

RESEARCH AS A HIKE IN THE MOUNTAINS

Couriers that run around the roadways of living cells at 200 steps per second. A repair protein cuts and pastes a DNA molecule. Biophysicist Erwin Peterman sheds light on these phenomena. "When others say: 'impossible', that's when I want it to make it happen."



By Rianne Lindhout

A Friday in 2011, five to seven in the evening. A PhD student and a postdoc came running into [Erwin Peterman's](#) office. The PhD student had been working like a madman for six weeks. He was exhausted, and he could finally shout: "I got the worm!" Peterman jumped. He wanted to check immediately whether they had really succeeded in modifying worms in such a way that they'd finally be able to show the world what he and his colleagues had been dreaming of for a couple of years. "Come on, let's put it under the microscope."

A fond memory of Peterman's, which also serves as an illustration of what a researcher's Friday evening can look like. All of his hard work was rewarded: a little more than a year later, in October 2012, he was appointed Professor in the [University Research Chair Programme](#) at VU University Amsterdam.

Figuring out how life works at the molecular level: that's the goal of this biophysicist. How strong is a DNA molecule? How do repair proteins bind to it? How does a transport protein turn calories into motion? He has been able to discover all these things by developing methods and equipment for conducting observations at ever smaller scales.

"There are researchers the world over who are envious of what we've achieved"

Those scientists from that Friday evening are working with Peterman on research into specialized proteins that travel along the road network within cells at a rate of 200 'steps' per second. This road network is the cytoskeleton, consisting of tiny tubes known as [microtubules](#). He has made beautiful video clips of these running [kinesin proteins](#). You can see the somewhat vague, small, luminous spots moving rapidly along a fixed route. These spots are not the kinesin molecules themselves: they are invisible. A few years ago Peterman managed to purify these proteins and make them visible by adding a luminous - fluorescent - bit. He was also able to illuminate the road network that they use. And he managed to bring all these elements together, add the required fuel [ATP](#) under the right circumstances, and film the

couriers as they started moving. Peterman was thus able to determine the exact pace of kinesin as it walks along the cytoskeleton.

MONUMENTAL NEXT STEP

Then it was time for something else. Peterman: "For me, research is like a hike in the mountains, my biggest hobby. I always look ahead, I always want to know what the next valley has in store. I am an impatient man. Once I've learned new things that begin to bear fruit, I want to move on to something else. I was looking for a project that really had the potential for being something revolutionary." That turned out to be a monumental next step in the single-molecule field: making kinesin motor proteins visible in a living organism. "It was ambitious, because we would skip the cellular level and go straight to go a whole organism." That fits Peterman's style, because: "When other say: 'impossible', that's when I want it to make it happen."

Peterman chose a tiny worm, [C. elegans](#), which has been thoroughly studied in the past. "It is a transparent creature, and that is handy under the microscope. A lot is known about it, in fact its entire genome has been mapped. It has about a thousand cells, making it an easy organism to work with, and it is very versatile." And so he had to find a way to modify the worms so that they would add fluorescence to their own transport proteins. This was done by injecting DNA that encodes for fluorescent proteins into the worms in the right spot, the egg cells. Not too much and not too little. And to think that the entire worm is just a millimetre long! Then it was a question of waiting to see if the offspring had the desired trait. It's no wonder that the PhD student who was observing the worms rushed to Peterman's office bursting with the good news. "The keystone had been put in place," says Peterman. "It was like reaching the summit after a long, arduous hike. Suddenly you can enjoy the vistas. The investment was not in vain." He proudly shows the clips. "I can watch these videos over and over and over and never get bored. There are researchers the world over who are envious of what we've achieved. We can measure the molecules' speed, we can see that they are blobs - agglomerations of thirty or so proteins - that move in unison toward the worm's posterior and back again. But now we want more. We want to follow one of these blobs, observe its position and composition. How do you get something like that out of your data?"

Peterman focuses on transport along the microtubules in the [cilia](#) of *C. elegans*. Cilia are tiny hair-like structures on the cells. People have cilia, too: many millions of cilia undulate in the lungs, for example, to clean out contaminants, which we then cough up or swallow. Nerve cells also have cilia such as the rods and cones in our eyes that perceive light. The worms that Peterman is working with have cilia that sense the salinity of water, or the pheromones of other worms of the same species. These observations are made using electrical signals, but the hairs also need transport: of nutrients, vesicles with neurotransmitters and receptor molecules, for example.

KIDNEY DISEASE

It is obvious that Peterman is driven by a fundamental interest. Nevertheless, there is also a clear societal relevance to further research into [transport proteins](#). A small mutation in the proteins involved in transport can have serious consequences, such as severe kidney disease. Peterman: "It's really awesome to work on therapies for these kinds of conditions. But I'm not going to have a solution in a year's time. The last thing I want to do is to raise false hopes. I look at it this way: there are 20,000 different proteins. You're really lucky if the one you're studying turns out to be important."

As Peterman pushes back more and more boundaries, allowing researchers to see and measure more and more, he is also pushing back the boundaries of technology. Working with live worms means dealing with thicker samples that you can't nail down on a flat surface. Microscope manufacturers are highly interested in his activities. Many other researchers can use

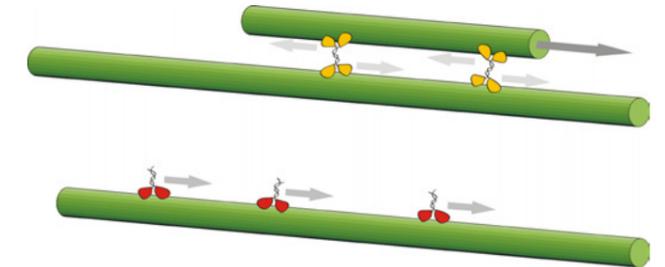
ERWIN PETERMAN & ALPINE MARMOTS

Erwin Peterman always wanted to understand how nature works. "I remember a holiday with my parents in Switzerland. They wanted to move to another location, but I was fascinated by marmots and did not want to leave." Upon entering university, he could not decide between the subjects of biology, chemistry, physics and mathematics. "Multidisciplinarity is in my genes." The molecular sciences programme at Wageningen University turned out to be perfect for him. While studying there he went on a number of different placements, including one with the VU biophysicist [Rienk van Grondelle](#), one of the world's top scientists in the field of photosynthesis research. He remained in Amsterdam for his doctoral studies on [fluorescence](#) and [spectroscopy](#), supervised by Grondelle. Then Peterman wanted something new. Where can you go for fun, new biophysics, he wondered. He was alerted to the single-molecule field, and learned all there was to know at the University of California, San Diego, and at Stanford University. That's where he started studying kinesin, and that has been his passion ever since. In 2000 he returned to VU University as a postdoctoral researcher on an [NWO](#) grant. He then acquired bigger and bigger NWO grants, became an assistant professor and later associate professor, and in late 2012 he became a full professor in the [University Research Chair Programme](#).

Peterman's innovations as they work on their own breakthroughs. For example, Peterman's VU colleague [Gijs Wuite](#) is being inundated with requests from scientists from around the world, because he alone is able to grasp a single molecule with a laser beam. Together with Peterman, he is using these [optical tweezers](#) to make fluorescence possible, too, so you can see repair proteins at work on a strand of DNA, for example. "One plus one became

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ten," said Wuite on this topic in [VU Magazine](#) (December 2010). "The strength of my lab is found in our interdisciplinary approach," Peterman explains. "That's what makes me tick. We are very good at making advanced biomarkers, in building microscopes, in analyzing data and making physical models." He appreciates the focus on multidisciplinary research at VU University Amsterdam. "I know biophysicists at other institutions who feel the need to convince their fellow physicists that what they're doing is really physics. That kind of parochial mentality has been done away with here."



KINESIN HAS TWO OR FOUR LEGS WITH WHICH IT RUNS ALONG THE MICROTUBULES, THE ROAD NETWORK OF THE CELLS.



"I CAN WATCH THESE VIDEOS OVER AND OVER AND OVER AND NEVER GET BORED," SAYS PETERMAN. THE MOVING DOTS SHOW THE KINESIN MOLECULES RUNNING ALONG THE MICROTUBULES.