

NOVEMBER 14, 2005

PET Imaging Reveals the Immune System at Work

For clinicians, the ability to look routinely inside the body and see — at the level of the cell — how it confronts disease is a distant dream.

But in a series of experiments with genetically engineered mice, a team of researchers from the Howard Hughes Medical Institute (HHMI) at the University of California Los Angeles has taken a key step toward realizing that vision by demonstrating the ability to peer inside the body non-invasively and see the immune system at work.

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— Owen N. Witte

The new research is important because it may one day aid physicians in the diagnosis and treatment of important conditions such as cancer and other diseases.

Writing in the November 15, 2005, issue of *Proceedings of the National Academy of Sciences (PNAS)*, a team of researchers led by HHMI investigator Owen N. Witte at UCLA's Jonsson Comprehensive Cancer Center reports the results of experiments that enabled the group to tune in to the cellular battles waged by the immune system deep in the body. Using positron emission tomography or PET, Witte and his colleagues were able to observe key cells of the immune system as they responded to tumors in mice.

"We know we can use PET to visualize cancer," said Witte. "Now we can use it to visualize the immune response to cancer" and other conditions.

This ability, he said, promises an unprecedented look at how the immune system attacks — or sometimes promotes — disease at the molecular level. It may help scientists and clinicians better evaluate specific immune responses to disease, making diagnosis and treatment more precise and effective.

When confronted with disease, the immune system deploys a complex network of specialized cells to defend the body. A malfunctioning immune system can cause such things as allergies, arthritis, cancer and AIDS as the body turns on itself.

Current technology to assess immune response relies on invasive procedures such as biopsies to gather tissue that can be analyzed to determine how well or how poorly the body is faring against disease. The advantage of using the new PET technique, said Witte, is that surgical procedures are avoided and a PET scan can give clinicians a picture not only of an afflicted part of the anatomy, but of the whole body over time and in a way that portrays the body's response to disease as it happens.

PET is already a widely used technology. In conventional clinical settings it produces images of the body by detecting radiation emitted from radioactive substances, such as fluorodeoxyglucose, injected into the body. In the work reported by Witte's group, PET was used to follow immune cells whose DNA included "reporter genes," genes engineered to help concentrate chemical tracers detectable by PET imaging.

The experiments conducted by Witte's group utilized mice whose immune systems had been suppressed and then replaced using bone marrow from another mouse. The donor marrow included cells with genes engineered to be detectable by PET. By inducing cancer in the mice, Witte and his team were then able to observe specific immune cells at work as they reacted to the tumor.

"The fact that we can visualize the cellular immune response without invading the body is an important advantage," Witte noted. "We can see immune reactions in the body that would otherwise not be easy to see. If you test blood, for example, it may not tell you what's going on in the liver or the spleen. With this technique, the sensitivity for monitoring the immune system is incredible because you're seeing the whole body."

That global perspective makes it possible to see critical ancillary responses in addition to the specific cellular battles of the immune system at the site of a tumor, for example. In their experiments Witte's group was able to see the lymph nodes, which resided at some distance from the tumor, spring into action. Lymph nodes are a critical part of the immune system, helping to recruit key disease-fighting immune cells.

"This lets us see not only how but where" the body is responding to disease, Witte explained. "The immune system resides throughout the body, and it is not going to be responding the same everywhere."

Moreover, a whole-body perspective, Witte said, may be especially useful as new therapies designed to modulate the immune system in response to disease become available. At present, there are very few tools available to follow the extent and duration of responses to such treatment.

The new approaches devised by Witte and his colleagues, can now be applied to "visualize immune cell expansion and activation (and) can be used for the evaluation and development of immunotherapies for cancer and other diseases," he said.

One intriguing possibility, according to Witte, is that these techniques could be turned to the study of autoimmune diseases, where the immune system mistakenly identifies native cells or tissues as foreign and mounts an attack.

The techniques they've developed should now enable scientists — and one day clinicians — to observe the ebb and flow of the immune system over the course of an episode of disease or autoimmune response, said Witte.

In addition to Witte, authors of the new *PNAS* article include Chengyi J. Shu, Amar Nijagal and Caius G. Radu, all of UCLA's department of microbiology, immunology and molecular genetics; Shuling Guo of UCLA's Howard Hughes Medical Institute; Young J. Kim of the department of otolaryngology-head and neck surgery at the Johns Hopkins School of Medicine; Stephanie M. Shelly of the UCLA department of molecular and medical pharmacology; and Pritha Ray and Sanjiv S. Gambhir of Stanford University's departments of radiology and bioengineering.