In a new microchip, cells separate by rolling away

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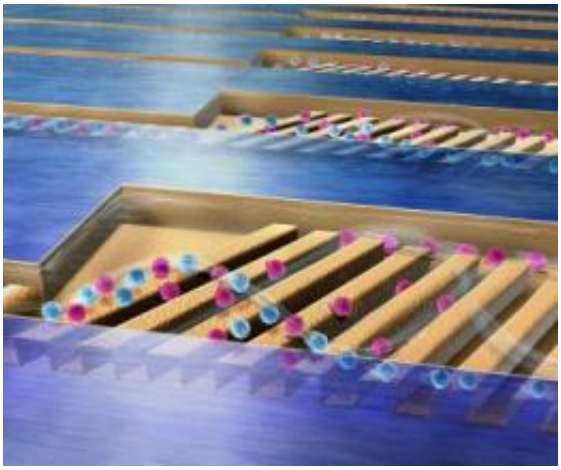

A new microfluidic device isolates target cells (in pink) from the rest of the flow by getting them to stick weakly to the device's ridges, then roll through trenches, and into a collection chamber. Image: Nicolle Rager Fuller

Cell rolling is a common mechanism cells use to navigate through the body. During inflammation, for example, the endothelial cells that line blood vessels present certain molecules that attract white blood cells just enough to divert them from the rest of the vessel's cellular traffic. White blood cells then roll along the vessel wall, slowing down to help in the healing of inflamed areas.

Researchers at MIT and Brigham and Women's Hospital have now designed a cell-sorting microchip that takes advantage of this natural cell-

rolling mechanism. The device takes in mixtures of cells, which flow through tiny channels coated with sticky molecules. Cells with specific receptors bind weakly to these molecules, rolling away from the rest of the flow, and out into a separate receptacle.

The cell sorters, about the size of postage stamps, may be fabricated and stacked one on top of another to sift out many cells at once — an advantage for scientists who want to isolate large quantities of cells quickly. The device doesn't necessarily require an external pump to push cells through the chip, which makes it a portable, affordable option for use in laboratories or clinics, where cell samples may be taken and sorted without specialized equipment.

"We're working on a disposable device where you wouldn't even need a syringe pump to drive the separation," says Rohit Karnik, the d'Arbeloff Assistant Professor of Mechanical Engineering at MIT. "You could potentially buy a $5 or $10 kit and get the cells sorted without needing any kind of [additional] instrument."

Karnik collaborated with postdoc Sung Young Choi of MIT and Jeffrey Karp, co-director of the Center for Regenerative Therapeutics at Brigham and Women's. The team reported their findings in a paper posted online in the journal Lab on a Chip.

While current cell-sorting technologies separate large batches of cells quickly and efficiently, they have several limitations. Fluorescence-activated cell sorting, a widely used technique, requires lasers and voltage to sort cells based on their electric charge — a complex system requiring multiple parts. Researchers have also used fluorescent markers and magnetic beads that bind to desired cells, making them easy to spot and sift out. However, once collected, the cells need to be separated from the beads and markers — an added step that risks modifying the samples.

Going with the flow

Karnik's team designed a compact cell sorter that requires no additional parts or steps. The team built upon their 2007 work with MIT's Robert Langer and others, in which they first came up with the sorting-by-rolling principle. Since then, the group has been turning principle into practice, designing a working device to sort cells. The initial proof-of-principle design was relatively simple: Cells were injected into a single inlet, which gave way to a large chamber coated on one side with sticky, roll-inducing molecules. The incoming cells flowed through the chamber; the cells that bound to the molecules rolled to one side, then out to a collection chamber.

However, the researchers found that in order to allow target cells to first settle on the chamber's surface, long channels were required, which would make the device too large. Instead, Choi came up with a surface pattern that causes cells to circulate within the chamber. The pattern comprises 10 parallel channels with 50 ridges and trenches, each ridge about 40 microns high. The researchers coated the ridges with P-selectin, a well-known molecule that promotes cell rolling. They then injected two kinds of leukemia cells: one with receptors for P-selectin, the other without.

They found that once injected, the cells entered the chamber and bounced across the top of the ridges, exiting the chip through an outlet. The cells with P-selectin receptors were "caught" by the sticky molecule and flipped into trenches that led to a separate receptacle. Through their experiments, the team successfully recovered the cells they intended to sift out with 96 percent purity.

Karnik says the device may be replicated and stacked to sort large batches of cells at relatively low cost. He and his colleagues are hoping to apply the device to sort other blood cells, as well as certain types of

cancer cells for diagnostic applications and stem cells for therapeutic applications. To do that, the team is investigating molecules similar to P-selectin that bind weakly to such cells. In the future, Karnik envisions tailor-made cell rolling, designing molecules and surfaces that weakly adhere to any desired type of cell.

“It’s really the ability to design molecules to separate cells of interest that will be powerful,” Karnik says. “There’s no reason to believe it cannot be done, because nature has already done it.”

The device is a “smart design,” says Milica Radisic, an associate professor of biomedical engineering at the University of Toronto, who was not involved in this research. Radisic says because the device relies on hydrodynamics within the chamber, it doesn't require external equipment.

“The design is probably good as it is for separation of leukemia cell lines,” Radisic says. “The question is if it can be adopted for other receptor/ligand pairs.”

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