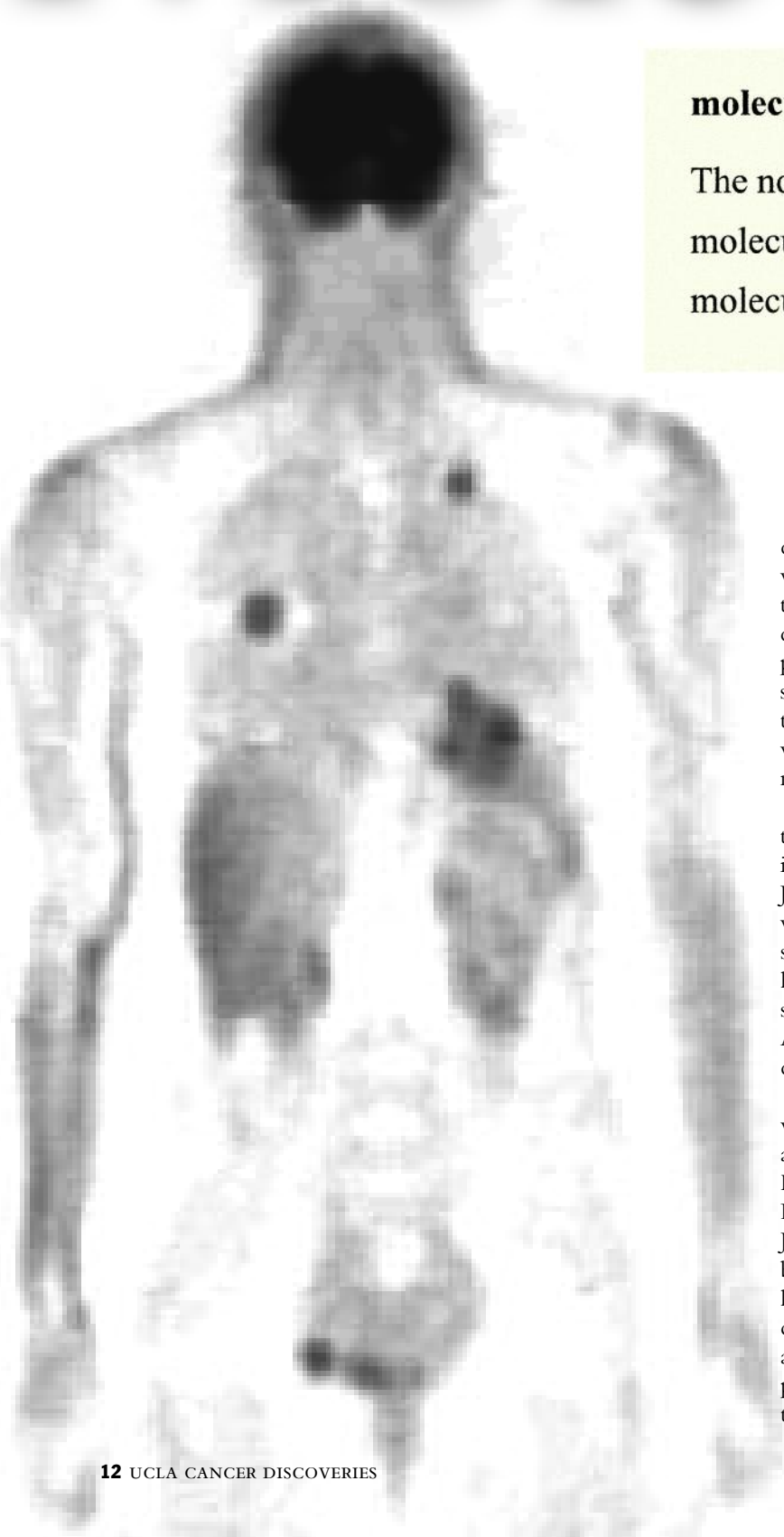
Molecular



molecular imaging (mə•lek′yə•lər im′ij′ing)

The non-invasive visualization of specific molecules, molecular processes and molecular events in a living organism.

For years, oncologists have been forced to work in a black box, prescribing treatments and waiting for months to see if the therapy was working. There was no non-invasive way to ensure the drugs got to the cancer cells or had a therapeutic effect until physicians observed whether or not the tumor got smaller, using conventional imaging techniques such as CT scanning. There was no method to detect cancer cells that had migrated from the primary tumor to other parts of the body until the secondary mass was large enough to show up on such scans. All too often it was then too late to help the patient. Most importantly, there was no way to determine when therapies weren't working, exposing patients to weeks and months of toxic treatments.

But molecular imaging is changing all that. A powerful new technology, molecular imaging has resulted in compelling insights into cancer. Molecular Imaging has allowed researchers at UCLA's Jonsson Comprehensive Cancer Center to track gene therapy at work in animal models and to watch, in real time, the immune system's first response to cancer. Molecular imaging may one day help oncologists find cancer spread in the human body when it's still too tiny to be detected by conventional imaging modalities. And it may allow oncologists to watch as treatments find the cancer and kill it.

"Oncologists have always wished for a way to non-invasively watch tumors inside the body and observe therapeutic treatments and the immune system as they try to eradicate the tumor," said Harvey Herschman, vice chair of the Molecular and Medical Pharmacology department and director for basic research at the Jonsson Cancer Center. "The problem is that the tumor is *inside* the body where we can't see it. We need to know where the tumor is, how much of it is there, if the immune system is activated and if so, did it find and is it trying to attack the tumor, and are our attempts at therapy successful? Can we sensitively and repeatedly monitor patients for tumor recurrence? We didn't have a way to answer those questions."

Imaging

By Kim Irwin

Not until Herschman had his eureka moment.

Herschman's work focuses on how cells in the body change function; that is, how cells start to perform new tasks in response to certain signals. He was interested in identifying genes whose expression is "turned on" in cells by new signals and determining how those previously "quiet" genes, now expressed in cells in response to a new signal, cause cells to change their function.

He was determined to find a way to image that "turned on" gene expression in living animals. Then it dawned on Herschman that positron emission tomography (PET) could help him accomplish his goal. If he could label or tag the products of those genes so that they showed up on the PET scan, he could watch when the genes were turned on, and where they were being expressed, in a living individual. The tagged proteins expressed from these genes would "report" on the cells in which they located.

A revolutionary technology, positron emission tomography or PET, was developed by UCLA's Michael Phelps, chair of the molecular and medical pharmacology department. Herschman and Phelps had worked together previously, and Herschman approached him about a collaboration. The two decided to work together to find a way to image gene expression in living individuals.

The PET scanner images many different biochemical functions in real time, acting as a sort of molecular camera. PET doesn't just take an anatomical snapshot of the structures of the body, it watches what the body is doing.

Initially, PET was used to identify cancer spread by showing how much sugar was being converted in the cells. Cancer cells, because they're growing uncontrollably, expend much more sugar than do normal cells, allowing them to be located using a specific PET probe that measures sugar metabolism. But the use of PET needed to be expanded to perform other, equally important functions, Phelps said.

Phelps believed PET could provide better diagnosis and staging of cancers, help monitor response or lack of response to therapy, stratify patients into responder and non-responder groups and monitor response to therapy almost immediately, maybe even within a single 24 hour period.

"We needed a way to measure which drugs were working and know it quickly," Phelps said. "Then you can separate patients out by whether the drug is effective for them or not."

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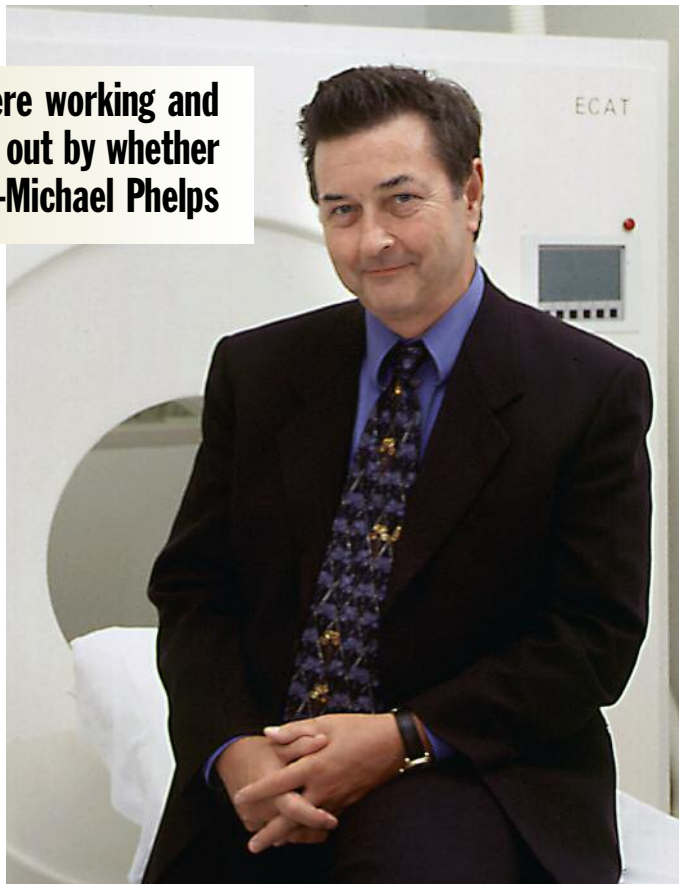
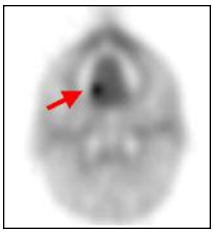
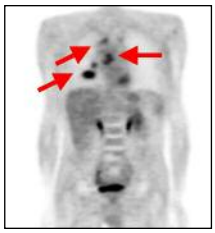
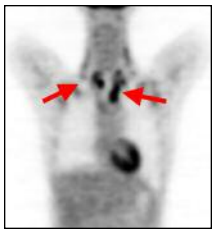
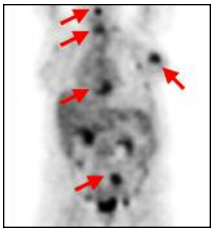


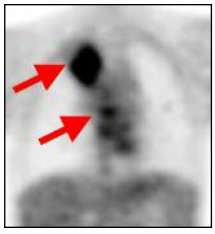
PET Imaging of Cancer

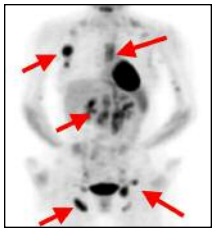

Head and Neck Cancer


Colorectal Cancer


Hodgkin's Lymphoma


Breast Cancer


Lung Cancer


Melanoma

When Herschman and Phelps sought funding from the Department of Energy to pay for their studies to image reporter gene expression in cancer cells, they were told it would never work.

"They said it was pie in the sky," Herschman said. "They basically told us to go away."

Herschman and Phelps pooled some existing funding. The Jonsson Cancer Center provided a much needed capital boost in the form of an interdisciplinary grant of $300,000 over two years, an investment that returned $30 to $40 million in grants from outside sources over the years.

Since this was new ground they were treading, Herschman and Phelps called in help from all over the campus.

They worked with radiochemists to develop reporter gene technology, creating genes that would encode proteins that capture positron-emitting agents inside cells, probes that would be visible by PET when they were "trapped." The team opted to use the gene for the Herpes Simplex virus thymidine kinase enzyme and the gene for the dopamine receptor as reporter genes to image gene expression in living individuals. At the same time, other members of the team were developing a MicroPET scanning system for use in small animal imaging that provided much clearer images than the full-sized clinical PET scanners.

"It was cellular and molecular biology, radiochemistry and imaging technology all coming together," Herschman said. "This was 12 to 15 years ago and not many people were doing this kind of research. Researchers were trained as cell biologists and looked at cells, while imagers looked at organs and whole bodies.

"If anyone had been trained in both fields, my eureka moment would have been obvious. If you can non-invasively keep looking at the same living individual over and over again to see how genes respond to external changes, if you can measure the time gene expression is up and down, where it is occurring, and how long the expression lasts, you could learn so much so much faster."

And it worked. The viruses they selected to deliver the reporter genes were easy to construct, and the reporter genes went to the organ to which they were meant to go. And they could be imaged by PET. In a mouse, Herschman was able to show that the reporter genes targeting the liver got to the organ and their reporter products "lit up" on the imaging screen.

Seeing the technology's potential in cancer, the National Cancer Institute (NCI) got involved. In 2000, UCLA was one of three centers nationwide to receive five-year, $10-million grants to develop innovative molecular imaging centers. UCLA's center, the UCLA Center for In Vivo Imaging in Cancer Biology, was the first such facility on the West Coast. The center brought together the expertise and experience of researchers from UCLA's Jonsson Cancer Center, the Molecular and Medical Pharmacology department, the Crump Institute for Molecular Imaging and individual investigators from other programs.

The grant was renewed in 2005, bringing the NCI's support of the UCLA imaging center to $20 million.

Herschman, principal investigator of the UCLA imaging center, said the goal of the initial five-year grant was to extend the development of non-invasive molecular imaging technologies

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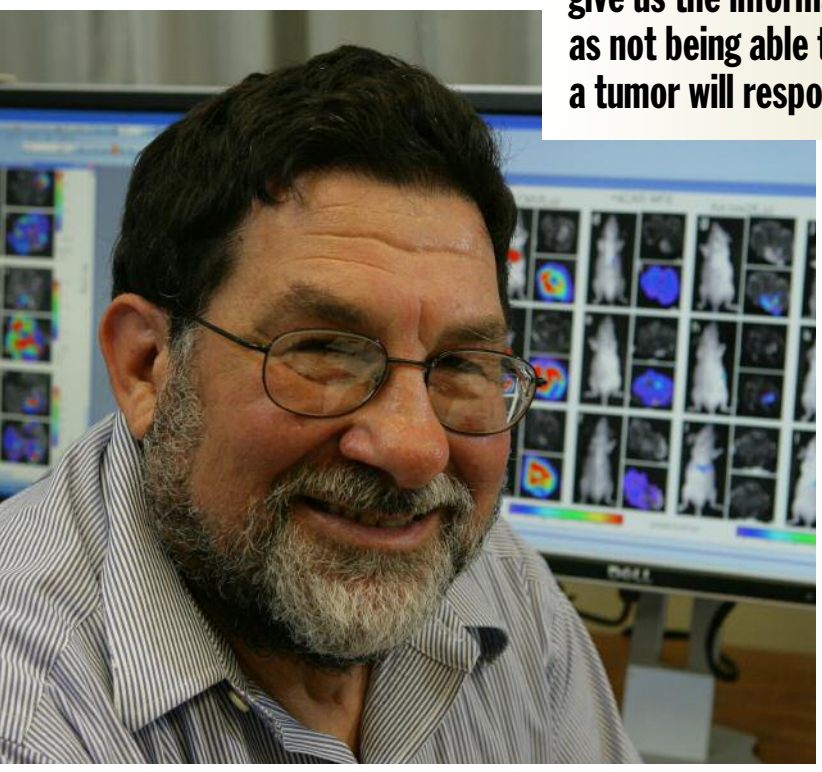
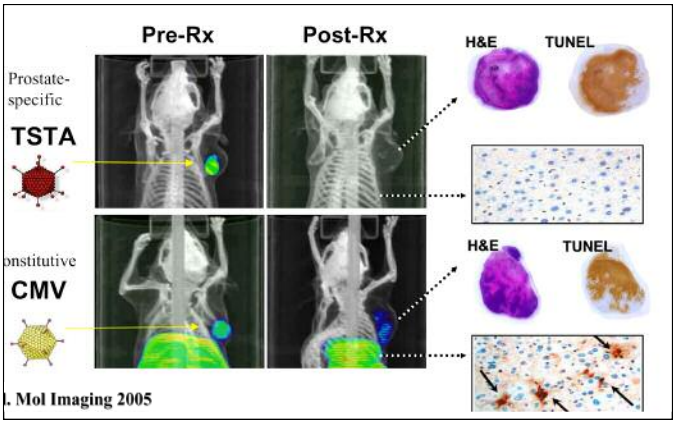


Imaging of Prostate Cancer Gene Therapy



An engineered virus that produces PET signals and includes a dormant killing function is shown under PET scan getting to and killing a prostate tumor in an animal model. The tumor can be seen in the animal on the left. It is eliminated in the same animal after treatment on the right.

pioneered at UCLA, and make these new technologies part of the regular "toolbox" used by molecular and cell biologists who are studying cancer in animal models.

"We accomplished these goals. Dozens of research labs on campus now use these technologies as routine tools in their research on cancer," Herschman said. "Going forward, our objective will be to translate into the clinic these new technologies and discoveries to improve diagnosis and staging of cancer and to much more rapidly distinguish those patients who might respond to certain therapies from those who would not. If we can do that, patients can receive the appropriate therapy for their cancer as soon as possible."

Owen Witte, a Howard Hughes Medical Institute investigator and director of UCLA's stem cell center, said the molecular imaging program in the Jonsson Cancer Center is the premiere program in the country.

"It integrates so many disciplines," he said. "We're building new machines, using chemistry to develop new molecular probes for PET scanning and working with computer programmers and code writers to develop programs to better evaluate our data. This technology will enable us to test and develop better therapies than we currently have."

Witte is most excited about a project based on research launched by Dr. James Economou, deputy director of the cancer center, and Dr. Antoni Ribas, associate director of the Tumor Immunology Program Area. The project, funded by a grant from the W.M. Keck Foundation, brings together experts from UCLA, the California Institute for Technology, Children's Hospital Los Angeles, the University of Southern California and the University of Connecticut. It would use reporter genes to mark modified immune cells. Those immune cells would then be used to stimulate the body's own response to melanomas. If it's successful, researchers will be able to trace the reporter genes using PET, and determine the location of the injected immune cells, their ability to target tumor tissue, their longevity in patients and their biological activity.

"I've been kicking around in science for 35 years, but I don't think I've been this jazzed up about a project," Witte said. "If this works, it will completely change the way we treat cancer. We'll be able to harness the power of the immune system to go after and attack a cancer in a sustained and prolonged manner that will be more effective than most chemotherapy regimes and even some of the targeted therapies."

Witte said there is "clear, indisputable evidence" that all common human cancers have tumor antigens that can be recognized by the immune system. But the most powerful defense in human biology against foreign pathogens, the immune system, is largely ineffective against cancer. This project, if successful, will make immune response against cancer as strong as it is against viruses and bacterial infections.

"I don't know that it's going to work, but I think the most important thing is that we're set up to understand why it doesn't work if the first few trials are not successful," he said. "Using molecular imaging, we should be able to see these cells and we should be able to locate them in the body. And if one or more of those steps doesn't go right, we can go back, change something and try again.

"If this idea works, it's not limited to melanoma. There's really no limitation to the types of cancers one can attack with this if one can develop the knowledge base about the specific type of antigens expressed in various cancers."

Other ongoing molecular imaging projects include:

The use of an engineered virus to deliver to prostate cancer cells the Herpes Virus thymidine kinase gene, which can be used to identify the site of virus infection by the imaging technology that Herschman and his colleagues developed, and can also provide a dormant killing function that can be activated later. (Lily Wu)

The use of molecular imaging techniques to define and monitor responses to targeted cancer techniques in living individuals and a study to validate and test new molecular imaging probes in the lab and in living individuals. (Johannes Czernin)

Development of radio-labeled antibodies for cancer imaging and ultimately for new, leading-edge treatments. (Anna Wu)

Development of an imaging system called OPET, a combined PET and bioluminescence imaging instrument to provide high sensitivity images. (Arion Xenofon Hadjioannou)

Use of PET to evaluate T-cell based immunotherapy against melanoma. (Caius Radu)

Research at the UCLA molecular imaging center already has shed new light on the safety and effectiveness of gene therapy and other gene-based treatments. Herschman said understanding cancer at its molecular and cellular levels will play a key role in improving diagnosis, treatment and prevention.

"Being able to non-invasively see what is going on in the body will give us the information necessary to overcome many hurdles, such as not being able to predict a tumor's behavior or not knowing how a tumor will respond to certain treatments," he said. "UCLA's work in molecular image will hasten development of safe, effective treatments for patients by allowing researchers to more rapidly and thoroughly evaluate the benefits and limitations of certain experimental therapies." ✶