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Scientists develop technique to decipher the dormant AIDS virus concealed in cells

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Scientists at the Gladstone Institutes have gotten us one step closer to understanding and overcoming one of the least-understood mechanisms of HIV infection—by devising a method to precisely track the life cycle of individual cells infected with HIV, the virus that causes AIDS.

In a paper being published online today in Lab on a Chip, the laboratory of Gladstone Investigator Leor Weinberger, PhD, announced the development of a device that can pinpoint and track HIV inside CD4 T cells—the type of white blood cell that the AIDS virus targets. This development is particularly important for understanding "HIV latency," a state in which the virus goes dormant after the patient begins standard antiretroviral treatment. Current antiretroviral drugs do not kill HIV—they only keep it at bay—meaning that those with HIV must continue a lifetime of drug treatment so as not to develop AIDS. If they discontinue the drugs, the latent virus "wakes up" within just a few weeks and begins an onslaught against the body's immune system.

The breakthrough comes as the AIDS-researcher community is beginning to speak publicly about the possibility of curing HIV/AIDS. Understanding—and consequently interrupting—HIV latency is a key element in the effort to discover a cure for this devastating disease.

"HIV latency is perhaps the single greatest obstacle to eradicating HIV/AIDS in the 34 million people who live with the disease worldwide," said Dr. Weinberger, who is also an associate professor of biochemistry and biophysics at the University of California, San

Francisco (UCSF), with which Gladstone is affiliated. "Existing techniques that try to uncover the cellular and viral mechanisms behind HIV latency are inefficient at studying very rare cells—and cells housing the latent HIV virus are one-in-a-million. Our technique presents a clear path towards understanding how HIV latency is regulated within a single cell, by tracking the individual cells that traditionally had been difficult to monitor."

Singe-cell, time-lapse microscopy—a state-of-the-art technique that scientists have lately used to track some viral infections and map antibiotic resistance to drugs—has not worked for tracking the HIV-infection cycle in CD4 T cells, especially in the latent state. This is because these cells are notoriously evasive. They spontaneously move around, attaching and detaching from their neighbors, making it nearly impossible to monitor individual HIV-infected cells over time.

However, Dr. Weinberger's team devised a clever system that essentially guides and suspends HIV-infected T cells into tiny finger-like channels—reducing their ability to move or detach from their neighbors.

"First, we load the T cells into a small well, allowing them to settle into the bottom—which is filled with nutrients that keep the cells well-fed and stress-free," explained the paper's lead author Brandon Razooky, a Gladstone and UCSF graduate student. "Next, we tilt the device and the cells slide into microscopic finger-like channels that are attached to the well. Finally, we return the device to its upright position, locking about 25 T cells inside each channel and essentially 'freezing' them in place."

The device has several advantages over current methods. First and foremost, individual cells stay in place so investigators can follow them over time with single-cell, time-lapse microscopy. Second, the fact that each T cell is suspended in nutrients in close physical contact with other cells results in near optimal conditions for keeping the infected cell alive

for the virus' entire life cycle.

"This means that we now have the potential to analyze the entire course of an HIV infection in an individual cell—especially during the crucial latency stage—for which we know so little," said Dr. Weinberger. "In the future, we plan to expand the device's design to include a larger number of wells and channels to track HIV infection on a larger scale. We want to use the information gleaned here to finally unravel the mechanisms behind HIV latency. With that knowledge, we hope to devise a treatment to bring the latent virus out of hiding in order to flush it from a patient's system, once and for all."

Provided by Gladstone Institutes

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