



## Whitehead's newest Member studies the ever-changing battle between pathogens and your immune system

Sit down and chat with Hidde Ploegh, and here's what immediately strikes you:

He's doing world-class research in immunology. He's very engaging. And he's wearing basketball-player-sized shoes that are bright, bright red.

The shoes make a statement that highlights a key theme in his science: "If science isn't fun, it's not worth doing," he says.

That attitude is just one of the reasons why Whitehead is so lucky to enlist Ploegh (rhymes, coincidentally, with "shoe") as its latest Member.

Ploegh will be setting up his lab at Whitehead this summer, after seven years running Harvard Medical School's immunology program. Before that, he spent five years as a Professor of Biology at MIT, working mostly at the Center for Cancer Research.

"We have a biblical situation here, welcoming back a prodigal son," says Whitehead Member Susan Lindquist, who helped to recruit Ploegh. "There is much merriment and rejoicing."

"It's great that Hidde will be joining the Whitehead family," adds Interim Director David Page. "He's among the world leaders in his field, and I look forward to many upcoming collaborations between him and other Whitehead faculty members."

# Ploegh season

by David Cameron



RICHARD HOWARD

## Hidde Ploegh

**BORN:** 1953, the Netherlands

**PHD:** 1981, Leiden University

**RESEARCH:** Biochemistry of antigens and how they interact with the immune system (antigen presentation)

**UPCOMING WORK AT WHITEHEAD:** Focusing on flu and herpes viruses, and the processes by which they evade the immune system

**PAPERS:** Co-authored more than 300

**SELECTED HONORS:** Correspondent of the Royal Dutch Academy of Sciences, National Institutes of Health Merit Award, Avery-Landsteiner Prize, member of the American Academy of Arts and Sciences

**HOBBY:** Fly fishing

**FAMILY:** Anne (spouse, above), Sophie and Anna (children)

**FAVORITE MOVIE:** Shohei Imamura: "The Ballad of Narayama"

**FAVORITE MUSIC:** Randy Newman, Schubert

## Making a move

Ploegh will be sorely missed at Harvard Medical School, where he transformed the graduate program in immunology, says Laurie Glimcher, Professor of Immunology. "He cares about the students and about teaching, and is a fine teacher himself as well as an outstanding and innovative scientist," she emphasizes.

But what would prompt a scientist who has such a comfortable position at Harvard to go through all the hassle of closing shop and moving his lab across town?

"I'm attracted to the intimate, collaborative atmosphere at Whitehead," says Ploegh. "I've been deeply impressed by the spirit that pervades the Institute." Noting the thousands of Medical School faculty, he adds that "I look forward to actually knowing everyone that I'll be riding the elevators with."

He already knows many of them. He happens to live next door to Whitehead Member David Bartel. And since 2001, he has served on the Whitehead Scientific Advisory Board. In that role, Ploegh has attended and enjoyed a number of the Whitehead annual scientific retreats, at which all research staffers spend a weekend in New Hampshire describing their current projects to each other.

## Immune cat-and-mouse

Ploegh studies the mechanisms by which the human immune system responds to pathogens, those nasty foreign invaders that sneak into our bodies when, say, the guy next to you in the elevator sneezes and forgets to cover his mouth.

"Someone sneezes, you inhale, the virus hits your lungs and establishes an infection, and your immune system is called into action. That's where my research begins," he explains. "What happens when the infected cell is present? How is the infected cell, with all the proteins that it contains, translated into a signal that the immune system can interpret?"

As Ploegh puts it, these invaders are not stupid. They try to evade the immune system, engaging it in a kind of measure/countermeasure battle. The immune system manages to eliminate most of the pathogens yet leaves behind some remnant that it can't

detect. It's this remnant that can gain the upper hand.

This is how, for example, HIV works. It mutates too quickly for the immune system to keep up. As soon as a suitable immune response would have been made, there are already new mutants. The virus selects for mutations that the immune system cannot see. And when this element of the virus starts proliferating unimpeded, the problem becomes serious.

"My lab is interested in the countermeasures that these viruses deploy," says Ploegh. He has been working on members of the herpes virus family and plans to begin studying the influenza virus once he settles in at Whitehead.

Over the last two decades, Ploegh's research has contributed in many ways to our understanding of the immune system. For example, he helped elucidate how a certain set of glycoproteins—molecules that help the immune system recognize invaders—are put together and are delivered to the right destination to help an immune response kick in. He discovered a new mechanism by which viruses evade the immune system. Lately Ploegh and his coworkers have been interested in generating the chemical tools with which to probe a family of enzymes called proteases that are a key component of the ubiquitin-proteasome system, one of the major mechanisms by which proteins are degraded in cells.

Ploegh's 300-plus research papers include the June 24, 2004 cover story for the journal *Nature*, which described one of the mechanisms by which the immune system eliminates misfolded proteins.

But he warns that "this insistence on always publishing in glamorous publications can be detrimental to the motivation of graduate students and postdocs. They get the impression that it's the only thing that matters."

When a lab really should celebrate, Ploegh says, is "not when it's accepted into some top-flight journal, but when the actual discovery is made. That's the best part."

And the most fun.