately, my decision to come to SKI was an easy one.

I have a number of research goals for my lab. We are currently employing the methodology that we have developed for Isw2 to study other chromatin remodeling factors, using genomic approaches to try to discover their roles. We have been able to uncover novel functions for a number of other enzymes, and we soon hope to develop a deeper understanding of how chromatin structures in general are able to regulate transcription of the genome.

We are also investigating the inheritance of chromatin states. Central to chromatin's role in regulating a number of basic cellular processes is its ability to adopt different states. These states may be differentiated by differences in nucleosome positions or post-translational modifications of the core histone proteins.

While particular chromatin states are associated with gene activation or repression, it is unclear if or how these states are passed on from one generation to the next. Consequently, we are developing genomic and biochemical approaches to investigate if particular chromatin states are maintained throughout the DNA replication process.

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