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People & Ideas

Ari Helenius: viruses under surveillance

At his headquarters in Zurich, Helenius uses imaging technology to track the movements of viruses.

As any CIA operative will tell you, the best defense is to know your enemy. Ari Helenius, veteran virologist, has spent the majority of his career learning the sneaky infiltration tactics of human and animal foes such as influenza, vaccinia, and herpes simplex virus.

And their tactics are many and varied. Helenius learned that Semliki Forest virus, for example, enters cells via endosomes and bursts into the cytoplasm when the endosome's acidic environment triggers fusion of the virus's membrane with that of the endosome (1). Vaccinia virus, on the other hand, first surfs the length of filopodia to the cell surface and then impersonates cell debris, tricking the host cell into gobbling it up (2).

"The question became, 'How does a virus enter its host cells?' And that's what I'm still working on."

Helenius's work on viruses has also led him into studies on more general aspects of cell biology. He has published extensively on the topic of endocytosis (3) and also protein folding (4). Helenius is Professor of Biochemistry at the Federal Institute of Technology (ETH) in Zurich, and was the 2007 recipient of the Marcel Benoist Prize, coined the "Swiss Nobel".

STATESIDE TRAINING

How did you get started in science?

At the age of 17, I was chosen as an exchange student to go to the States. There was a program called the American Field Service. It was originally started by the Quakers, who had set up an ambulance service during the First and Second World Wars.

After the Second World War, they decided not to dismantle their organization but instead to start something that might help prevent future wars. The exchange program brings high school students from all around the world to study for one year in the States and to live with American families. I think 70 or so students are chosen from Finland every year. I went in 1961 and stayed with a family in Pennsylvania.

It was an interesting phase for American education, because the Russians had recently succeeded in launching the Sputnik satellite, and the Americans were shocked by this event and poured huge amounts of money into science education.

I happened to be there at just the right time. My high school education in chemistry was extremely good. I was surrounded by a very enthusiastic group of students, and had a great teacher. I was totally taken by the whole thing, and decided to become a chemist.

So I think the key thing that got me started in science was the excellence of the American high school education.

You don't think this would have happened had you stayed in Finland?

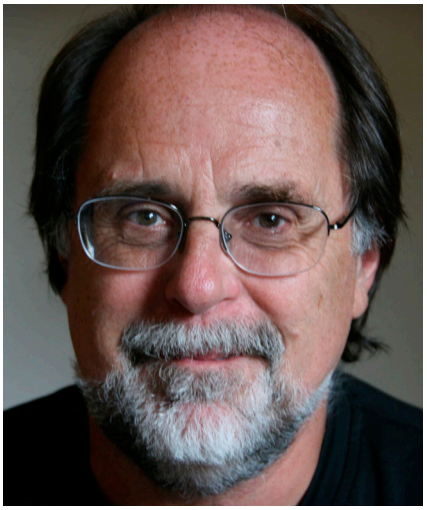
No. I was always very interested in nature, but nothing scientific. I grew up on a farm in Northern Finland and I was fixed on becoming either an agronomist or a forestry major, because that's what one did up there. Also, the science teaching in school was uninspiring and out-of-date, so I was really turned off by that.

Where did you go to University?

I went to Helsinki University to study chemistry, but I was disappointed because I had learned so much in the States and felt that I wasn't learning anything new. So I switched to biochemistry, which was new to me and more challenging.

Then an interesting thing happened. In my second year of studies I had a girlfriend Majlen (who is now my wife), whose brother, Kai Simons, was a postdoc at The Rockefeller University in New York. He returned to Helsinki after a year and started to put together a research group. He convinced me to join him.

Kai was a few years older than me, and I became his first undergraduate student and started working day and night in his laboratory. The work went well, and I ended up working with him for 13 years, first as an undergrad, then as a PhD student, then as a post-doc. In 1975 we moved together to the newly founded European Molecular Biology Laboratory (EMBL) in Heidelberg.



Special Agent Ari Helenius

It was like a family enterprise. Kai and his wife Carola had three children, and we had two. We built a house together, which was designed so we could take care of the children jointly. As all the parents were working full-time, we hired a child-minder to take care of the five children. Every working day, one of us would have to be back by 4:00 pm to take care of the children. My day was Thursday. It's a big problem juggling a scientific career and a family, but by having this joint family arrangement it worked really well for everybody.

Like a mini commune.

Sort of. We had our own apartments and our own kitchens in that house, but there were doors between the apartments, so the children could come and go.

KNOWING THE ENEMY

What did you study with Kai?

I worked out how to use different detergents to remove lipids from membranes and to analyze membrane proteins in solution. Little was known about membranes in those days, and practically nothing about membrane proteins. Detergents are now

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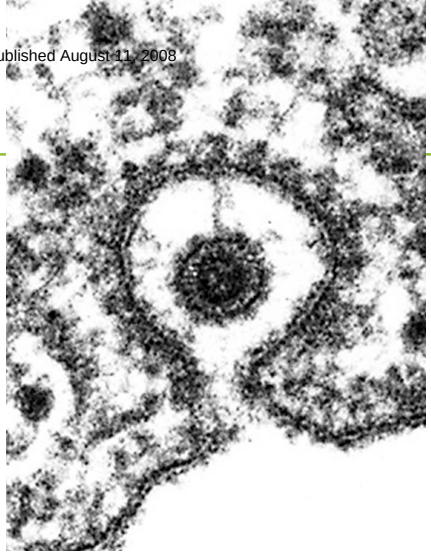

Semliki Forest virus sneaking into the cell via a clathrin-coated pit.

used daily, of course, to solubilize membranes and characterize, isolate, and purify membrane proteins. It's interesting that the papers we produced in those early days, describing the methods, are the most cited papers I have produced.

What eventually made you decide to head for the States?

Although we had produced lots of good work in Kai's laboratory, I was told that it wouldn't be easy to find a job because I'd stayed in one laboratory for so long. And it was true; I had great difficulty. Luckily, I happened to meet George Palade—one of the fathers of cell biology. He was originally at Rockefeller, but when I met him he had moved to Yale. He took pity on me [laughs]. Actually, he wanted to expand his section at Yale and bring in someone who worked on viruses, which I did.

So you'd been working on viruses as well as membranes with Kai?

Exactly. For the membrane solubilization work we had been using a virus called Semliki Forest virus, because its membrane coat is very simple. Then, when I moved to Yale I changed topics entirely and the question became, "How does a virus enter its host cells?" And that's what I'm still working on.

Ira Mellman, your chief editor, and I started at Yale at the same time, and we shared a laboratory for 16 years. We worked on different topics, but the laboratory was one big joint space with everyone and everything mixed together.

Aha, another commune!

Yes! I was very happy at Yale.

PROJECT ZURICH

So what precipitated your move to Zurich in 1995?

I became chairman of the department of cell biology at Yale, but somehow, even as chairman, it was hard to get funding to do what the department needed and also what I wanted to do in my own group. I wanted to start live cell microscopy so we could follow virus entry, but it was almost impossible to buy the equipment when you're in fragmentary grant systems. We needed something like $1.5 million to start an imaging facility, and to get that as a lump sum without having any record of being able to use the equipment was very hard.

You had to convince the funders you could use the equipment before they'd give you the money to buy it. Tricky.

Yeah. And I was unsuccessful in convincing them. But I was able to buy most of the equipment when I came here to ETH Zurich. This place is quite special. I'm spending less time here worrying about money than I ever did in the United States.

There were many other reasons for moving, though. My wife and I had never really intended to stay forever in the States. So when I got this offer out of the blue, I thought, "Hey, why not?" Every time I have moved laboratories it's been a boost in my scientific productivity. So there's much to be said for it.

What are the current projects in your lab?

One of the major projects has been to study how proteins fold in the living cell. This work came about because we worked a lot on influenza virus entry into cells. A viral glycoprotein called hemaglutinin is produced in large amounts in the infected cell. We realized that we had all these tools, antibodies, etc., to look at the synthesis and maturation of this protein, which thus provided the ideal means for looking at how proteins fold in general in vivo—because the virus borrows all the host cell machinery for this.

We've also been looking at Simian Virus 40 entry. We discovered that this virus uses a totally new type of endocytic pathway. It goes from caveoliae to the endoplasmic reticulum. This prompted us to look at other viruses, and we found that there are many more endocytic pathways than we had ever thought of.

Are these newly discovered pathways unique to virus entry, or do they have a normal cellular function?

This question always comes up. The macropinocytic pathway that vaccinia virus uses, as we described in a recent *Science* paper, is normally used by the cell to take up apoptotic material. The clathrin-mediated uptake pathway used by many viruses is of course used by the cell for internalization of numerous ligands, receptors, and plasma membrane components. As for the other pathways, we can't be completely sure, but we are looking into it.

"It is clearly a direction in which virology should be going—to focus on the host in addition to the pathogen."

Another project we are doing now is to use siRNA screening to identify all the host proteins that a given virus needs to enter and infect a cell. We are doing this project together with two other groups here, that of Urs Greber, who used to be a post-doc in my laboratory, and Lucas Pelkmans, who used to be a graduate student in my laboratory.

With all this screening information, a huge amount of biology opens up. We can start to understand what the virus is doing. And in addition, the identified host proteins are all potential antiviral targets.

It sounds like you're generating a lot of data.

It is. It's a lot of computing, a lot of bioinformatics, and a lot of lists of genes. But it is clearly a direction in which virology should be going—to focus on the host in addition to the pathogen. JCB

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