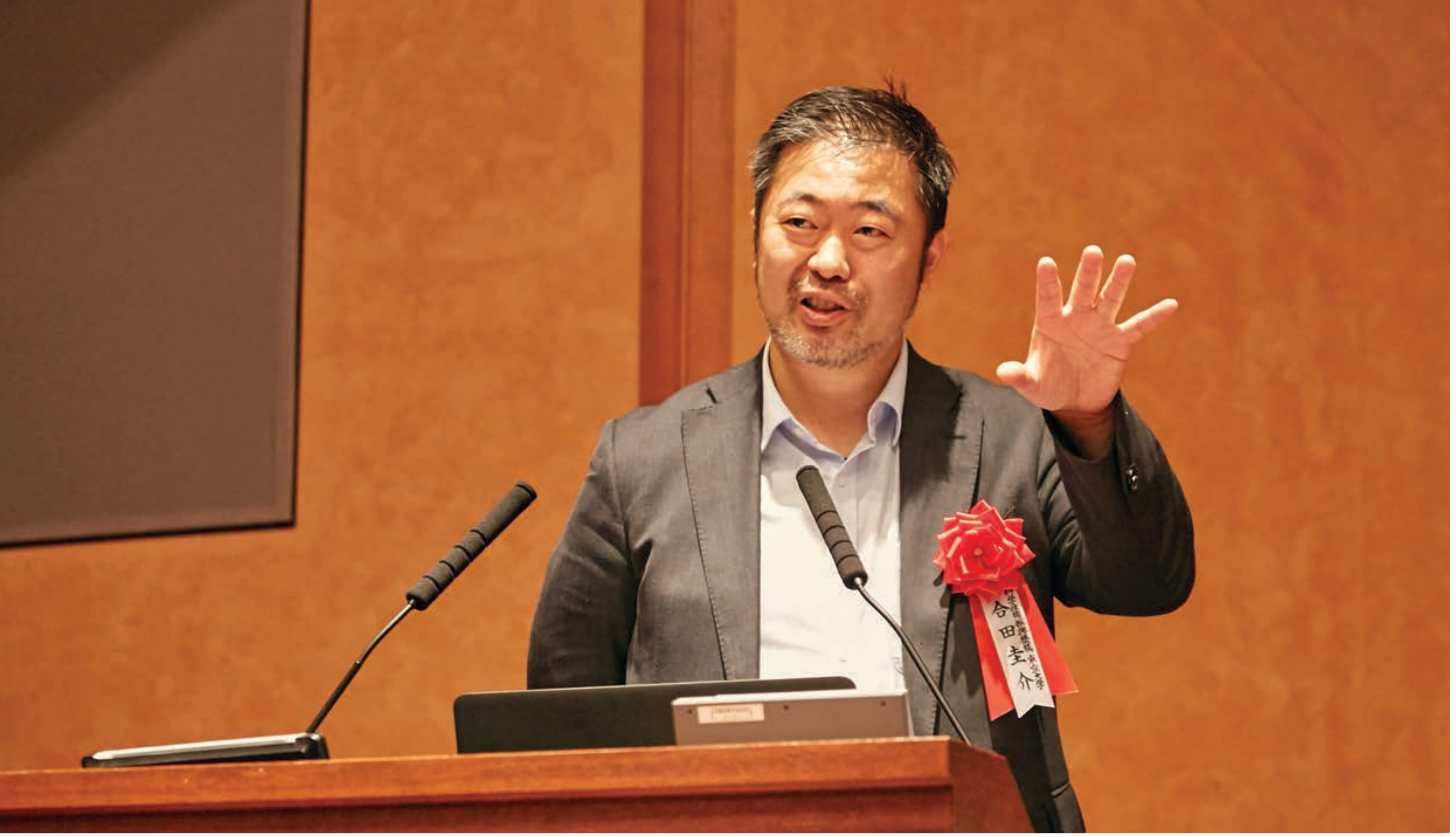

Keisuke Goda describes his dream of producing a cell-selection tool that would be like a web search engine for cells.

Rosetta Stone for single-cell biology

A cell-sorting method that uses artificial intelligence greatly reduces processing time without sacrificing accuracy

[ImPACT Program]
Planned Serendipity

The analysis of cells underpins the study of many biological and medical fields, including immunology, genetics, pharmaceuticals and biofuel research. Part of that analysis requires accurately sorting the myriads of microscopic cells that make up a sample.

At a recent symposium at the University of Tokyo, researchers from the university and other centres in Japan and the United States discussed the development of a breakthrough technology that harnesses artificial intelligence to provide cell sorting that is both specific and speedy.

DETAILED AND FAST

Conventional cell-sorting methods rely on two approaches. The more traditional one employs a microscope to investigate individual cells, and pick out relevant ones with a pipette. While highly accurate, this method is time consuming and inefficient. The other approach is fluorescence-activated cell sorting, a type of flow cytometry developed in the 1970s that sorts cells automatically based on their fluorescence and light-scattering properties. Although much faster than optical microscopy, it cannot distinguish single cells from aggregates, nor can it identify cells based on features such as their shape and internal structure.

Intelligent image-activated cell sorting (iIACS) combines the best aspects of the two conventional approaches, achieving detailed cell analysis with a high-throughput automated system, researchers told the Planned Serendipity symposium, held on 9 November 2018.

"We wanted to create a cell-selection tool that can produce high-resolution data at high throughput," Keisuke Goda, a professor in the Department of Chemistry at the university's Graduate School of Science, told delegates. "It would be like a web search engine, but for cells. That was the goal of this research."

"The technology is highly versatile and expected to enable machine-based scientific discovery in biological, pharmaceutical, and medical sciences," Goda and his 50 co-authors wrote in a *Cell* paper published in August (Nitta *et al.* Intelligent image-activated cell sorting. *Cell* **175,** 266–276; 2018). The research, supported by the Council for Science, Technology, and Innovation (CSTI; Cabinet Office, Government of Japan), was operated by the Japan Science and Technology Agency, where Goda is a programme manager for ImPACT, which aims to foster disruptive innovations. Conceived 10 years ago and funded by the CSTI in 2014, the iIACS project involved 200 researchers from more than 10 fields and 20-plus institutions.

MULTIDISCIPLINARY APPROACH

The iIACS can image and sort various cell types, including microalgal, human blood and cancer cells, and it features three-colour imaging in high-speed flow of cells ranging in size from 3 to 30 micrometres.

In an overview of the platform, Goda and several of his co-authors described how iIACS incorporates various technologies to produce results. A mixture of cells can be imaged one by one with a frequency-division multiplexing microscope, analysed in real time by an intelligent processor incorporating deep-learning algorithms, and classified so that target cells are isolated. At the heart of the platform is a microfluidic chip that incorporates a three-dimensional hydrodynamic focuser, an acoustic focuser and a push–pull cell sorter. The iIACS platform can process about 100 cells or cell aggregates a second and has a sorting purity of 99%. Several of the study co-authors involved in the underlying technologies of iIACS spoke at the symposium, including Hideharu Mikami, an assistant professor at the University of Tokyo's Department of Chemistry, who said, "We've realized the best confocal fluorescence imaging in the world using frequency-division multiplexing microscopy, with a record-high 16,000 frames per second."

Nao Nitta (left) and Hideharu Mikami explain about the iIACS platform, which can be used for a wide range of applications in research.

The research could lead to the **EFFICIENT PRODUCTION OF BIOFUELS** from algae

A QUANTUM LEAP IN SPEED

"Just as the Rosetta Stone described the same concept in hieroglyphics, demotic and ancient Greek, iIACS can be a Rosetta Stone for single-cell biology, covering microscopy, flow cytometry and gene analysis," said Nao Nitta, an ImPACT associate programme manager. Nitta is also founder and president of a startup founded to commercialize the iIACS technology.

As commercialization proceeds, Kyoto University researchers are already using iIACS to screen for mutant versions of the alga *Chlamydomonas reinhardtii* to find genes essential for carbon concentration. They used the iIACS to analyze more than 200,000 events, of which it identified less than 1% with rare mutations. This would have normally taken six months with conventional labour-intensive approaches, but it took a mere 40 minutes with the iIACS system. The research could lead to the efficient production of biofuels from algae.

Meanwhile, researchers from the University of Tokyo Hospital are using the iIACS system to study platelet aggregates, a potential biomarker for blood clots that can cause common medical conditions such as stroke and heart attack. Detailed analysis of platelet aggregates could yield new techniques for diagnosing and treating blood clots.

"Work that would take one day when done manually can now be done in a minute with iIACS — roughly 1,400 times faster," Goda noted. "This technology could be used via directed molecular evolution to develop functional molecules for anything from food supplements to drug molecules. It simply depends on the target."

Cabinet Office: www.cao.go.jp/index-e.html
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