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ThinkCyte, Inc.: Machine vision-based cell sorting transforms cell therapy and drug discovery

Combining cell sorting technology with artificial intelligence, Japan-based ThinkCyte aims to discover novel high-value therapeutic cells, new functional genes, and novel drug candidates for itself and its partners worldwide.

It is often said that a picture is worth a thousand words, but half a century since the first fluorescence-activated cell sorting (FACS) was launched, researchers still do not have a commercial tool to sort single cells at high speed based on image information.

Overcoming the technological challenges, ThinkCyte has developed Ghost Cytometry, a proprietary machine Vision-based Cell Sorting (ViCS) technology that integrates a novel ultrafast imaging technique with artificial intelligence (AI) to identify and sort cells based on image information at record high-throughput rates—even above 3,000 cells per second (Fig. 1). In contrast to the single spotlight used in conventional FACS, ViCS involves obtaining cellular image information from the motion of cells relative to a static patterned optical structure, and thereby compressively converting it into temporal waveforms. Applying machine-learning methods directly to the compressed waveforms—without time-consuming image reconstruction—enables real-time 'image-free' vision-based cell sorting[1].

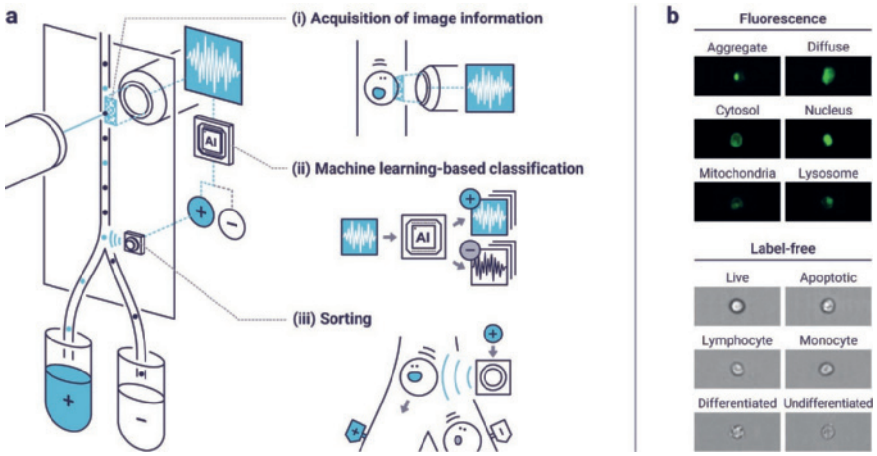

Fig. 1 | Machine vision-based cell sorting (ViCS) technology overview. (**a**) Schematic of the ViCS. (i) Image information of each cell is first compressively converted into a temporal waveform as the cell passes through a light illumination pattern projected onto a microchannel. This waveform is then recorded by using a single pixel detector. (ii) A trained AI model is applied directly to the waveforms for predicting the cell types. (iii) The cells classified based on the machine prediction are gently isolated by fluid pressure. (**b**) Examples of phenotypes which ViCS can distinguish in fluorescence and label-free modes. All images were taken by Amnis FlowSight.

Broad applications

This high-throughput vision-based classification and isolation of cells has broad potential applications, ranging from cell therapy and regenerative medicine to drug discovery and diagnostics.

A key focus is cell therapy, as ViCS enables the detection and isolation of target cells without using cell surface markers or stains. Cells can be classified and isolated according to not only apparent morphological differences (such as those between live and dead cells, activated and resting T cells, and differentiated and undifferentiated stem cells) but also more subtle characteristic morphological variance in cells and organelles (such as cell-cycle phases, glycolytic levels, and apoptotic status). Unwanted cells and particulates, including cancerous cells, monocytes, and plastic beads, can also be monitored and removed without using markers. In 2020, ThinkCyte and Hitachi, Ltd. jointly announced a collaboration to develop an AI-driven cell analysis and sorting system using ViCS for the use in cell manufacturing processes.

"The unprecedented speed of our ViCS technology offers significant advantages over cell surface marker-based selection methods currently prevalent in cell therapy," explained Hikaru Nagahori, CBO at ThinkCyte. "The high-throughput ability to characterize and isolate cell populations based on their image information without the use of markers or stains is highly compatible with cell manufacturing automation and enables stable, affordable, large-scale, high-quality standardized cell manufacturing processes."

Another area that ThinkCyte's ViCS is set to impact significantly is high-content screening of genes and drugs. Conventionally, a pile of microplates and a microscope have been used for high-content screening to identify functional genes and drug candidates that alter cell image phenotypes including changes in protein localizations, aggregation, cell morphology, and intracellular organelles. Although powerful, this arrayed format method is a relatively time-consuming and costly process and is not suitable for suspended cells. Using ViCS, however, ThinkCyte has developed a workflow to perform such high-content screens in a pooled format (starting from a suspension of pooled cells in a tube).

"Our screening platform significantly accelerates the screening processes and is applicable to a variety of libraries, including CRISPR/Cas9 sgRNA, shRNA, and even small compounds," said Asako Tsubouchi, head of Drug Discovery at ThinkCyte. "Furthermore, label-free distinction of disease-associated cells that have subtle morphological differences provides a new way of linking genotype to phenotype and will offer unique phenotypic endpoints, including those which are often difficult to distinguish using the human eye."

Partnering goals

ThinkCyte has already partnered with multiple leading global pharmaceutical companies and research institutes to utilize ViCS in life science and medical fields. ThinkCyte is seeking new partners interested in conducting collaborative research using its platform to discover novel high-value therapeutic cells, new functional genes, and novel drug candidates and/or collaborating on instrument development to customize its cell analysis and sorting system to suit partners' cell-manufacturing processes.

"Our unique ViCS is a high-throughput and high content cell sorting system that has the potential to revolutionize cell therapies and drug discovery to benefit patients and their families worldwide," said Waichiro Katsuda, ThinkCyte's co-founder and CEO. "We are confident that our unique and innovative technology will solve key issues in the biopharmaceutical industry and look forward to establishing new partnerships to make a better world together."

1. Ota, S. et al. *Science* **360**, 1246–1251 (2018).

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