

Hide Ploegh: Immunologist, journeyman

From the moment he finished his Ph.D., Hide Ploegh has been a wanted man. Invited to join one institution after another, he always packed with him his keen interests in the immune system.

Alternating between positions in Europe and the U.S., Hide Ploegh has studied immunology from all sides of the equation and on both sides of the Atlantic. As a bicontinental graduate student, Ploegh first entered the competitive world of immunology by cloning a cDNA for a human major histocompatibility complex (MHC) molecule (1)—one of the glycoproteins that present antigens on the cell surface.

Since then, his focus on MHC has not wavered, although it has broadened. In addition to MHC synthesis and trafficking (2), Ploegh has also studied pathogens that hide by impairing MHCs (3) and the cellular protein degradation pathways that provide MHCs with their antigens, including the ubiquitin–proteasome system. He has developed new chemical tools to study proteasome activity and the roles of lysosomal and ubiquitin-specific proteases (4).

In 2005, Ploegh joined the Whitehead Institute, whose members hold faculty appointments at MIT. He recently discussed with us the career path that led him there, what he sees as some of the drawbacks of doing research at a medical school, and his zest for fishing and science.

POSTDOC IMMUNITY

What first piqued your interest in immunology?

As an undergrad, I read an interview in the Dutch equivalent of *Ladies' Home Journal* with one of the leading Dutch immunologists, Jon van Rood. I wrote him a letter asking whether I could work in his lab, but I never got an answer.

At the time, I was working for my

undergraduate advisor, whose interests were in bacterial cell walls and membrane structure. He had some financial resources to allow his graduate students to go abroad to learn techniques and bring these back to his lab.

Since his two graduate students weren't particularly interested in this opportunity, he turned to me. He wrote letters explaining the purpose to a number of investigators, mostly in the U.S. One of the few who wrote back in the affirmative was Jack Strominger, who was working at Harvard on bacterial cell wall synthesis.

To my surprise—this was before Internet days—when I arrived, it turned out that half the Strominger lab was working on the biochemistry of transplantation antigens. Then and there, it became clear to me that that would be a great topic to return to. My six-month visit concluded with an agreement that I'd return as a graduate student and work on transplantation antigens.

For that, I got some financial support from the Dutch government. And who should be sitting on the selection committee but van Rood. As luck would have it, he even became my formal thesis advisor. I did the practical work for my graduate studies in Jack Strominger's lab, but defended my thesis in the Netherlands.

In 1980, I left the Strominger lab and took my first independent position.

You never did a postdoc?

Correct. My thesis project consisted of cloning cDNA for a major histocompatibility antigen. I think that work attracted the attention of Klaus Rajewsky, who was the head of immunology at the University of Cologne in Germany. He wondered whether I would be interested in taking a junior group leader position at that institute.

What was it like, running a lab directly after your Ph.D.?

I think the first students you work with suffer the consequences. You have no ex-



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perience leading a lab, you make all the mistakes that you can make. Objectively speaking, not much was produced, but I do think I learned how *not* to run a lab.

RAMBLING MAN

But you didn't stay there long. In fact, you rarely seem to stay at any one place very long.

No, my next slot was at the Netherlands Cancer Institute. I was invited to join in 1984 by Piet Borst. He had just become the institute's director and was interested in infusing some fresh blood. I led a group in the cell biology and biochemistry of antigen presentation.

In '92 I was approached by Susumu Tonegawa. He asked whether I might be interested in moving to MIT. That was an opportunity that I couldn't turn down.

I stayed there until '97, when Harvard Medical School wanted to know if I was interested in moving there. I had gotten to know several colleagues there when we served as editors for *Immunity*. I also had a very strong interest in the didactic missions of school, and they were looking for a person to take charge of the graduate program in immunology.

That lasted until 2005, and then I was recruited to Whitehead.

How was returning to the States in the early '90s?

I think the scientific climate in the U.S. to this day is more vibrant and lively than most places in Europe. I'm not dingy Europe in the least, I enjoyed every moment

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Ploegh and fishing partners Tom Look (middle) and Fred Alt (right) enjoy fishing for ideas and the occasional bluefin tuna.

I lived in Amsterdam, but I think the intensity with which people pursue their science is just on a different level. 15 years ago, that was certainly true, although the difference seems to be less pronounced today. The resources available, the intellectual firepower, the Boston academic climate with MIT, Harvard, and Harvard Medical School, it's just beyond compare.

You seem to have an affinity for the Boston area.

Yes, I do. As it happens, I like to fish. I would say Boston is the saltwater fly-fishing capital of the world. I co-own a little fishing boat, *The Rampage*, with my Harvard colleague, Fred Alt. We go out for striped bass, bluefish, bluefin tuna with varying degrees of success.

What made you decide to leave Harvard Medical School for Whitehead/MIT?

There are several issues associated with working at a medical school. Many have hospitals affiliated with them, and the economics and logistics of that imposes a certain organizational structure. The primary mission of a medical school is naturally to

train doctors. To give you an example, I had to talk to the head of our public affairs department two years in a row before the annual Dean's report began highlighting the various graduate programs. It would showcase the medical students and the M.D./Ph.D. students, but the graduate programs seemed like an afterthought.

I felt that the Whitehead/MIT environment was more curiosity driven and less concerned with medically relevant research. There's nothing wrong with that in principle, but for me, it's like the difference between Italian and French cuisine. They're both outstanding if properly prepared, but some people prefer French, others, Italian. It has nothing to do with quality per se, just a difference in style.

My recent research interests are also better aligned with what MIT is really good at: chemistry, materials science, engineering, and so forth. Lately, I've become more and more interested in engineering-based approaches to biological questions.

If you enter the building where the mechanical engineers are, and you see the posters on the wall, you'll see so much

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ingenuity, such diversity of approaches. I'm always struck by the eagerness of faculty in other departments to get involved, get their hands dirty, think about possibilities for joint projects. There's a growing awareness that interdisciplinary interactions—where one can combine, say, physics with biology—can produce so much more. Compare that with your typical medical school, where everything of necessity is focused on either basic biology or translational stuff.

WHERE THE PASSION LIES

In all your locales, one constant has been your interest in MHCs.

Yes, that is perhaps unusual. Most graduate students change tack when they do a post-

doc and maybe again once they become independent, but I haven't really felt the need. The work I started as a graduate student still continues today, in a different incarnation, of course. Ever since I started working on these MHC products, I've been interested in how they're put together from their building blocks, how they travel from the site of synthesis to their destination.

Another unusual aspect of your career is that you were always invited to your next position.

True, I've never even applied for a job. I have been in a very privileged position, but I think a big part of it is just being enthusiastic about what you do.

What I've learned is that the single most important thing is passion. You also have to take pleasure in the details: the duplicates of a calibration curve falling right on top of one another or bands on a gel coming out razor sharp, in addition to real discoveries. To this very day, there's almost nothing I'd rather do than look at autorads. Get a life, right?

And why do you have such a passion for research?

It's the most exciting profession I could imagine. It's like a stem cell, continuously self-renewing. The next day is almost always as exciting as the preceding one.

It's hard to imagine finding a working environment that is so dependent on the social aspects. Many students are under the mistaken impression that being a scientist means being somewhat of a recluse. Some future medical students think that because they see patients, they get a richer experience of interpersonal interactions. Sure, if you enjoy dealing with HMOs rather than working with your peers, debating puzzles, and thinking creatively... But I know which side my bread is buttered on. **JCB**

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4. Schlieker, C., et al. 2007. *Mol. Cell*. 25:677–687.