

MicroPET Imaging Comes of Age

Preclinical molecular imaging is a rapidly evolving technology that is revolutionizing the ability to drive medical research from the laboratory bench to the patient's bedside.

By Tim Friend



SIMON CHERRY, PhD: his main field of research involves the rapidly growing field of molecular imaging.

The hallmark of preclinical molecular imaging, used worldwide today by approximately 100 biomedical research institutions, is the Siemens/CTI Concorde microPET® imaging system. Developed in 1995-96, microPET has since been making traditional methods of studying disease processes obsolete and moving experimental drugs through the pipeline much more quickly.

Simon Cherry, PhD, professor of bioengineering at the University of California-Davis, pioneered the development of the microPET technology. It may come as no surprise that Cherry built the first prototype of a miniaturized PET imaging system while working as an assistant professor at the University of California-Los Angeles (UCLA) with Michael Phelps, PhD, inventor of the original PET scanner.

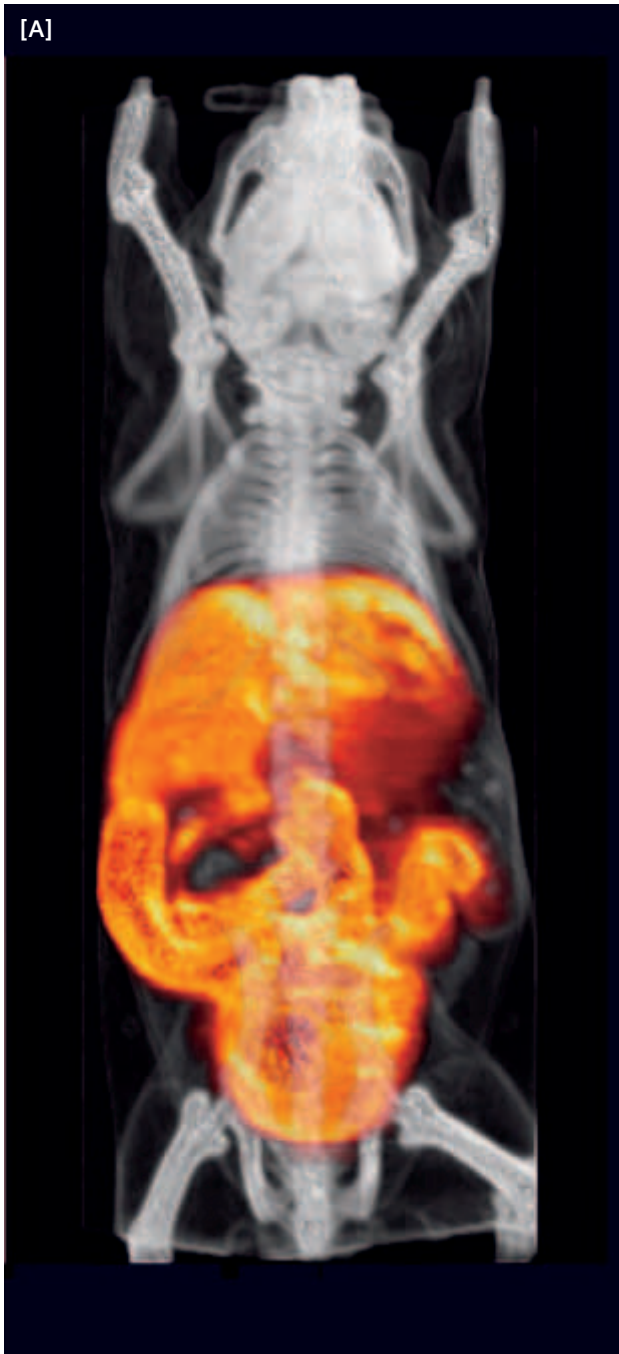
In an exclusive interview, Cherry explained that a number of key forces converged to give rise to microPET imaging and to accelerate its evolution and dominance in the realm of translational research. Cherry credits the Human Genome Project (HGP), completed in 2003, in which the genes of the human body have finally been decoded, with laying the groundwork for change. "Several trends are changing the face of development of new therapeutics," says Cherry. "Today we now

know a lot about the human genome. The completion of sequencing has thrown out huge numbers of possible targets for therapeutic applications, because when you know the function of a gene and its protein products, it gives rise to many potential targets."

Transforming Current Knowledge Into Successful Therapies

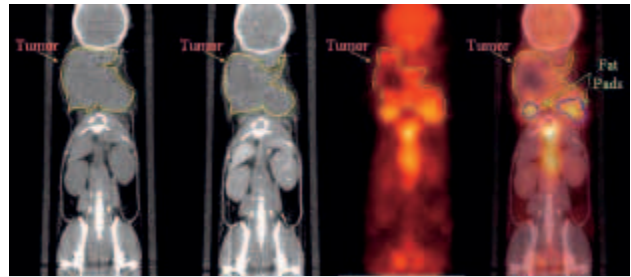
Because of the success of the HGP, scientists have at their fingertips data on thousands of genes involved in basic molecular pathways and they can determine the gene products involved in normal cellular function and in the progressive stages of disease. But even with this vast new knowledge, translating the ideas, insights, and discoveries generated from basic test tube and animal studies into successful therapies for human diseases has remained one of the most challenging endeavors in biomedical research. Traditional approaches involving the testing of compounds on cells and in animals have been tedious, time-consuming, and expensive. Pharmaceutical companies routinely spend billions of dollars and countless years processing new compounds through their pipelines, only to discover that the compounds fail once the leap is made to clinical trials.

"Drug companies and academia have developed high throughput combinatorial chemistry methods that enable them to screen massive numbers of molecules to interact

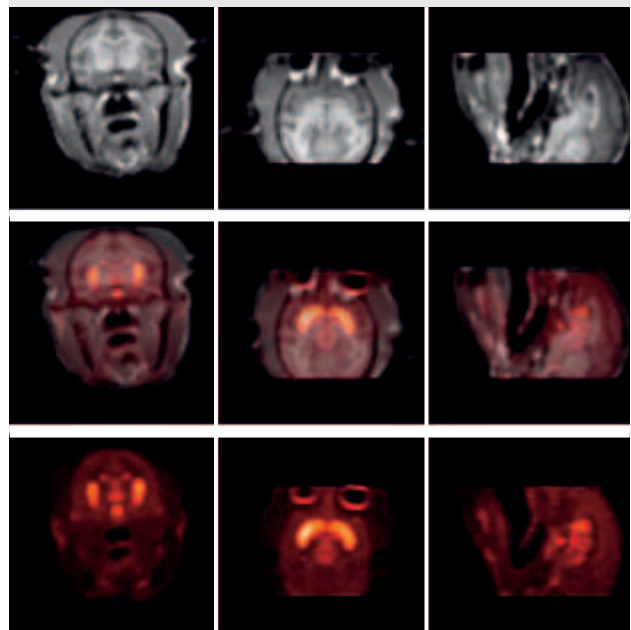


[A] MICROCAT & MICROPET fused images. microPET fast dynamic FHBG scan of HSV-tk transfected liver. Data courtesy of Crump Institute for Molecular Imaging.

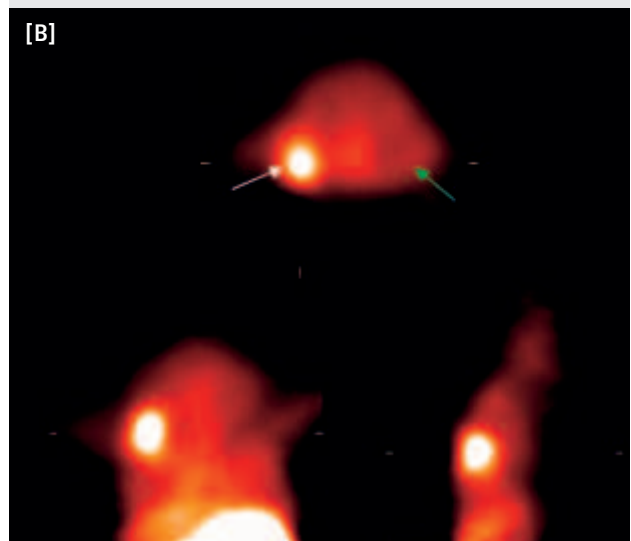
[B] DYNAMIC MICROPET imaging with $58\mu\text{Ci}$ injected ^{18}F -FHBG. MC26 tumor to the left and right upper flanks. Virus hrR3 to the left tumor. Dynamic scan time: 120 minutes. Data courtesy of Radiology Department, Massachusetts General Hospital.

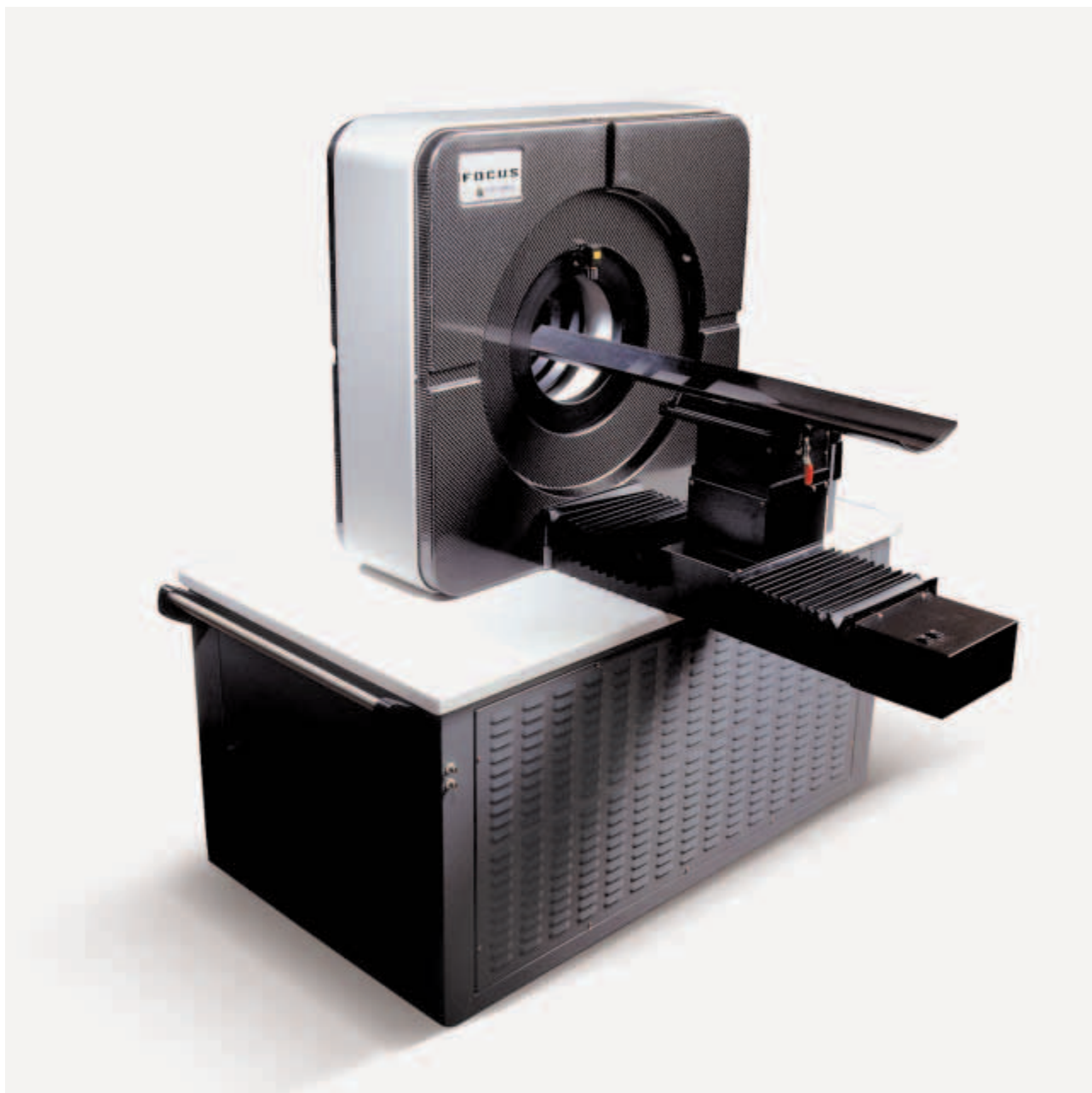


MICROCAT & MICROPET fused images of 20 g Balb-c mice with EMT6 tumors in the nape. Courtesy of Washington University and Mallinckrodt Institute of Radiology.



FUSED MICROCAT AND MR: Co-registered microPET and MR images of rhesus monkey. Data courtesy of Vanderbilt University Institute of Imaging Science.





MICROPET SCANNERS from Siemens Medical's MI division provide functional imaging of molecular processes in non-human subjects – from laboratory mice to non-human primates. By performing noninvasive, in vivo imaging on the same animal over time, the progression of the disease or the therapeutic response can be monitored.

with each potential target. But how we get from there to choosing a molecule that will make it as an approved drug is where the bottleneck has been," explains Cherry. In developing the first microPET imaging system for in vivo studies of small animals, Cherry and his colleagues recognized a substantial unmet need in several arenas:

- The promising results of basic laboratory studies of experimental compounds in cells and small animals have a long history of failing to meet expectations in human clinical trials.
- An abundance of new molecular targets for disease were being generated by combinatorial chemistry and high

throughput screening programs, but traditional laboratory and animal testing methods used to push drugs through the pipeline could not keep pace with the vast potential.

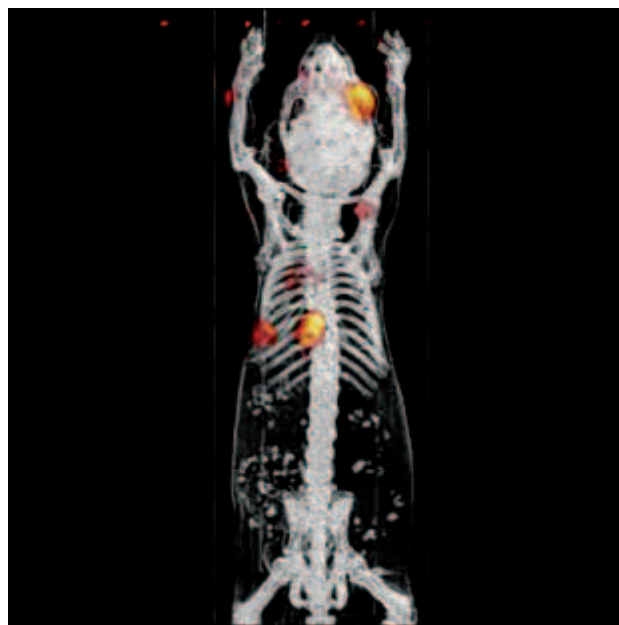
- Increasingly sophisticated and expensive transgenic animal models of human diseases, such as very early-stage breast and prostate cancer, as well as numerous degenerative neurological disorders, were generating increased demand for technology to study diseases in vivo.

As Cherry points out, the whole drug discovery process can be complicated, “Combinatorial chemistry and high throughput screening are well developed areas – and are very efficient at producing compounds. But now, you want to start testing to decide which drugs to move into clinical trials. Pharmaceutical companies and academics have a lot of in vitro tests with cell cultures and different tissues. And they can conduct toxicology studies in animal models. But none of this tells you whether the drug is doing what it is supposed to be doing in a patient.

“With in vivo testing, when you put a drug in a living system, the results can be very different than what you see in cell culture. Usually, a drug company knows that if a drug can reach the target cells it will do what they want, but the real question is whether the drug can get to the cells and how much of it will get there. In a perverse sense, it may be that preclinical molecular imaging will speed drug development by killing experimental drugs earlier. It will tell us that this drug doesn’t get where it is supposed to go, and it has major side effects because it goes to organ systems we don’t want it to get to. Preclinical imaging will never prove that the drug will work in humans, but it will tell you that there is something you didn’t think about or expect, and it will perhaps provide an early indication that this drug will not work as intended in the living biologic system.”

Diagnostic Assays

The microPET scanner makes it possible to follow drugs inside the body, to determine whether they reach their intended target, and to quantify the concentration of drugs at that target. Cherry says this is speeding the transition of new therapeutic strategies from the lab to the clinic and also is producing a new range of diagnostic assays that can be used to detect and track human disease with better sensitivity and specificity. A broad array of new imaging agents and an ever-expanding set of disease targets are also being identified. Preclinical molecular imaging is having an impact far beyond what scientists could imagine just a decade ago. The microPET imaging technology has become the new gold standard for all imaging studies involving transgenic animal models of human disease. MicroPET is a PET system designed specifically for the extreme demands of small animal imag-



FUSED PET/CT human colon cancer xenograft, with I-124 labeled anti-CEA engineered antibody fragment (tunable anti pharmacokinetics). Courtesy of Crump Institute for Molecular Imaging, Los Angeles, California.

ing. It is relatively mobile, standing a mere 4.5’ tall and measuring 4’ x 2’ at its base. It is primarily used for conducting in vivo studies of all varieties in laboratory animals, including mice, rats and monkeys. The technological breakthrough achieved by Dr. Cherry and his colleagues was improving the resolution of standard PET scanners from about 4-5 mm in humans to 1-1.5 mm, which was necessary for imaging small animals. The resolution continues to improve. The latest, second-generation microPET scanners have over 20,000 tiny detector elements, compared with just 2,000 larger detector elements on the first model developed by Cherry in the mid 1990s. But the most difficult challenge in the early development was not technical, Cherry reports. It was convincing the scientific community of the value of conducting preclinical molecular imaging in small animals.

“There really is no fundamental difference between PET and microPET scanners. The technical challenge in small animal imaging was getting the resolution down into the 1-1.5 mm range versus the range of resolution in a clinical scanner,” Cherry says. “But the big revolution was convincing other scientists and federal funding agencies that there was a role for a mouse PET scanner.” The Department of Energy’s Office of Science eventually offered early support for technology development.

As a noninvasive imaging system, microPET allows scientists to conduct a wide range of preclinical animal studies in vivo without the need for biopsies or sacrificing animals to determine results. Cherry notes that scientists can perform serial and longitudinal studies on the same living animal, making it possible to follow a single animal over time and monitor the progression of disease and the effects of interventions. MicroPET is particularly valuable for studying transgenic animals that exhibit high variability or are unique or valuable. As more research centers adopt the use of microPET imaging systems, the costs and amount of time associated with developing new therapeutics are expected to dramatically decrease.

Significant Impact of Preclinical Molecular Imaging

Ongoing studies involving mouse models of human cancer conducted by Dr. Cherry and his colleagues at the University of California-Davis, using Siemens’ microPET imaging system, illustrate the significant impact that preclinical molecular imaging is having on translational research. The team has been actively investigating animal models of cancer to learn how healthy cells are transformed into tumor cells and how intermediate precancerous cells respond to various types of therapeutic approaches.

Recently, they demonstrated the ability of preclinical molecular imaging to detect and track the earliest transition of ductal carcinoma in situ to an invasive tumor in a mouse model of human breast cancer. Cherry believes this model could be used to test treatments that would slow or stop that transition in human patients, as well as to ask basic questions about how cancers develop. “This was an example of a fairly sophisticated mouse model of breast cancer,” he says. “We were trying to characterize the development of cancer in this mouse and show that the FDG (glucose uptake) signal correlated with the endpoint pathology. We are fortunate to have one of world’s best mouse cancer pathology groups here at UC Davis. We showed that the PET image was reflective of what you get when you extract tissue from the mouse and look at it under a microscope. The study showed that the FDG signal was a good predictor of what point the mouse

was at in cancer progression. We can see a signal in the hyperplastic phase where the cells are not completely normal but still have not transitioned to neoplastic disease. We can see the progression of the cancer reflected by FDG uptake, slowly increasing at first, and then dramatically increasing when the transition to neoplastic disease occurs. The point at which that happens is somewhat variable from animal to animal, and that is another value of imaging.”

The UCLA-Davis group is currently documenting the response to treatment at various stages of cancer progression in its transgenic mouse model, using a known chemotherapy agent for human breast cancer.

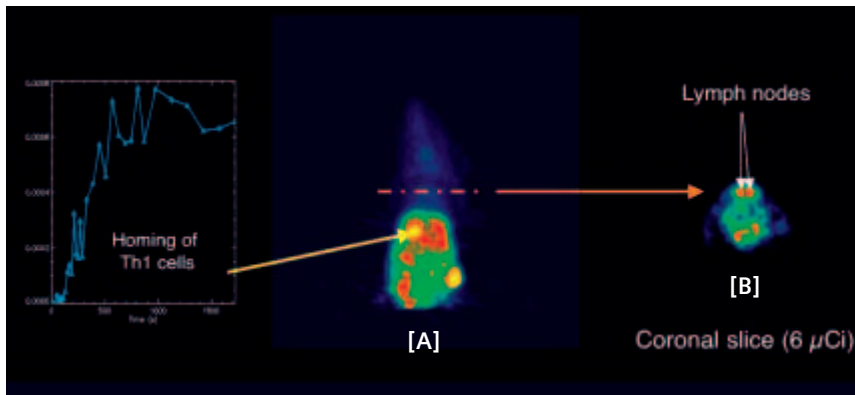
Uptake of Different Biomarkers

As studies mature and grow more sophisticated, microPET imaging is taking scientists far beyond correlating FDG uptake with staging of cancer. Because glucose uptake is ubiquitous in the body, scientists need more precise markers to study more subtle forms of cancer progression and diseases in which glucose metabolism plays no role. Many groups, including Cherry’s, are experimenting with more targeted types of biomarkers and reporter genes to track molecules through different pathways and cells, and also to track specific types of cancer cells as they migrate from primary tumors.

“For example,” says Cherry, “we can study the process of metastasis to see when it occurs. Reporter genes are one approach. The clusters of metastatic cells themselves will be very small and hard to see. If you are looking for a glucose signal, the background signal will be high and you won’t see metastatic cells in very small numbers. With a reporter gene approach, there is no background.”

Scientists participating in the National Cancer Institute’s mouse models of cancer consortium are currently using reporter genes to track prostate cancer cells as they migrate through the bloodstream. The reporter genes are targeted to all prostatic cells and then observed as they begin to migrate over time in the same animal. Similar studies could be done for any type of solid tumor. A reporter gene carries a simple marker that does not affect the function of the cell but can be easily detected by the PET scanner.

Siemens’ microPET imaging system is making it possible for researchers worldwide to visualize and characterize many different types of cancers in animal models before invasive tumors develop. The numerous studies being conducted to examine new therapeutic strategies designed to halt or reverse the initiation of cancers and to study the biology of cancer progression will enable scientists to develop imaging tests that more specifically diagnose not only cancer, but a wide variety of human diseases, and better determine which

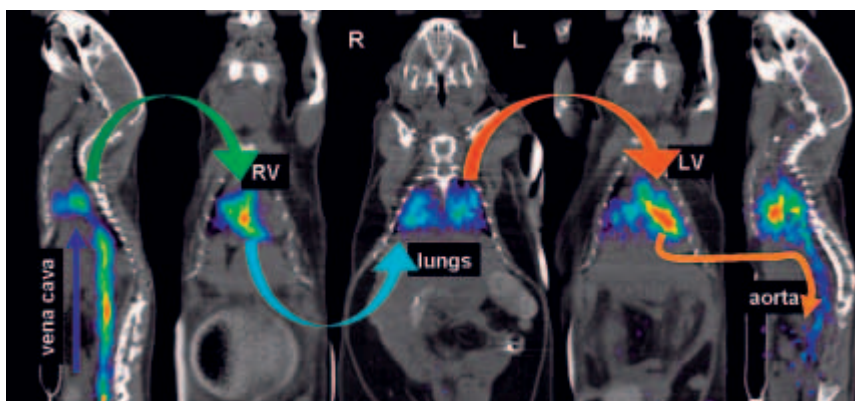


DYNAMIC MICROPET IMAGING of Th1 cell trafficking in an inflammation mouse model.

[A]: Dynamic imaging for 30 minutes post injection of 16×10^6 [^{64}Cu] labeled Th1 cells.

[B]: Dynamic imaging for 14 hours post injection of 16×10^6 [^{64}Cu] labeled Th1 cells.

Data courtesy of Laboratory for Preclinical Imaging and Imaging Technology, Dr. Bernd Pichler.



MICROPET FUSED WITH MICROCAT.

First pass angiography in mice by ultra high temporal resolution in microPET fused with microCAT.

Data courtesy of Crump Institute for Molecular Imaging, Michael Kreissl, MD; Hsiao-Ming Wu, PhD; David Stout, PhD; Patrick L. Chow, MS; Arion Chatzioannou, PhD; Sung-Cheng Huang, DSc; Heinrich R. Schelbert, MD, PhD.

of a range of therapeutic strategies should be followed for a specific patient. Scientists also have begun tagging T-cells with radioactive markers and watching as they mount responses to tumor cells. But nearly any type of cell that is of interest to a researcher could be tagged and watched as it moves through different pathways. This "cell trafficking" is becoming one of the most active new areas of preclinical molecular imaging. In these types of studies, scientists can tag both the cells of interest and their targets and begin to paint a more dynamic picture of molecular and cellular activity. Preclinical in vivo imaging of small animals has truly opened a window into the molecular soul of living beings. Achieving one of the ultimate goals of imaging – the ability to visualize multiple genes or proteins simultaneously – may be just around the corner.

Cherry is optimistic: "The hope is that microPET imaging will help us answer basic questions regarding disease development, the role of specific genes in that development, and the efficacy of therapeutic strategies, and at the same time – because of the translational nature of PET imaging – help us understand the similarities and, more importantly, the differ-

ences between animal models and humans. The challenge is that right now, we can only look at one target or pathway at a time."

But it may not be too much of a reach to design families of reporter genes and imaging probes that can be used to study multiple genes and proteins interacting in networks or pathways. Cherry makes the analogy that the initial imaging studies conducted over the past decade were merely soloists playing individual parts of a larger symphony. As scientists learn more about their molecular music in the future, he believes, we may be able to bring the soloists together and begin to play the whole symphony.

Author: Tim Friend is a science writer based in Alexandria, Virginia. He is the author of *Animal Talk: Breaking the Codes of Animal Language*, and is writing a second book on the discovery of a new form of microbial life discovered in the earth's most extreme environments. He has written for numerous magazines and was a science and medical reporter for *USA Today* for 17 years.