TECHNOLOGY

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How One Company Turned Military Research Into a Hi-Tech Weapon for Cancer

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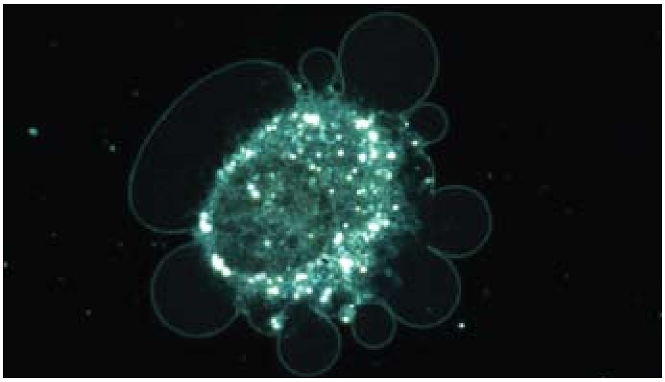
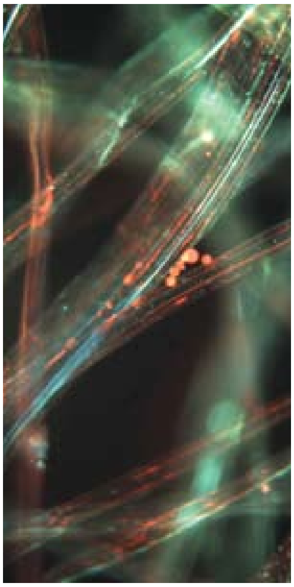
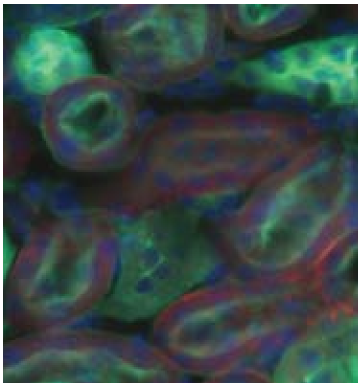
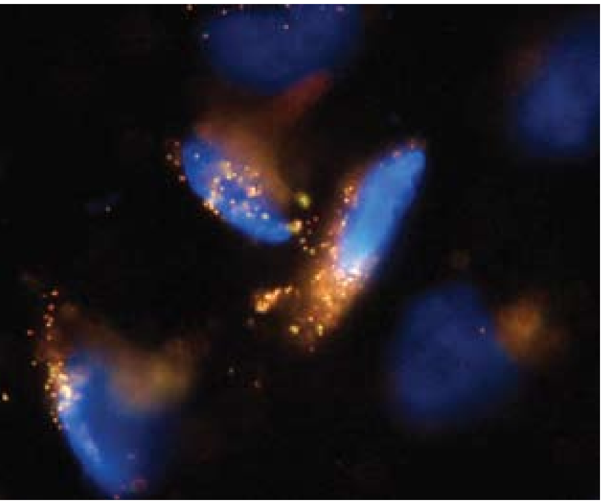
FROM SATELLITE TO MICROSCOPE

By Eric Fleischauer









The conceptual journey from identifying an enemy military tank to identifying a nanoparticle is a distant one for most of us, but not for the folks at CytoViva Inc., a subsidiary of Auburn-based Aetos Technologies Inc.

The company started with an innovative development in microscopy, but what may turn out to be its greatest contribution will wed that technology with one developed for the military.

Two decades ago, the Department of Defense began developing software to assist it in reading aerial reconnaissance. In the early days, that meant identifying an airfield or, with luck, enemy troop formations through analysis of a black-and-white photograph.

Improved optics, digital imaging and computer power have transformed those early efforts. Using hyperspectral imaging software, the military now compares broad-spectrum digital imagery compiled by satellites or reconnaissance planes with an ever-increasing library of spectral signatures. At the core of the technology is the recognition that every item on the battlefield scatters different wavelengths of light in a unique way. The signature of a U.S. Abrams tank is different than that of an Iraqi Asad Babil tank. The signature of a roadside explosive device is different than that of a roadside trashcan.

The software is so advanced that it not only can identify targets through their spectral signatures, it can identify anomalies. An image of a field, for example, may present no evidence of a threat to the closest scrutiny by the human eye, but the software can identify a hyperspectral anomaly. A perfectly camouflaged tent is not perfectly camouflaged under the glare of hyperspectral imaging software. Searching its library of signatures, the software finds the signature for a tent in a place where no tent should be. Useful stuff for wars, but hardly of interest to cancer researchers.

Now we go to December 2004, when CytoViva released the microscopy system that bears its name. Its most innovative components are the CytoViva illuminator and the dual mode florescent module.

CytoViva's microscope, coupled with the military's hyperspectral imaging software, is changing the way researchers view nanoparticles and their interactions within the body.

(Top, left) A polyester microfiber containing 605nm quantum dots (red) and titanium dioxide nanoparticles (green). (Bottom, left) Lung cancer cells containing 100nm gold nanoparticles. (Top, right) Ovarian cancer cell dying from interaction with gold nanoparticles containing cytotoxins transported into the cell and bound to targeted cell structure. (Middle, right) Several types of metastatic breast cancer cells with 80nm gold nanoparticles used as diagnostic imaging sensors and drug delivery vehicles. (Far right) Cancerous kidney cells stained with traditional labels designed to establish cancer concentration and location.

Without venturing into the physics, the illuminator is an improvement on illumination sources that all microscopes have. It provides the scientist with a view of nanoparticles that are brightly illuminated against a dark background.

The dual mode fluorescent module is a breakthrough. When scientists want to examine a nanoparticle, they often do so by attaching a fluorescent protein to it. This permits identification of the particle under the microscope. The problem with conventional microscopy is that the scientist can view the fluorescent particle, but he cannot simultaneously view the non-fluorescent particles. Consequently, it is difficult to watch the fluorescent nanoparticle interacting with other particles.

The dual mode fluorescent module permits the viewer to see the fluorescent particle and the non-fluorescent particles simultaneously and in real time.

Byron Cheatham, senior vice president of CytoViva, explains how the device assisted an Alabama researcher who was studying spotted fever, caused by the rickettsia bacteria. The researcher dyed the rickettsia bacteria with a fluorescent protein.

He wanted to be able to see the florescent and non-florescent components of the sample simultaneously in real time. He wanted to observe and record the interactions between the two, Cheatham explains. This dual-mode florescent system that we are showing allows them to see both the florescent and the non-florescent samples simultaneously and in real time.

To these components, CytoViva added a live chamber that mounts to the microscopes stage. Instead of squeezing the particles between glass slides, the enclosed chamber has a controlled environment so researchers can examine living cells.

“They’ll say, ‘Look, I would like to study the full cycle, the lifecycle, of this particular structure and watch it as it grows and dies.” Or, ‘I would like to have in a sealed compartment some cancer cells and be able to introduce some level of chemistry, of cytotoxin, and kill it’”, Cheatham explains.

With the environmental chamber, combined with high-resolution digital imaging systems CytoViva adapted for its system, they can do so.

“There are other environmental chambers that were already out there,” Cheatham says. “What is unique about ours is we allow you to see those experiments in real time at high resolution.”

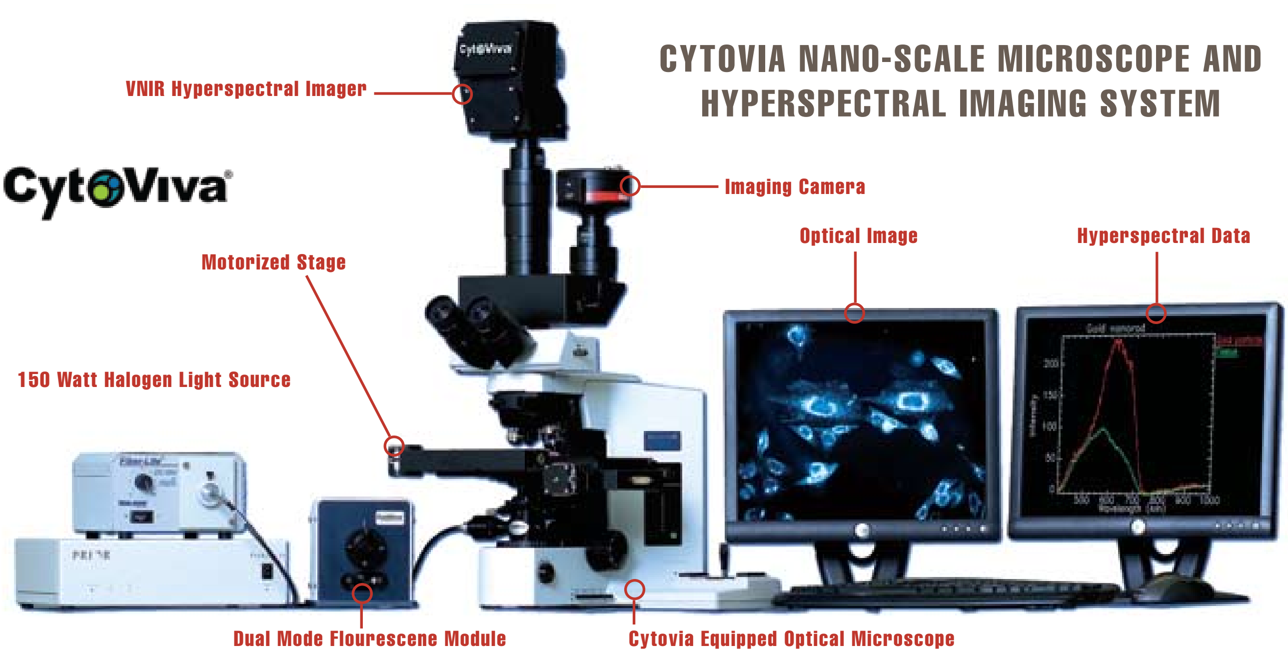
The CytoViva microscopy system is a collection of breakthrough technologies and modified existing technologies that, combined, give researchers a unique ability to view nanoparticles and their interaction with cells or other viewed images.

“I will give you an analogy”, Cheatham says. “Right now in the middle of the day, the stars are out in the sky. However, because of all the noise in the air from the sun, you are not able to see the stars. As nightfall approaches, you have more contrast. The sky gets dark and you can see the stars. Even in a big city you can see them in the ambient light, but if you get out from the city — you get away from the ambient light — there is more contrast and you can see the stars better.”

Take it one step further. If you go up on a mountaintop where the atmosphere is thinner, then the stars actually get even brighter. What CytoViva did was take the microscope out of the city at night on to the top of the tallest mountain.

Opening the Box

The advancements created by the CytoViva system caused a problem. Suddenly scientists were seeing nanoparticles they had not seen with traditional microscopy, and they wanted to know what they were.



As CytoViva President Charles Ludwig explains, “As great a tool for optical imaging as CytoViva has been, so many of the customers have said, ‘I am seeing things that I’ve never seen before. I don’t know what they are and I need to quantitatively determine what those particles are.’ Or, often, the researchers felt sure they knew what the particles were, but needed a way to prove to others that they were identifying them correctly.”

As Cheatham put it, the researchers told CytoViva, “While a picture may be worth a thousand words, I need 2000. I need to quantify.”

The issue was how to use a high-resolution digital image of a broad spectrum of light scattering from a nanoparticle.

It just so happened that the software technology to do precisely what CytoViva customers wanted not only existed, but its development had been heavily funded for two decades.

You guessed it. We’re back to the tanks.

The principle underlying the hyperspectral imaging software used by the military is that every object has a more or less unique spectral signature. When viewed from overhead, remember, different tanks have different signatures. Even if invisible to the naked eye with its narrow spectrum capacity, a camouflaged tent has a different hyperspectral signature than a tree.

What if, the folks at CytoViva wondered, the same principle applies to nanoparticles?

Ludwig flashes an image on a screen. It clearly is a cell, but there is a collection of much smaller white dots below it, visible against the CytoViva dark background.

“While you see white spots, we don’t know what those white spots are, “Ludwig explains, “without the use of the hyperspectral imaging technology. So this is the way to be able to confirm that yes, in fact, that metastatic breast cancer has taken those particles, and we can identify or quantify the particle. And in fact we believe that soon we’ll have a signal that represents the drug load. You can watch the release kinetics as that drug load is released into the cell.”

In other words, researchers can watch particles that were barely visible with conventional microscopy, see how they pick up the chemotherapy drug, see how the malignant breast cell absorbs it, and watch the cell die. All in real time, and with the ability ó through hyperspectral imaging — of quantitatively identifying the drug-carrying particles.

Cancer research is an especially promising subject of nanotechnology, and thus of the CytoViva system.

“We learned early in the game that because cancer cells are very fast growing masses and they are fairly diffuse — they are kind of spongy — they are able to take in particles in the nanoscale, like 50 to 100 nanometers in size, where normal cells would not,” Ludwig says. The hope is that nanotechnology will provide a weapon that cancer cells will ingest but healthy cells will leave alone.

Another potential use of the combined technologies: a surgeon removing cancerous tissue can know immediately whether any remains by looking at the hyperspectral signature of the remaining tissue.

“Rather than going through the extended process of staining and preparing the sample, which may make take hours to a day, there is a strong feeling that they would be able to scan over that tissue just like they scan over a field to identify a tank,” Ludwig says. “Or, using the anomaly detection software developed for military use, CytoViva equipment could scan large sections of tissue with no known malignancy and alert doctors of any abnormality.”

The Possibilities are Limitless

Ludwig is excited at the amazing list of potential applications, and so are his customers. Remember the desperate post 9/11 efforts to track the source of anthrax? Ongoing tests with the CytoViva system suggest that each strain of anthrax has a unique hyperspectral signature. Log each strain in CytoVivas growing signature database, and the source responsible for infecting an individual could be determined almost immediately.

The hyperspectral imaging software designed for aerial images has the potential of being far more functional in the CytoViva context. The camera creating the image in a reconnaissance mission is on a shaking, moving plane. It is taking its pictures through thousands of feet or even miles of air, clouds and haze. The light source — the sun — is beyond the researchers control.

Compare that to the CytoViva system. The camera is perfectly stationary. The environmental chamber is free of distorting impurities. The researcher has total control over the light source and of the spectrum it emits.

“What the military does from 20,000 feet under unpleasant conditions — you are bouncing around and you’re trying to get a controlled spectrum — we are doing it in a very controlled, elegant way,” Ludwig says.

The conceptual journey from identifying a tank to identifying a nanoparticle is not so distant on the path forged by CytoViva. And with the combined technologies, the path toward major breakthroughs in nanotechnology is getting shorter all the time.

Eric Fleischauer is a freelance writer for Technology Alabama.