

# A New Window on Cancer Therapies

By Kambra McConnel

**A**t work and in his spare time, Harvey Herschman's passion has been to tame things that can rage wildly out of control.

As a volunteer fire fighter for 12 years in the Topanga Canyon area of Los Angeles, he spent hundreds of back-breaking hours battling fast-moving flames. And as a renowned scientist and director of basic research at UCLA's Jonsson Comprehensive Cancer Center, Herschman has spent 31 years searching for ways to stop cancer in its tracks.

Unlike firefighters, who can gauge their strategies' effectiveness relatively quickly, cancer researchers need considerable time to know whether gene therapy and other gene-based treatments are reaching targeted cells and working safely and effectively.

"Conventional imaging technologies help us detect tumors, and they indicate tumors' growth or regression," says Herschman, who has a doctorate in cell biology. "However, physicians have only known later — by imaging patients weeks or months after they have received treatments, or by waiting to see if the patients improve — whether or not the treatments are working."

But, after four years of pioneering investigation, a team of UCLA researchers organized by Herschman has created two state-of-the-art gene tracking systems that render the body virtually transparent. The systems, tested successfully in the lab, are designed to report visually on the progress of gene therapy and other gene-based treatments in patients, and to determine quickly whether the therapies are reaching targeted cells.

"It's an important step forward to non-invasively see what's happening in a living body in real time," Herschman says. "For the first time, we can test new therapies, currently in laboratory mice and ultimately in humans, in a repetitive and quantitative way that doesn't require surgical biopsy to determine whether a therapy has reached tumor cells and remained active over time."

The research team rapidly is earning accolades for its discoveries. As part of a

National Cancer Institute initiative to fulfill imaging technology's potential in basic cancer research and translate resulting discoveries into clinical applications, the team has been awarded a \$9.8 million five-year grant to support a new imaging "center-without-walls." The UCLA Center for In Vivo Imaging in Cancer Biology — the first such molecular imaging program on the West Coast and one of three in the United States — furthers gene tracking systems research by combining the expertise of UCLA scientists and physicians at the Jonsson Cancer Center, the Crump Institute for Molecular Imaging, the Department of Molecular & Medical Pharmacology and the Laboratory of Structural Biology & Molecular Medicine.

In addition to testing the effectiveness of certain experimental cancer treatments, some of the researchers are investigating how to thwart tumor growth by suppressing angiogenesis, the process by which tumors create their own blood supplies for nourishment. Others are using the tracking systems to learn how cancer cells metastasize, or spread, and how they interact with the immune system. Other projects evaluate the DNA delivery systems that enable gene-based treatments to target tumor cells.

"All of the projects revolve around cancer imaging, either by following cancer cell growth and migration, viewing distribution of therapeutic genes or monitoring engineered-virus attacks on tumors," says Herschman, who directs the imaging program as its principal investigator, along with co-principal investigator and positron emission tomography (PET) inventor Michael Phelps. "We're poised to answer fundamental questions about the biological mechanisms of cancer."

Answering those questions will be critical to improving cancer treatments.

**I**t's as if we've been playing pin-the-tail-on-the-donkey and suddenly the blindfold has been lifted," says Dr. Sanjiv ("Sam") Gambhir, director of UCLA's Crump Institute and a lead researcher on molecular imaging strategies.

**UCLA researchers are inventing a better way to see whether cancer treatments are working.**



**Dr. Sanjiv Gambhir**   **Dr. Michael Phelps**

"We've basically been flying blind, making educated guesses about how to treat some cancers. These new tools should eliminate the guesswork."

The tracking systems rely on PET imaging and two kinds of specially engineered genes, called reporter genes, that can be attached to any kind of gene therapy.

PET creates images of biological processes, unlike conventional imaging technologies — such as X-ray, magnetic resonance imaging (MRI) and computerized tomography (CT scan) — which depict static images of tumor lesions and anatomical structures like bones and organs. With PET, researchers can measure enzyme reactions, blood flow, oxygen consumption, glucose metabolism (the way cells break down sugar for nourishment) and other processes, such as the way in which hormones and growth factors carry out communication within and among cells.

"We've achieved a wonderful marriage of technologies by combining reporter gene technology with PET's capability to image and measure biological processes in bodily organs," says Phelps, who has a doctorate in chemistry and is chairman of the Department of Molecular & Medical Pharmacology at the UCLA School of Medicine. "The gene tracking systems have major implications for advancing gene-based therapies and for improving our understanding of cellular and molecular processes of tumors in patients."

The critical step in creating effective tracking systems was designing reporter genes

that could be linked with a variety of therapeutic genes and detected by PET to form images that would report on what the therapeutic genes were doing in the body.

“Previously, a researcher would’ve had to develop a separate way to track each gene,” says Gambhir, who holds both a Ph.D. in biomathematics and an M.D. “But with all-purpose reporter genes, you don’t have to develop a new system every time you want to study a specific gene’s behavior.”

**W**ithin one to two years, the UCLA team plans to begin testing tracking systems on lung and prostate cancer patients. To operate the systems, researchers will pair the reporter genes with therapeutic genes and deliver them into patients, who then will receive injections of special “reporter” molecules. The reporter genes produce proteins that trap those molecules, which emit signals that the PET scanner uses to form an image. The PET scanner reveals the locations and activity levels of the reporter genes, which in turn indicate how the therapeutic genes bound to them are functioning. Researchers then can determine quickly and repeatedly whether the therapy is attacking cancer cells or traveling elsewhere in the body, potentially subjecting patients to serious side effects.

Gambhir compares watching the tracking systems at work to watching the news on television.

“It’s like watching a reporter talk about the president,” he says. “The president doesn’t discuss what he’s doing, but the reporter who follows him fills you in.”

Herschman uses the analogy of the LoJack System for tracking stolen cars.

“When we want to know where the therapeutic genes are and whether those genes are being expressed, we activate the system and look for the reporter signals,” he says.

These explanations make gene imaging sound simple. As most scientists can attest, the greatest discoveries often *are* simple, but they require the perfect blend of expertise among researchers from vastly different disciplines. Bringing together the talents of UCLA physicists, chemists, biologists, enzymologists, pharmacologists and physicians was essential to developing the gene tracking technology and establishing the new imaging program.

The genesis of the tracking systems is rooted deeply in UCLA’s scientific history. In 1973, Phelps and his colleagues invented the PET scanner. In 1995, the UCLA Gene

Imaging Consortium, which includes Herschman, Gambhir, Phelps and Drs. Jorge Barrio, Simon Cherry and Nagichettiar Satyamurthy, began developing the reporter genes for use with PET. Early research by this group of scientists, funded in part by the Jonsson Cancer Center Foundation, established that these first-of-a-kind reporter genes can successfully be imaged in living subjects by a PET scanner.

**H**erschman’s motivation to develop gene imaging systems arose from a previous discovery in his laboratory, in which he and his colleagues identified a gene called COX-2. COX-2’s protein product is a target for Vioxx and Celebrex — drugs used to

“Building the team was a huge challenge because our research interests had developed so independently. There are not many institutions in the world where you’ll find such breadth and depth of expertise and the sense of a common goal,” he says. “It took substantial time and effort to learn one another’s ‘languages,’ and to develop the methods to make all of the components work. But the payoff has been terrific, both personally and professionally.”

The researchers are not limiting their team approach to UCLA — or to cancer. They are collaborating with cancer researchers around the world and with other scientists who may be able to apply tracking system technology to illnesses such as cardiovascular disease and cystic fibrosis. Biotechnology and pharma-

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**—Dr. Harvey Herschman**

treat arthritis and other inflammatory diseases.

COX-2 also has become a popular focus for research on prevention and treatment of various cancers because protein production from this gene is activated by agents that promote tumor growth and the spread of cancer cells. To study elevated expression of COX-2 in cancer cells without surgically removing tissue from research subjects, Herschman and his colleagues needed a non-invasive procedure to measure gene expression.

“So we built a diverse team to develop a technique that would allow us to do this, hoping that our work also would help physicians monitor gene-based therapies in patients,” Herschman says.

**Dr. Harvey Herschman looks through the detector ring of a microPET scanner used for imaging reporter genes.**

ceutical companies also have established programs that use PET for gene imaging and other applications in the drug discovery and evaluation processes.

“By sharing our findings with researchers worldwide, we’ll be in a tremendous position down the road to improve the lives of patients with life-threatening diseases,” Herschman says. “We’re entering an exciting era in molecular medicine. By learning how to attack diseases like cancer at their basic, molecular levels, we’re really learning how to put out the fire.” ★

