Providing A Live View Of The Cellular World

Auburn University

When Vitaly Vodyanoy wanted to see something that had forever been invisible, he figured out a way to see it. Cobbling together glass lenses and playing with the angles of various light sources, he built a novel microscope that allowed him to see the miniscule workings of living cells in real time. It enables live cell images to be visualized for the first time. Like the inventors of the first microscopes, Vodyanoy has provided us with a new perspective on human life.

A professor of physiology and director of the Biosensor Lab at Auburn University in Auburn, Ala., Vodyanoy had been conducting research on biological membranes, and specifically, olfactory function. A biophysicist and biologist, he was intrigued by the molecular phenomenon of olfactory function — how the olfactory sensors interact with the receptors on neurons, and the multitude of biochemical events that provide us with the sense of smell.

He'd been searching for cilia under his microscope. Cilia are the delicate hair like structures found in great numbers on the surface of a cell, and used, in many organisms, in locomotion. Vodyanoy was studying the cilia that are projected from olfactory sensory neurons.

“I wanted to look at cilia in the mucous of the olfactory, but they are very small, one billionth of a meter — only a few microns in length,” he says. “All of the olfactory receptors are embedded in this structure, but they are essentially invisible. So I started looking around to find a way of doing this.”

An “Illuminating” Discovery

As a physicist and biologist, Vodyanoy was a veteran user of microscopes, and he understood how they worked. Optical microscopes use refractive lenses, usually made of glass, to focus light into the eye or another light detector. Various wavelengths of light are used for special purposes — the study of biological tissue, for example. Today, biologists frequently use ultraviolet light combined with fluorescent tagging to make certain parts of an organism “glow” under the microscope, enabling the researcher to see those tagged components as distinguished from other parts.

Vodyanoy had visited Gaston Naessens, a scientist in Canada in the early 1990s and seen him use a microscope with a special kind of illumination system. Illumination is critical to microscopy because it gives an image a three-dimensional appearance and enables the user to see otherwise invisible features. According to Vodyanoy, this particular microscope had a light condenser that converted a beam of light into a cone, effectively illuminating the subject at a high resolution. Years later, when Vodyanoy was unable to see the olfactory cilia, he decided to create a better illumination system for his microscope.

“It’s really an old kind of technology,” he says, “but I made a special kind of illumination system, one that produces annular illumination. It’s a special structure that produces empty cones of light, which has advantages for looking at small particles. So it’s a combination of old technology put together in one unit to produce new, higher resolution on smaller subjects.”

Vodyanoy is not a microscopist. His main research interests are in cellular dynamics, chemical sensing and the physics of interaction. But he is also, according to those who know him, a renaissance man — someone who loves music and art, a good cook, a charmer.

“He is this wonderful man, a Russian scientist, who created this instrument because he couldn’t see what he needed to see,” says Jan Thornton, director of the technology transfer office at Auburn. “He is just the type who seeks knowledge and will do whatever it takes to find things out.”

According to Thornton, her team had been invited to Vodyanoy’s lab to see another discovery, when they happened upon the microscope. He had created it with his own money, and hadn’t even thought of disclosing it. But after the technology transfer professionals had seen it, they disclosed the invention to the U.S. Department of Defense. The government, which has become more interested in highly sensitive tools for detection of disease agents in the wake of the 9/11 terrorist attacks, asked for a prototype.

Vodyanoy obliged.

The Start of a Collaborative Partnership

Around the same time, Thornton had begun meeting with a venture capitalist in Memphis. The investor, Thomas Lawrence, had experience bringing new inventions out of a university setting and into the marketplace. He’d been approached by Auburn University alumni to take a look at their technology transfer efforts and help them develop a sustainable model for bringing in licensing income in the era of declining government support.

Once Lawrence and his son Sam saw the microscope and the prototype Vodyanoy had built for the government, they were impressed enough to work with Auburn to form a collaborative partnership. Together, they launched Aetos Technologies in 2003 to commercialize discoveries made at Auburn and other universities, and the first technology they wanted to bring to market was Vodyanoy's microscope.

"We immediately understood the importance of this," says Sam Lawrence. "This microscope gave us the ability to see live, real-time cellular interactions in a completely analog manner — just light and lenses, no software manipulation."

Lawrence brought in experts in microscopy, a variety of medical fields, nanotechnology and engineering to look at the tool and it met with excitement and enthusiasm.

"The base technology was really exciting," Lawrence says, noting, "The importance of this to basic research in biology and medicine was immediately recognized."

> *While the product had an enormous amount of potential, the company had to first invest time, money and energy into fitting the scope to the needs of the market. Researchers at Aetos and Auburn spent the next year collaborating to develop the product from a bench top prototype to a device that could be compatible as an add-on component to the standard bench microscopes.*

The first commercial product, called the CytoViva optical illuminator, was launched in 2004. It's an "add-on" that provides ultra high-resolution, high-contrast images. Less than two years later, the company developed the CytoViva Dual-Mode Florescence unit. This tool enables researchers to use fluorescent tagging in combination with high-resolution, high-contrast, real-time imaging. In the same year, 2006, Aetos launched CytoViva as a separate company.

Biologists use fluorescence to visualize intracellular interactions, marking portions of cells with fluorescent tags to better observe the biomechanics that are occurring. The dual-mode fluorescence unit allows users to combine morphological data with fluorescent data, making it possible to see all the structural data and all the dynamic data, and to switch back and forth between the two.

"Heretofore, researchers would have to take a picture of the cell with one technique, then take another picture of the other data, and nothing allowed them to look at both at the same time," says Sam Lawrence. "Now, they can do both and do it in real time."

The tool allows researchers to see the morphological structures of cells responding to and interacting with other cells. This is especially important in the study of infectious disease, where it's important to see how cells infect one another, or in the development of drug delivery tools, as it allows researchers to see how much of a chemical is entering a cell.

"We can offer a full system to scientists that allows for a robust qualitative and quantitative picture of their research," Lawrence says.

Continuing a Successful Track Record

Aetos Technologies and Auburn University have won several awards and accolades for the CytoViva products, including being selected as one of the 100 most significant new products by R&D Magazine in 2006, and winning a Nano 50 award in 2006 and 2007. The company's products are being sold worldwide for applications ranging from cell biology to bioinformatics.

One customer, an oncologist, is using the microscope in a predictive, diagnostic way to understand the way cancer metastasizes inside a living human being. Next to the market: a scope with a CytoViva-compatible environmental chamber that will enable researchers to keep a sample alive for hours or days while it's being studied.

Even as CytoViva begins to sell its components and prepares for future product development, Vodyanoy says researchers in a variety of fields on the Auburn campus have been flocking to his lab to use his microscope.

"We've had many visitors to our lab," he says. "We've seen nanotubes, the insides of cells, and we've visualized the transport of protein in blood vessels."

And yet he remains modest about his discovery.

"I don't look at this as an invention, it's really just a tool," Vodyanoy says. "It's a real workhorse."

The development of the first microscope in the 16th century revolutionized biology and today it remains an essential tool in science. Vodyanoy's microscope might very well continue the revolution, as it provides scientists the first tool with which one can study both the qualitative and quantitative aspects of life at the smallest scale.

This story was originally published in 2008.

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