

People & Ideas

Lucas Pelkmans: Taking it from the top

Pelkmans takes a systems biology approach to endocytosis and viral entry.

Endocytic pathways in mammalian cells are too varied and complex to ever be fully understood by traditional cell biological methods, thinks Lucas Pelkmans. Instead, data-driven omics approaches and mathematical modeling will be more effective in revealing how the endocytic system works as a whole.

Crucial to Pelkmans' studies are mammalian viruses, which enter and infect cells via many different endocytic routes. Pelkmans first worked on virus entry as a graduate student in Ari Helenius' laboratory at the Swiss Federal Institute of Technology (ETH) in Zurich. There, he discovered that the SV40 virus triggers local rearrangements of the actin cytoskeleton at its sites of entry, passing through a novel organelle called the caveosome on its way to the ER (1, 2). As a postdoc with Marino Zerial in Dresden, Pelkmans revealed a new mechanism by which caveolin coat proteins sort cargo within endosomes (3) before he took a broader approach to the subject by performing an RNAi screen to identify kinases involved in endocytosis (4). Combining the results of this screen with careful observations of caveolin coat dynamics at the cell surface, Pelkmans was able to study the specific functions of kinases in the assembly and local recycling of caveolae (5).

In 2005, Pelkmans returned to the ETH as an assistant professor in the Institute of Molecular Systems Biology. He has continued to perform quantitative and global analyses of virus entry, looking for patterns in the data that can illuminate fundamental rules of endocytosis and virus infection. In a recent interview, Pelkmans explained this "top-down" approach, and how it compares to Lavoisier's experiments that laid the foundations of modern chemistry (6).

ENTRY POINT

What do you think you'd be if you weren't a scientist?

I love snowboarding and sailing, but I doubt I could ever make a living out of that! I would probably be a biology teacher; that's something I'd like. I also launched a bio-science company with Ari Helenius and Urs Greber, and the management aspects of that were appealing. In the past, I thought of becoming a medical doctor, though that's still rather close to science of course.

When did your interest in science begin?

I grew up in the Netherlands in a small city called Nijmegen. I went to one of those typical Dutch schools, called Gymnasia, which focus on training science students. So I was already inspired a lot, in physics, mathematics, and biology. One time, our regular biology teacher was on sick leave and was temporarily replaced by a molecular biologist from the University. The way he talked about biology was really exciting. My mother says that I came home after school and told her I wanted to be a scientist. That probably influenced me to study biology at university, where I really got hooked.

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Why do you use viruses to study endocytosis?

Mammalian viruses have coevolved with their host; mammalian cells have multiple endocytic pathways and viruses hijack them, often in very specific ways. Once you know that a virus takes endocytic pathway A and another virus takes pathway B, you have two very good tools to specifically

study and compare the pathways.

Viruses are generally easy to grow and purify in large quantities, and it's quite easy to make them fluorescent. So you can produce biologically active virus particles that infect cells via these pathways, and easily follow them with time-lapse imaging, especially



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with the powerful single molecule detection capabilities of modern light microscopes.

Also, viruses tend to amplify certain signals or stimulate certain activities to become more pronounced than in a noninfected cell, making the signal or activity easier to pick up. This isn't just true for endocytosis, but for molecular cell biology in general. If you think about the first studies of gene transcription or the early days of protein folding, protein production, and exocytosis, they also all started with viruses.

GOING GLOBAL

As a postdoc in Marino Zerial's group, what made you start taking a more global approach to studying virus entry?

Omics-based approaches were basically missing from the field of virology, and from our understanding of how mammalian viruses enter cells. And that was because genetic tools weren't easy to apply, certainly not in a high throughput fashion in mammalian cells. That all changed with the advent of RNAi, and so, while in Marino's laboratory, I did the first RNAi screens on virus entry.

My focus was definitely on understanding the endocytic pathways themselves. But these experiments also launched a new era in virology—we're now able to look at what we call the infectome: the part of a host cell's genome that is important for infection by a pathogen, be it a virus or an intracellular bacterium. Many people are doing this now, and the screens are getting larger and more sophisticated. We'll probably reach saturation at some point, but it's an essential phase to map out all the host genes involved in entry and infection.

That's something you can only do with such an approach—I wouldn't quite call it a systems biology approach, but it's heading that way.

How do you define systems biology?

In the truest sense of the term, I would say that you try to study a system's properties: things that emerge from the interactions between components. Complex assemblies work together in ways we often don't fully understand in order to make a system happen the way it does—be it membrane trafficking, vesicle internalization, or whatever. We try to get a quantitative feeling for the system's behavior, so that we can start to describe it formally, and perhaps we'll even be able to predict what will happen to it if we induce a certain perturbation. It's more than just omics, that's clear. But omics is definitely an important first step.

In one review you compared the impact of systems biology to the transition from alchemy to modern chemistry during the 18th century. What did you mean?

That referred to the data-driven aspect of systems biology, what people call the top-down approach. I think most molecular cell biologists would ultimately aim to be bottom-up: to be able to describe everything by knowing all the molecules involved and all of their interactions and dynamics. Perhaps in *E. coli* you might be able to get there; but for something as complex as a mammalian cell, I think it's questionable whether we'll ever be able to do that, certainly in the near future.

Why am I skeptical about bottom-up approaches based on our current knowledge? Because whenever you start to do new experiments, be it an RNAi screen or a proteomics analysis or a quantification of large cell populations or intracellular objects, you realize that there's this tremendous complexity that we just didn't know about. And when you realize that these are just the first experiments, the complexity becomes completely overwhelming. That doesn't mean bottom-up approaches are useless, they're definitely very important, but I like to think about systems biology from a top-down view.

That's where this reference to Antoine Lavoisier came from, because, in a way, you can see him doing something similar.



Favorite scenes from Pelkmans' snowboarding and sailing excursions.

In his case he looked at chemicals and substances, started to weigh them and measure their volume and so on. From the patterns in that data, something like a systematic periodic table emerged. In our case, we can start to see nonrandom patterns in cellular activities, and we can then follow up and try to explain them molecularly. That's where data-driven approaches to cell biology can reveal new aspects of cellular behavior that, in the short term, can be more productive than bottom-up approaches.

FINDING THE PATTERN

Interpreting these data involves a lot of mathematics and computer modeling. Is that something you've always been comfortable with?

My background is in biochemistry and molecular cell biology; I didn't have any training in data-driven modeling. So I had to learn these methods by trying them out with laboratory members and colleagues at the ETH who are experts in statistics and mathematics. In my case, I'd say it took about three years to get a feeling for which methods are appropriate and which aren't. That doesn't mean you can do all the formal mathematics, but you can at least understand the concepts and what each of the methods can do.

It's very important for biologists to realize that it's easy to make big mistakes if one uses the wrong multivariate statistics methods. So it requires a nice interaction with mathematicians and statisticians because there's a clear question from the biology side, and they can really help you out. But sometimes they have to revise their statistical methods to address the question, so both sides end up improving their own science.

What are you working on at the moment?

During virus infections, which cells become infected by viruses is thought to be a more or less random process. But the truth—and this came out of our RNAi screens—is that these patterns are specific for different viruses. You see very specific patterns of infection. But which cells can be infected, and why?

Perhaps the ability of a virus to infect a cell correlates with a specific phenotypic state of the cell. For instance, if a virus hijacks an endocytic pathway that is regulated by mTOR signaling, you expect that pathway to be active in cells that are actively growing. So the phenotypic state of a cell affects its endocytic activity which, as a consequence,

determines whether the cell can be infected or not. We've tested this idea, and it turns out to be largely true: you can nicely correlate infections with particular phenotypic states of cells. These are specific for different viruses.

For some viruses, like SV40, we're starting to explain how this is determined at the molecular level. Certain kinases increase the

formation of lipid rafts and are more active in some cells than in others, allowing this virus to infect them. We're studying infection patterns a lot at the moment: it touches on the fundamental concept of heterogeneity within cell populations.

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