Looking through the eyes of a mouse, scientists monitor circulating cells in its bloodstream

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A team of researchers from the Wellman Center for Photomedicine at Massachusetts General Hospital (MGH) and Harvard Medical School (HMS) have developed an optical device that allows them to peer through the eyes of a mouse and monitor the cells passing through its bloodstream.

In the Dec. 1 issue of the journal *Optics Letters*, published by the Optical Society of America, the team describes how they used the device, called a retinal flow cytometer, to non-invasively sample the blood passing through the vessels in the retinal tissue in the back of the eye. There they were able to detect circulating fluorescently labeled cells as they wound their way through the mouse.

"We could detect and count circulating cells continuously without drawing blood samples," says MGH/HMS investigator Charles Lin.

The ability to count circulating cells is important in diseases like multiple myeloma because the number of cancer cells in the bloodstream at the onset of the disease may represent only a tiny fraction of circulating cells in the bloodstream.

Though few in number, these rare cells nevertheless can be relentless. Multiple myeloma starts when cancerous immune system cells residing in the bone marrow quickly multiply out of control. Rather than forming

a solid tumor, though, they spread throughout the body and crowd out other cells in the bloodstream. Multiple myeloma cells can invade bones throughout the body, eroding and weakening them and leading to fractures and sometimes paralysis because of compression of the spinal cord. Eroding the bones can also drastically increase the calcium levels in the blood, sometimes causing kidney failure. Moreover, multiple myeloma cells can crowd out the oxygen-ferrying red blood cells in the bloodstream and cause anemia.

Multiple myeloma is treatable, but the disease has a high rate of recurrence. Scientists like Lin and his collaborator Irene Ghobrial of the Dana-Farber Cancer Institute are interested in helping people with multiple myeloma by finding better drugs and treatment strategies. The new optical device may become a valuable tool because it allows them to test the effect of various experimental chemotherapy agents and therapeutic strategies in mice with multiple myeloma.

Testing the effect of new chemotherapy agents in the bloodstream of a mouse has traditionally been difficult because there was no way to monitor the blood continuously. The best scientists could do was to draw blood samples at various time points and count the number of cancer cells in these samples. But looking for rare cancer cells required drawing a lot of blood. Repeated blood sampling from a single mouse was impossible, though, because mice only have a few milliliters of blood in their body.

A few years ago Lin and his colleagues devised a way to monitor cancer cells in rodents directly. They adapted a technique called flow cytometry, which scientists have used for decades to sort cells in the laboratory. Basically it involves streaming a complex mixture of cells in liquid past the focus of a powerful microscope and looking for particular cells—distinguishable because they have particular markers that are visible under the microscope.

Lin and his colleagues developed a way to use flow cytometry in vivo and monitor a mouse's bloodstream directly. Initially they designed a device that could focus on a vessel in the ear of a mouse. While effective, this device was limited because the one tiny vessel in the mouse's thin external ear did not have enough flow to adequately sample the bloodstream. It was a bit like trying to sample the traffic in New York by looking at a single side street in the Bronx. A better strategy would be to monitor several avenues at once—or in vascular terms, a cluster of several vessels at the same time.

This is exactly what the researchers are doing by looking into the back of a rodent's eye. The retinal tissue is rich with blood supply, and Lin and his colleagues were able to sample a greater number of blood vessels and a much larger volume of blood. In initial feasibility experiments, they monitored a million circulating cells in the mouse that were fluorescently labeled with a marker that allowed them to be spotted with a microscope. The cytometer allowed them to track these cells as they trafficked though the bloodstream. They could observe approximately 250 cells per minute, and over time statistically model the flow of the cells.

This new device is not designed for humans and has not been tested in clinical trials. As a laboratory tool, however, it will allow the team to observe what happens when different chemotherapy agents are given to rodents—a standard early approach for evaluating the effectiveness of new chemotherapy agents and treatment strategies for humans.

Source: Optical Society of America