GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE
NEWS

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FOR YOUR INFORMATION
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NEW ROBOTIC MICROSCOPE TO HELP SCIENTISTS TRACK CELLS OVER TIME

A new invention—a robotic microscope—is opening the way for scientists to track changes in cells over time as genes are expressed and the resulting proteins go into action. Tracking this dynamic process is extremely difficult using conventional techniques. Part of the problem has been the cells' need for the warmth and atmosphere of an incubator such that cells can only be taken out and viewed for brief periods of time.

The robotic microscope, the brainchild of Steven Finkbeiner, MD, PhD, investigator in the Gladstone Institute of Neurological Disease and UCSF assistant professor of neurology and physiology, overcomes this problem.

At first glance, the robotic microscope looks like an ordinary inverted microscope. The differences are in the fast and precise motors and sophisticated computer programs that automatically focus the objective, move the stage, and photograph cells growing in a plastic tissue culture plate.

For each plate of cells, the microscope first focuses on an internal reference point. It then moves the plate a precise distance, refocuses itself, and takes a photograph, repeating this process until it has obtained images of the entire plate or any specific area.

Hours or days later, the plate can be returned to the microscope, and the same cells can be identified and re-examined. A computer program, also developed by Finkbeiner, automatically analyzes the photos within minutes. He can ask the computer to measure cells with specific morphologies, specific amounts of proteins, or other features.

"The pieces of the puzzle were out there, it was just a matter of putting them together," said Finkbeiner, referring to the components he used to build the microscope.

The microscope was developed to facilitate his studies of Huntington's disease, an inherited neurological disorder that causes involuntary movements, cognitive decline, and personality disturbances, usually beginning in midlife, Finkbeiner said. Huntington's disease is caused by a mutation in the gene that encodes huntingtin, a protein of unknown function. Scientists know that mutant huntingtin is responsible for the neurodegeneration, but they don't know how it causes individual neurons to die.

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Does neurodegeneration result when the mutant huntingtin molecules clump together to form aggregates? Or does the mutation cause harm by changing the activity of huntingtin molecules that are not tangled up in the aggregates?

To answer those and other questions, Finkbeiner uses his robotic microscope to study neuronal cells that express mutant huntingtin tagged with fluorescent reporter molecules. The fluorescence from the mutant protein can be easily visualized with special filters on the microscope. By examining the same cells repeatedly over time, he can correlate the appearance and aggregation of the mutant huntingtin with cellular changes indicative of degeneration.

Before developing the robotic microscope, Finkbeiner used immunocytochemistry to view the neurons. But this technique is limited because it provides only a “snapshot” of cells at a single point in time, but no information about the dynamic process of neurodegeneration. And neurons that would degenerate later could not be assessed at all because there was no simple or reliable way to find them again.

In addition, analyzing the cells was laborious and time-consuming. In a typical experiment, 300,000 cells are analyzed, a task that used to take six weeks. With the robotic microscope, it takes only 15 minutes. Another advantage of the new device is that the criteria used to define features of interest, such as markers of degeneration, are clearly defined and applied consistently by the computer program, eliminating possible bias, Finkbeiner said.

Perhaps most importantly, the ability to track individual cells over time allows Finkbeiner to identify factors that predict the fate of the cell. “We can examine neurons well before they die, make measurements of whatever we wish, and then determine which factors have prognostic value, whether they predict survival or neurodegeneration, and how strong the prediction is. This is a powerful new way to guide our investigation into the underlying mechanisms of neurodegeneration,” he said.

The microscope is a breakthrough for research into Huntington’s disease and many other diseases or processes that requires high-throughput cell biology.

“Use of the microscope isn’t limited to neuroscience,” Finkbeiner said. “Many scientists who need to study developmental, adaptive, or maladaptive responses in cells over time and provide quantitative descriptions of them could benefit from using the system.”

The Gladstone Institute of Neurological Disease is one of three research institutes that comprise The J. David Gladstone Institutes, a private nonprofit biomedical research institution affiliated with UCSF. The institute is named for a prominent real estate developer who died in 1971. His will created a testamentary trust that reflects his long-standing interest in medical education and research.

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