Scientists invent new way to sort cells by type using light

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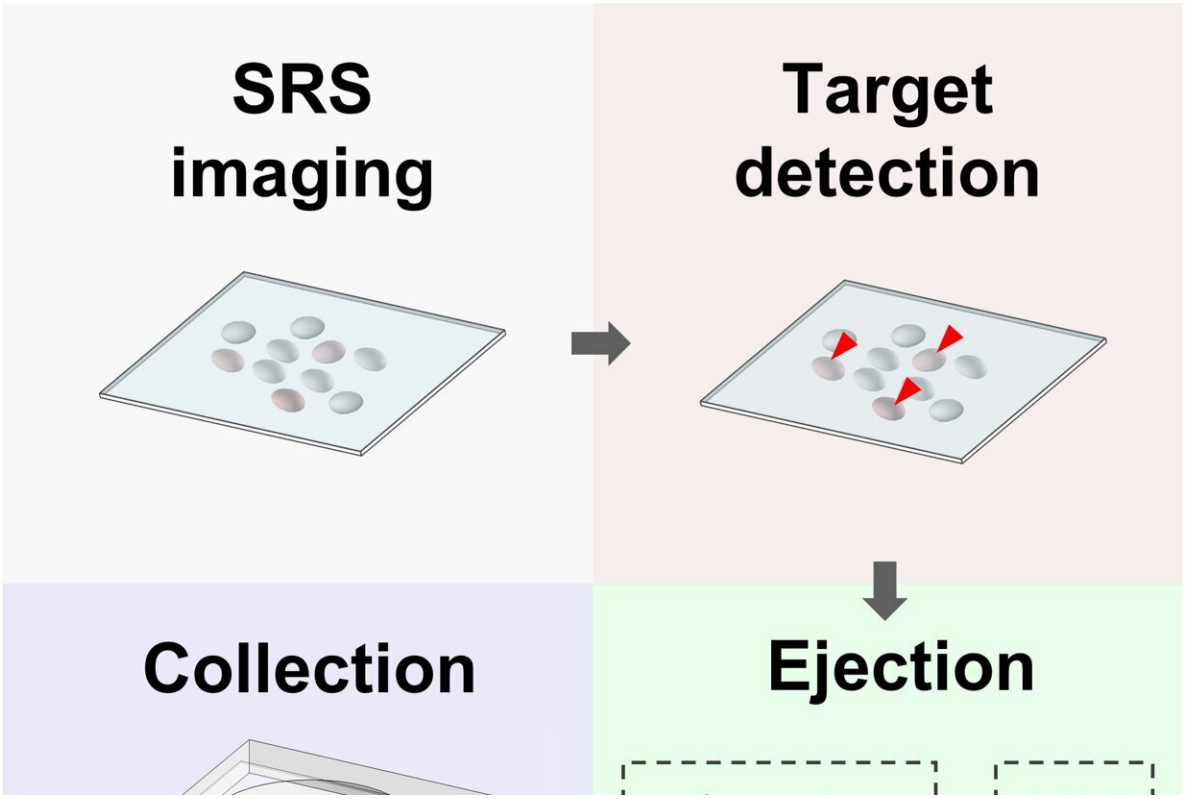

Workflow of stimulated Raman activated cell ejection (S-RACE). Credit: Jing Zhang, Boston University

Researchers have developed and demonstrated a new method for high-throughput single-cell sorting that uses stimulated Raman spectroscopy

rather than the traditional approach of fluorescence-activated cell sorting. The new approach could offer a label-free, nondestructive way to sort cells for a variety of applications, including microbiology, cancer detection and cell therapy.

Jing Zhang from Boston University will present this research at Frontiers in Optics + Laser Science (FiO LS), which will be held 9–12 October 2023 at the Greater Tacoma Convention Center in Tacoma (Greater Seattle Area), Washington.

"Our approach (stimulated Raman-activated cell ejection, S-RACE) offers an innovative way to sort cells based on their intracellular chemical composition in a high-throughput manner," explains Zhang.

"Various downstream phenotypic and/or genomic analysis could be applied to the separated cell populations. Furthermore, its compatibility with small cells is advantageous for sorting bacteria and other microorganisms. For example, by employing S-RACE, pathogens or cells exhibiting specific metabolic profiles could be directly captured from their natural habitat, e.g. water bodies, soil, or gastrointestinal tract. Subsequent sequencing enables tasks such as cell taxonomy identification and ecological function assessment."

Flow cytometry is used in many biomedical fields to rapidly count and characterize various types of cells, including blood cells, stem cells, cancer cells and microorganisms. Sorting cells based on their size, granularity or expression of cell surface and intracellular molecules can be used to gain insights into biological processes or to separate out cells with certain characteristics for additional analysis.

Although most current high-throughput cell sorting methods rely on fluorescence signals for sorting, fluorescence labels can disturb cell function and can't be used with small molecules. Raman spectroscopy is

a promising alternative because it offers label-free and non-destructive single-cell measurement by obtaining a chemical fingerprint of the cell. However, it has been difficult to achieve both a strong Raman signal and a practical microfluidic setup for imaging cells.

In the new work, the researchers describe how they overcame this challenge by using stimulated Raman spectroscopy, which produces a signal several orders of magnitude higher than the more commonly used spontaneous Raman scattering. For sorting, stimulated Raman images are acquired to identify objects or cells of interest, and then 2D galvo mirrors point a 532-nm pulsed laser to the cell. Finally, an acousto-optic modulator is used as a fast pulse picker so that single laser pulses can be used to push the selected cell into the collector. Each ejection takes only about 8 milliseconds.

The researchers first demonstrated their stimulated Raman-activated cell ejection method using a mixture of 1-micron polymer beads, achieving around 95% purity and 98% throughput with about 14 ejections performed each second. They also showed that the method could be used with fixed bacteria.

To apply the sorting method to live yeast cells, the researchers added a thin layer of agar to the ejection module to protect cells from heat and drying and used an agar dish as a collector to provide more cushioning and moisture during cell landing. The researchers used the system to eject approximately 340 yeast cells and observed successful cell growth in the receiving dish after around 40 hours. They also showed that other genomic analysis approaches such as quantitative polymerase chain reaction could be integrated with the sorting approach.

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