People & Ideas

Doug Hilton: At home with blood cell biology

Hilton's passion for blood makes his pulse race.

Doug Hilton found his home in science as an undergraduate, when he took a summer job in Canberra, Australia that introduced him to the biology of blood cells. It's a vast subject, but Hilton has explored much of it: from the cytokines that control blood cell differentiation (1) to the receptors that bind those cytokines (2), the signals those receptors set off within cells (3, 4), and the feedback mechanisms that help to regulate them (5).

As a graduate student with Nick Nicola, Hilton worked to identify factors controlling blood cell growth—a project that unexpectedly led to the identification of leukemia inhibitory factor, or LIF (1). After a two-year postdoctoral stint studying the erythropoietin receptor with Harvey Lodish at MIT (2), Hilton returned home to Australia. There, a search for factors regulating cytokine signaling uncovered the suppressor of cytokine signaling (SOCS) family proteins (3, 4).

Having recently been appointed Director of the Walter and Eliza Hall Institute in Melbourne, Hilton put off adding the finishing touches to his new office to talk with us about his career, and his scientific and personal interests.

> "LIF turned out to be a big deal, but not for the reason we suspected."

HOME EARLY

You've spent most of your career in Australia?

I suppose I haven't ever strayed too far from home. [laughs] I still live in the town in which I grew up—although I did live abroad for two years while I did my postdoc at MIT. But I've always been comfortable here, a small suburb about 30 kilometers from the center of Melbourne.

It was quite early on in my career, too, that I found a research subject with which I felt at home. I've always been interested in the genes that regulate blood cell formation, even as a third-year student in college. I remember taking a laboratory job over summer vacation where I worked on the same types of questions that I'm still working on 25 years later. I continue to find them fascinating. My work has taken a few twists and turns, though. Early on my research focused on cytokines, their receptors, and signal transduction. Now I'm interested more generally in the genes that regulate blood cell production.

So right away as a graduate student, you knew what you wanted to do?

I completed my undergraduate studies at Monash University in Melbourne, and then switched to the University of Melbourne specifically to work in Nick Nicola's laboratory because I wanted to study cytokines. I also ended up working pretty closely with Don Metcalf, whose laboratory abutted Nick's, and with whom Nick collaborated closely. Don and Nick had just finished purifying the cytokine G-CSF, a white blood cell growth factor. There was some uncertainty about how many other cytokines regulated blood cell production. So I trained as a protein chemist, and tried to identify these other factors. I ended up doing chromatographic purification of different factors, and that's how we purified leukemia inhibitory factor, or LIF.

LIF turned out to be a big deal, didn't it?

Yes, but not for the reason we suspected. We purified it on the basis of its function on a particular blood-derived cell line. But as it turned out, the real excitement around LIF is that it is the factor that stops mouse embryonic stem (ES) cells from differentiating, which allows you to manipulate them genetically in culture. The idea of looking at whether LIF might be responsible for keeping ES cells undifferentiated came about from a conversation at a meeting in Europe, between Nick Gough from Melbourne and Lindsay Williams from Heidelberg in Germany. They noticed that the way LIF eluted from an anion exchange column resembled a factor that Williams was trying to purify from embryonic stem cell lysates. Based on that rather tenuous possibility, we sent him some cloned recombinant LIF. His laboratory put it into their culture systems, and the rest is history.

Doug Hilton

HOME AWAY FROM HOME

How did you end up doing a postdoc with Harvey Lodish?

I suppose there was an expectation at that time in Australia that everybody should go abroad for their postdoc. He is obviously a fabulous protein chemist, and I thought his laboratory would be a good place to learn some molecular biology; I had trained almost exclusively as a protein chemist and didn't know my way around a plasmid. I ended up with a couple of decent papers from my work there. But more than anything else, just working in his laboratory, in the environment of MIT, was eye opening for a small-town boy like me.

Text and Interview by Caitlin Sedwick
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How so?

Looking back, I think I was very young and naive. I remember walking into Harvey's office on my first day. He said, "What do you want to work on?" And I was floored because I hadn't really given it that much thought.

I was sharing a bench with an older Israeli postdoc. He was a lovely guy, but every morning in my first five weeks I would come in and he would say to me, "What are you going to do?" I would give him an idea, and he would say, "That is rubbish." [laughs] I eventually came up with some ideas, collaborated with the other postdocs, and ended up having a great time.

But you soon returned to Australia?

My wife and I had bought a house here before we went to Boston, so we had a home to come back to. I still wanted to work on the molecular regulation of blood cells, so I came back as a kind of junior laboratory head within Don Metcalf and Nick Nicola's unit.

In Australia the tradition has been to make a gentle transition to running a laboratory. You can still collaborate with your mentors if you like; there's no imperative to show you're independent by working on a completely different problem. It's a different way of doing things than other places, and I think people recognize that can be a good way to work. Initially Nick supported me on his grants, but when I returned I started bringing in more and more money and eventually became financially—and intellectually—independent.

HOMING IN

This was when you identified suppressor of cytokine signaling (SOCS)?

A lot of work had been done on the positive mediators of signal transduction, and we knew that while many cytokines are beneficial, they can produce some ill effects when they're present in excess. So, we presumed there must be negative feedback signals that tempered cytokine action. I had a very talented postdoc, Robyn Starr, and we set out to identify them. Very quickly we pulled out an extraordinarily powerful inhibitor of signaling and showed that it was part of a family of negative feedback regulator proteins. It was just one of those magic moments.

Since then, I've been lucky to continue with that story, which has turned out to have quite some depth to it. By homology we found eight members of the family that had SH-2 domains, and also this protein module at the C terminus that we named the SOCS box. Then we found a whole suite of other less-related molecules that also contained a SOCS box, and we found that this domain is what couples these proteins to E3 ubiquitin ligases. The canonical SOCS proteins seem to regulate virtually every cytokine that acts through the Jak/STAT pathway, which generated lots of interest from people in different subfields of cytokine action. It's also taken us down some interesting paths; for example, we found that SOCS-2 regulates growth hormone signaling, so when we knocked it out the animals had gigantism.

> "The identification of SOCS proteins... was just one of those magic moments."

What paths are you taking now?

In my laboratory, we're working on three or four genes that are related to some pretty severe stem cell defects. At least one of these genes regulates Jak/STAT signaling, which is taking us back to cytokine signaling again. We're also interested in transcriptional networks that regulate lineage commitment in stem cells.

Six months ago I was appointed Director of the Institute, which is located in the wonderful research precinct of Parkville near the center of Melbourne, so lately I've been occupied with that. But I am hoping things will soon settle down a little bit and let me get back to the laboratory some more. We'll see what happens, after I come back from holiday with my family.

Where are you going on holiday?

My wife and I love to take our two kids out camping and hiking, so we're taking a trip to do some of that. I like tramping about outdoors, partly because it lets me pursue my hobby, moth collecting. There are around 30,000 moth species in Australia, and probably two thirds of them have never been described or even collected. So I got these wonderful insect cabinets on loan from the National Insect Collection in Canberra. The idea is that I fill the cabinets and when I die, they go back to the Collection. I bring my net and collecting kit with me on our family hikes, and I fairly often come back with something new.

1. Williams, R.L., et al. 1988. *Nature.* 336:684–687.
2. Hilton, D.J., et al. 1996. *J. Biol. Chem.* 271:4699–4708.
3. Starr, R., et al. 1997. *Nature.* 387:917–921.
4. Alexander, W.S., and D.J. Hilton. 2004. *Annu. Rev. Immunol.* 22:503–529.
5. Majewski, I.J., et al. 2008. *PLoS Biol.* 6:e93.

Hilton's hobby decorates a laboratory monitor.