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BY KATHERINE UNGER BAILLIE

By pairing an intimate knowledge of immune-system function with a deep understanding of statistical physics, a cross-disciplinary team at the University of Pennsylvania has arrived at a surprising finding: T cells use a movement strategy to track down parasites that is similar to strategies that predators such as monkeys, sharks and blue-fin tuna use to hunt their prey.

With this new insight into immune-cell movement patterns, scientists will be able to create more accurate models of immune-system function, which may, in turn, inform novel approaches to combat diseases from cancer to HIV/AIDS to arthritis.

The research involved a unique collaboration between the laboratories of senior authors Christopher Hunter, professor and chair of the Pathobiology Department at Penn Vet, and Andrea Liu, the Hepburn Professor of Physics in the Department of Physics and Astronomy. Penn Vet postdoctoral researcher Tajie Harris and physics graduate student Edward Banigan also played leading roles in the research.

The study, published recently in *Nature*, was conducted in mice infected with the parasite *Toxoplasma gondii*. This single-celled pathogen is a common cause of infection in humans and animals; as much as a third of the world's population has a dormant form of this infection present in the brain. However, in immunocompromised individuals, such as those with HIV/AIDS or undergoing organ transplantation, this infection can have serious consequences, including brain inflammation and even death.

Earlier work had shown that T cells — a key immune-cell type — are central in preventing disease caused by *T. gondii*. In the new study, the Penn researchers used the infected mice as a natural model system to learn how the movement of T cells in the brain affects the body's ability to control this infection.

Among immunologists, it's widely believed that the movement of immune cells is governed in part by signaling proteins called chemokines. The Penn-led team demonstrated that a specific chemokine, CXCL10, and its receptor were abundantly produced in the brains of *T. gondii*-infected mice. When CXCL10 was blocked, mice had fewer T cells, a greater parasite burden and actively reproducing parasites.

Next the researchers sought to pinpoint the exact movement patterns of individual T cells in living tissue from *T. gondii*-infected mice. This was possible with multi-photon imaging, a technique that relies on a refined yet powerful microscope that can display living tissues in three dimensions in real time. Using this approach, the team found that CXCL10 appeared to play a role in the speed at which T cells are able to search for and control infection.

To the extent that immunologists had considered T-cell movement patterns at all, many assumed that they moved in a highly directed fashion to find infected cells. But when the researchers analyzed the movement of T cells, they found their data did not match what would be expected: the T cells showed no directed motion.

That's where the statistical physics expertise of Dr. Liu and Banigan came in.

"We looked at a much more complete way to quantify these tracks and found that the standard model didn't fit at all," Dr. Liu said. "After some work we managed to find a model that did fit the tracks beautifully."

"The model that finally led us down the right path," Banigan said, "had a strong signature of something really interesting," a model known as a Lévy walk.

This "walk," or a mathematically characterized path, tends to have many short "steps" and occasional long "runs." The model was not fully consistent with the data, however.

"Rather, I had to look at variations on the Lévy walk model," Banigan said, because the researchers also observed that the T cells paused between steps and runs. Like the movements of the cells, the pauses were usually short but occasionally long.

Dr. Hunter likened the model to a strategy a person might employ to find misplaced keys in the house.

"When you lose your keys, how do you go about looking for them? You look in one place for a while, then move to another place and look there," he said.

"What that leads to is a much more efficient way of finding things," Dr. Liu said.

And, indeed, when the team modeled the generalized Lévy strategy against other strategies, they confirmed that the Lévy walk was a more efficient technique to find rare targets. That makes sense for T cells, which have to locate sparsely distributed parasites in a sea of mostly normal tissue.

Interestingly, T cells are not alone in employing a Lévy-type strategy to find their targets. Several animal predators move in a similar way — with many short-distance movements interspersed with occasional longer-distance moves — to find their prey. The strategy seems particularly common among marine predators, including tuna, sharks, zooplankton, sea turtles and penguins, though terrestrial species like spider monkeys and honeybees may use the same approach to locate rare resources.

This parallel with animal predators also makes sense because parasites, like prey species, have evolved to evade detection.

"Many pathogens know how to hide, so T cells are not able to move directly to their target," Dr. Hunter said. "The T cell actually needs to go into an area and then see if there's anything there."

The model is also relevant to cancer and other immune-mediated diseases, Dr. Hunter noted.

"Instead of looking for a parasite, these T cells could be looking for a cancer cell," he said. By knowing what controls T cell movement, "you might be able to devise strategies to make the T cells more efficient at finding those cells."

On the physics side, while the Lévy-walk model is not new, the fact that T cells pause in between their steps or runs is something that hadn't been recognized before when mapping the paths in other contexts.

"From a physics point of view, to have runs and pauses is a new model," Dr. Liu said. "Biological phenomena can illustrate what we wouldn't have thought about otherwise."

The Penn collaborators are working to plot the tracks of other cell types and credit their unique partnership for their discovery.

"We've said all along that this study could only happen because [our physics colleagues] had such a great expertise and we had our own separate expertise," Dr. Harris said. "They took a chance working with us, and it turned out to be something really rewarding."

Additional Penn contributors to this study included Penn Vet's David Christian, Christoph Konradt, Elia Tait Wojno and Beena John.

The Penn team partnered on the work with Kazumi Norose of Chiba University in Japan; Emma Wilson of the University of California, Riverside; Wolfgang Weninger of the Sydney Medical School; and Andrew Luster of Massachusetts General Hospital.

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