# Ari Helenius

European institutions don't kid around with mandatory retirement and, for better or worse, the renowned Helenius lab, now at the Eidgenössische Technische Hochschule Zürich (ETH Zurich), will fold up forever in the fall of 2014 when Ari Helenius turns 70. Helenius moved to ETH Zurich in 1997 after 16 years at Yale where with Ira Mellman he was half of the merged "Melenius" lab, which pioneered research on the endosomal pathway. Before that, Helenius was in Heidelberg, Germany, with his brother-in-law, Kai Simons, as one of the founding investigators at the fledgling European Molecular Biology Laboratory (EMBL). Before that in his native Finland, Helenius was first pulled into research by Simons while Helenius was still an undergraduate at the University of Helsinki. Forty-three years later, his workload is as heavy and his working day as long as ever, but Helenius admits, "I'm having a hard time thinking about leaving science. Right now I have a problem with long weekends."

One long weekend on the Helenius calendar is already taken this December when he will give the Keith Porter lecture at the ASCB Annual Meeting in San Francisco. The lecture is still to be written, but it is no great guess that his talk will address the ancient dance between eukaryotic cells and invading viruses.

Viruses are the threads that run through his career and yet Helenius considers himself a cell biologist, not a virologist. Only recently has Helenius turned on his old friends, the viruses. For the first time, he is officially treating them as pathogens and searching for translational applications to frustrate viral infection. Before that, Helenius regarded the viruses chiefly as elegant tools to pry into host cells, dissecting membranes, unraveling trafficking, and tricking cells into divulging the secrets of protein folding and quality control. Now viruses are the enemy at the gates.

## Greeks and Trojans

Helenius turns to Homer's epic of the Trojan War for his metaphor. "I usually start my presentations with a picture of the Trojan horse deposited outside the city. The horse contains a lethal payload but in order to infect the cells, it needs the help of hundreds of Trojans to carry it inside and open it up. We are interested in those Trojans. Who are they, and can we stop them from responding in this way?"

To identify the Trojans, Helenius and collaborators are using small interference RNA to identify the hundreds—perhaps thousands—of host cell proteins that vaccinia, influenza, and other viruses co-opt. Nearly all antiviral drugs today work by attacking or inhibiting the viral "Greeks" emerging from the horse, says Helenius who proposes a different fighting strategy. "The problem with existing antiviral drugs is that they target the virus itself and the virus becomes resistant. This is true for HIV and influenza. But if you target a specific cell function, point mutations don't help the virus. You have to find some genes or proteins which the virus absolutely needs but which aren't essential for the cells."

Much can be accomplished in two years, but once his lab winds down, Helenius hopes that his science will go on. He will hand over his systems, materials, and considerable know-how to collaborators and departing lab members. Along with a grudging admiration for viruses, departing students and research fellows leave the Helenius lab with a foot-tall plastic garden gnome, a garishly painted figurine with a pointy hat and dopey expression. Helenius calls his gnomes "Alfreds," in honor of Alfred Nobel, and carefully numbers and engraves each one himself.

## The Faint Line

Maurizio Molinari has Alfred #90. His wife and fellow Helenius lab alum, Carmela Galli, has Alfred #89. Their Alfreds are prominently displayed in the Molinari laboratory at the Instituto di Ricerca in Biomedicina (IRB) in Bellinzona, Switzerland. "It's the first thing I see in the morning," says Molinari of the Alfred in his IRB office, "and the last thing when I go home at night."

He learned many things in the Helenius lab, says Molinari. There were the Finnish drinking customs and drinking songs. Lab celebratory dinners began by quickly downing a glass or two of vodka and loudly singing the never-translated songs, all on empty stomachs. It made for lively parties. And there was Helenius himself. "He's massive, both scientifically and as a physical body," says Molinari. "He's a huge man with

Credit: Peter Walter

*Ari Helenius with Peter Walter's parrot, Beaker.*

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a beard. He has a sense of humor that not everyone understands. If you understand it, he's very funny. If you don't, you might find it a little intimidating but he's really a very nice person."

What Molinari learned most clearly from Helenius was the potential significance of even minor details. At ETH Zurich, Molinari worked on the structure of disulfide bonds involved in protein folding inside the endoplasmic reticulum (ER).

Molinari recalls the time he showed Helenius a diagonal gel film. Molinari was proud of having mastered the difficult technique and was delighted to point out the clearly visible diagonal of nascent, radioactively labeled polypeptides that did not have any disulfide bonds between cysteines. "But Ari was not looking at my finger showing the black traces. He was looking just above and asking, 'What is this?' And I said, 'No, Ari, not there. Here below, look how sharp, how nice ..." Just above the nice sharp lines, Helenius pointed again to a very faint line that Molinari had not noticed. These turned out to be chains acquiring intramolecular disulfides during the synthesis. "This faint line was published in *Nature* in 1999," Molinari reports. "I had missed the trace, but I have learned to look at details, which makes the difference."

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## Sputnik Hysteria

Helenius says he owes his science career to the excellence of American high school chemistry, his college girlfriend, and the Semliki Forest virus (SFV). From a farming community in northern Finland, Helenius was sent as an exchange student in 1961 to a high school close to Wilmington, DE. He arrived in the wake of the Sputnik hysteria when American science education jumped (temporarily) to the top of the national agenda after the Russians beat the United States into space with the first satellite. His chemistry class in Kennett Square was a blast—two hours a day, every day, with a heavy emphasis on bench work. Helenius went home to Finland, fluent in English and on fire to study chemistry. But after another two years in school and a year of military service, he found chemistry at the University of Helsinki a tepid rehash. He found solace in biochemistry courses and his new girlfriend (now wife), Majlen Simons. Majlen had a brother, Kai, an MD just back from a research fellowship at the Rockefeller University, the epicenter of the cell biology earthquake in the 1960s. Kai Simons needed a biochemist and recruited his soon-to-be brother-in-law for his soon-to-be-notable membrane protein lab.

It was the start of a 13-year scientific partnership that continues today as an extraordinarily tight family partnership. Raising their five children cooperatively in Heidelberg, the Helenius and Simons families shared a house, a home childcare provider, and a strict rotation in which the adults took turns to be home by 4:00 pm, no excuses. "My day was Thursday," Helenius recalls proudly. Their families still spend much of the summer together, vacationing in a compound of houses on an island in the Gulf of Finland.

The original Simons-Helenius scientific impetus came in a Helsinki cafeteria in 1969 during a conversation with Leevi Kääriäinen, another Finnish postdoc just back from New York. He told them about the wonderfully tractable SFV, an animal virus discovered in a Ugandan forest. It had a central capsid protecting a single RNA molecule, all surrounded by a lipid bilayer. Simons realized at once that here was a possible model system for in vivo and in vitro studies of membrane composition, structure, biosynthesis, and mechanics. It started Simons down a long research road that eventually led to his celebrated lipid raft model of membrane microdomains. In the short run, SFV led Helenius to his doctoral thesis on isolating integral membrane proteins by manipulating their solubility with detergents. The lab's early papers based on the SFV membrane model led to an invitation for Simons *et al.* to join EMBL in 1975. Over time, Helenius found himself working on his own projects in the Simons lab, using a variety of viruses to explore endocytosis and membrane fusion, in particular looking for sites where imported molecules including viruses were sorted, processed, and transported for degradation or recycling. He initially called them "prelysosomal compartments," and later endosomes.

## The Melenius Lab

Mellman and Helenius are the names most closely associated with the endosome story. The Melenius lab came together through a subterfuge engineered by George Palade, the Nobel laureate who was trying to build up his cell biology "division" at Yale. At the time, Mellman and Helenius had yet to meet but were already well aware of each other. They were following different approaches, but their interests—and the implications of their papers—seemed to be converging. Palade sealed the Yale deal by telling each that the other had

already agreed to come. Palade also said that he had no objection to a merged lab.

To talk about such a merger and to seal the deal on a personal level, Mellman flew to Heidelberg to meet the Helenius family. Helenius says that the prospect of moving to Yale particularly unnerved his daughter, who was nine at the time. Her name is Ira, the Finnish form of Irina. "She said she could not go to live in the United States," her father recalls, "because she could not live in a country where her name was a boy's name." In the end, Ira Mellman convinced Ira Helenius by promising the girl a puppy from his golden retriever in New Haven. For his part, Helenius points out that Mellman's golden had no puppies when they arrived, and that Majlen had to go out and buy Ira and her older brother, Jonne, their own retriever.

That was the first in a line of Helenius family retrievers, a position currently held in Zurich by Emil, who takes Ari and Majlen hiking or skiing on weekends in the Swiss mountains. Ira Helenius is now an associate professor in Medicine at the University of Virginia Medical School in Charlottesville where she lives with her husband and their five-year-old daughter, Maija. "A bit far away unfortunately," says her grandfather. Closer to home, his son, Jonne, is a research biophysicist working in atomic force microscopy in an ETH Zurich department located in Basel.

Of their time in New Haven, Mellman, who is now at Genentech in South San Francisco, fondly remembers a partnership of laboratories but also of families. "Our spouses got along so well," says Mellman, and the two Helenius kids became the virtual older siblings and actual babysitters of the three much younger Mellman children. There also were the cross-cultural rituals of the Melenius lab, such as the vodka toasts and Scandinavian drinking songs. Mellman recalls, "Ari built a sauna in his backyard and virtually every Sunday we'd get together there to plan the week's experiments. With drinking and smoking cigars it meant that by Monday we'd entirely forgotten what we'd talked about the night before."

## Critical Thinking

It made for a great partnership, says Mellman. It also made for breakthrough discoveries about the "prelysosomal compartments," which they would name "endosomes" and in which Helenius would unravel many of the key steps in virus entry. Their research programs pursued separate tracks but in their 16 years as one lab, Mellman says the joint system paid enormous dividends. "Our lab groups were joined at the wrists and ankles and that was a major advantage," Mellman says. The payoff came from having a large, diverse group working on a wide range of problems but still listening to each other's progress reports. That's the model Mellman tries to foster at Genentech.

Mellman has never completely understood the Helenius devotion to viruses, which has persisted long after new techniques allowed most endocytosis studies to work directly with eukaryotic models. But he points out what makes his friend such a singular scientist—his uncanny ability to see clear significance in faint details. "Ari thinks bottom up rather than top down. And at the bottom, there's always a virus. And you can't say it hasn't worked. He is one of the most creative people I know."

Fashions come and go in science and if viruses went out of style, they have been coming back of late, says Helenius, as new technologies give them new powers. "When I started in the lab of the high school in '61, the big new thing was the graduated pipette that they'd bought so instead of doing one ml, five ml, 10 ml, 20 ml, you could actually pipette 2.2 ml. That made a big difference in how experiments were done," he says. In contrast, his ETH Zurich lab recently finished a preliminary experiment—"a figure 1," he explains. "We had 3 million pipetting steps, all done by robots. All the tissue culture, everything, all was automated. The readout was done by microscopy. We took 1.2 million pictures. Then they were automatically analyzed by computer and out came a big list of data, evaluated and statistically tested. And that was just the first part of the project."

The rush of mathematicians and engineers into biology is exhilarating and a little humbling, says Helenius. "This is where it's going and I have no problem with that. It's incredibly exciting. It's also very expensive and it requires the expertise of many, many people. I used to have a philosophy that I taught everybody in my laboratory: Don't believe anything you don't understand because it's dangerous. I had to give up on that principle long ago."

But it's an exciting time for classical cell biology, says Helenius. There are so many new tools available, for example, the hundreds of inhibitors that are available almost off the shelf. New methods, old models, they have a lot to tell us yet.

*—John Fleischman*

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