milestone

THE PARALLEL EVOLUTION OF *ORGANOIDS AND HIGH-CONTENT IMAGING*

Over the past three decades, two powerful trends have converged: 3D organoids and imaging technologies built to study them. As scientists learned to grow tiny tissues to model disease and test therapies, engineers continually advanced imaging tools that enabled more ambitious experiments. Their intertwined efforts have reshaped how researchers observe, measure, and understand complex human biology.

1996

A faster way to see living cells

In the 1990s, confocal microscopy had become indispensable for imaging thick, three-dimensional biological samples, such as tissues and small organisms. Its major limitation, however, was speed. Because point-scanning confocal microscopes illuminated a single spot at a time, live-cell imaging was slow and phototoxic, often resulting in blurred, ghost-like images.

Around this time, Yokogawa — then best known for industrial measurement systems — began exploring life science imaging. To understand what biologists needed, engineer Takeo Tanaami and his colleagues at Yokogawa trained at a university medical school. During one imaging session, a professor watched the confocal microscope struggle to keep up with beating cardiac cells and noted, "We need a confocal system about a thousand times faster" (1).

To reach that speed, Tanaami found promise in the spinning disk — a rotating metal disk with a spiral array of pinholes, originally invented for video transmission. However, this disk had not been widely used for biological imaging since most of the illumination light could not pass through the pinholes, making images extremely dim, like "trying to see stars during the day" (1).

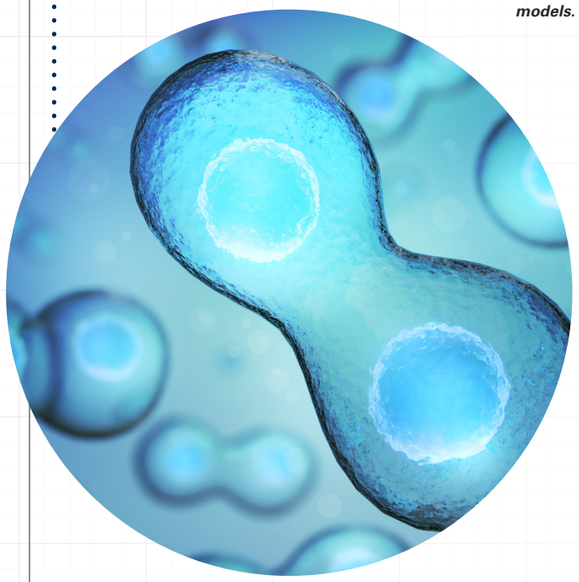
The breakthrough came when Tanaami realized that placing a microlens in front of each pinhole could collect far more light. By precisely aligning a microlens array disk with the pinhole disk, the Yokogawa engineers developed the game-changing dual microlensed spinning disk technology, achieving both speed and brightness, which serves as the backbone of Yokogawa's imaging platforms.

In 1996, Yokogawa released the CSU10, its first spinning-disk confocal scanner unit capable of imaging living cells and 3D biological samples in real time — roughly a thousand times faster than conventional confocal microscopes.

Meanwhile, stem cell biology was advancing quickly. From isolating mouse pluripotent stem cells to developing human embryonic stem cell lines, researchers were laying the foundation for organoids and 3D cell models that would soon follow (2,3).

CREDIT: YOKOGAWA

IMAGE LEFT: The CSU10 introduced a dual spinning-disk design, enabling real-time, gentle imaging that overcame the speed limits of traditional confocal systems. IMAGE BELOW: Breakthroughs in stem cell biology laid the groundwork for the organoids and other 3D cell models.



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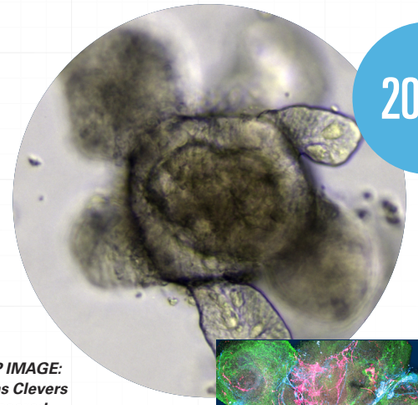
2000s



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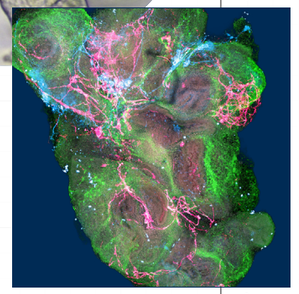

CREDIT: INTERO BIOSYSTEMS

***TOP IMAGE: Hans Clevers pioneered organoid research by generating self-renewing intestinal organoids from single stem cells. RIGHT: Organoids are defined as miniature 3D tissues that self-organize and differentiate into functional cell types, recapitulating key features of organs* in vitro.**

The dawn of organoids

Advances in stem cell biology hinted that cultured cells might be capable of more than forming flat, monolayer sheets. In the early 2000s, a few laboratories began to explore whether stem cells, when given the right cues, could grow into tissues the same way they do inside the embryo.

In 2008, Yoshiki Sasai, a stem cell biologist at RIKEN Center for Developmental Biology, developed a culture system that mimicked the early embryo environment. Within days, mouse embryonic stem cells cultured in it spontaneously arranged themselves into polarized, multilayered cortical tissue that later produced neurons resembling those in the developing mouse cortex. By adding a few signaling molecules, the team could even steer the emerging tissue toward different regions of the cortex, or into neighboring structures (4).

Half a world away, molecular geneticist Hans Clevers at the Hubrecht Institute made a similar discovery in a different organ. In a dish supplied with a handful of growth factors, intestinal stem cells marked by the gene Lgr5 — a key identifier of stem cells in the gut — generated miniature gut-like structures complete with crypts, villus-like domains, and all major epithelial cell types. These structures could maintain themselves for months without their native supporting mesenchymal niche.

Clevers published this work in 2009 and used "organoids" to describe the self-organizing tissues (5). Since then, organoid — a word that once described small tissue fragments taken directly from organs — has taken on a widely recognized new meaning: mini clusters of cells grown *in vitro* that self-organize and differentiate into functional cell types, recapitulating the structure and function of an organ *in vivo* (6).

Imaging going high content

As organoid research quietly gathered momentum, Yokogawa's engineers were wrestling with a new strategic question. Drug screening was moving toward automation, and they realized the spinning-disk unit on its own could not meet this need. They set out to build a complete imaging system that could run complex experiments by itself.

Yasunori Yokoyama, an optics engineer, joined the company in 2005 just as this project was starting. His first task was to help build the optical system for a high-content analysis (HCA) platform. At the time, most microscopy systems changed focus by moving the entire turret of objective lenses. Such an assembly was simply too heavy and too slow for an automated platform expected to scan hundreds of wells.

"We developed the mechanics to move only one objective despite that there are multiple objectives on the turret," Yokoyama explained. The redesigned system would select a single lens and move only that piece to adjust focus.

With much less mass to move, the system could focus more quickly and remain stable during long automated runs. The first prototype, Yokoyama recalled, had "thousands of wire cables and hundreds of terminal blocks" — a light-yellow bundle the team nicknamed "spaghetti."

After years of iteration, the pieces came together. In 2008, Yokogawa introduced the CellVoyager CV6000, its first fully integrated HCA system. Three years later, the CV7000 followed, boosting processing speed roughly fourfold and enabling imaging of a 384-well plate in just four minutes. Although originally designed for drug screening, these systems, which integrated fast 3D spinning-disk confocal imaging with high-content formats, laid the technical foundation needed for organoids that were becoming instrumental in drug discovery.

TOP RIGHT: Yasunori Yokoyama (center) played a key role in developing Yokogawa's HCA platforms and is pictured here with colleagues. Back row (left to right): Koji Oohashi, Yasunori Yokoyama, Yousuke Kawabata, Takumi Fukuda. Front row: Nao Koishihara, Katsuya Tajiri. BOTTOM RIGHT: The CellVoyager CV6000 was Yokogawa's first fully integrated HCA system for automated 3D imaging.

2008

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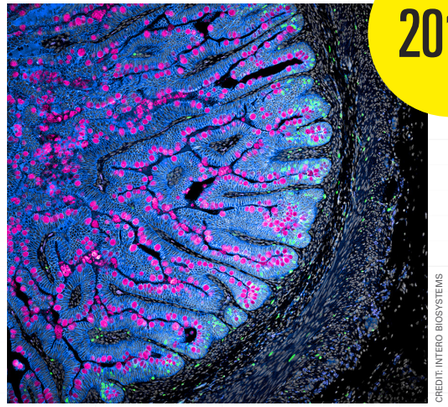
2010s

Expanding organoid models, expanding imaging needs



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CREDIT: ILYA LUKONIN

TOP IMAGE: Organoid models rapidly diversified across organs and diseases.RIGHT: Ilya Lukonin entered the emerging organoid field to investigate how cell-to-cell variability shapes tissue development.

By the 2010s, organoids were rapidly diversifying. Laboratories around the world generated 3D models of many major organs, from cerebral organoids that mimic fetal brain development to liver, kidney, pancreatic, and retinal organoids that recapitulate early tissue structure and function (6). Researchers also began growing patient tumor samples into patient-specific organoids that served as promising models for personalized cancer therapy (7).

Ilya Lukonin, now a researcher at the Institute of Human Biology, entered the field during this transitional period. As a doctoral student in Prisca Liberali's group at the Friedrich Miescher Institute for Biomedical Research, he worked with mouse intestinal organoids to investigate how cell-to-cell variability influences cellular decision-making as tissues form.

Answering these questions required quantitative methods. "We wanted to image thousands of organoids over time in a data-driven manner to infer information about how those systems form, develop, and evolve," Lukonin said.

But that posed new challenges. Unlike 2D cell culture, where every cell is analyzed as one datapoint, an organoid contains thousands to millions of cells. A single experiment could generate terabytes of data, with many levels of organization among cells and the structures they form. "This hierarchy was not supported by any image analysis software that was initially developed for high content screening," Lukonin explained.

To keep pace, researchers improvised — repurposing standard microscopes and manually developing analysis pipelines. Companies like Yokogawa recognized the growing need for imaging platforms that could match the scale and complexity of organoids. "In the 2010s, the hurdle of handling such huge data became low," Yokoyama said. "We started to develop platforms for 3D cell analysis."

2017

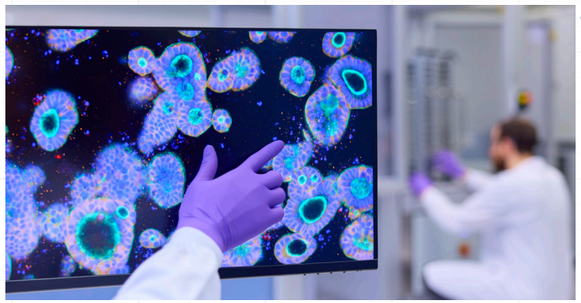
Rising to prominence

By the mid-2010s, organoids captured the scientific mainstream. Laboratories were embracing organoid models to study human development, disease mechanisms, and drug responses. That momentum culminated in 2017, when Nature Methods named organoids its "Method of the Year" (8).

During this time, Lukonin's research on mouse intestinal organoids expanded to an unprecedented scale. He and his colleagues developed an image-based chemical screen, profiling about 450,000 organoids treated with over 2,000 compounds to see how different pathways influence tissue regeneration and differentiation (9). In that study, he "generated the probably largest imaging datasets in organoids at the time," as he recalled.

Also in 2017, Yokogawa unveiled the CellVoyager CV8000, which combined dual microlensed spinning disk confocal imaging with multiple cameras to support simultaneous multichannel acquisition. An automatic water-immersion lens mechanism further sharpened images deep inside thick tissues. The system also improved environmental control, allowing organoids to grow stably inside the imager for days. These features made the CV8000 one of the fastest, highest-resolution high-content systems at the time.

CREDIT: YOKOGAWA



CREDIT: ROCHE'S INSTITUTE OF HUMAN BIOLOGY

ABOVE: With multichannel imaging and AI-powered analysis, the CV8000 brought high-throughput phenotyping to living organoids. RIGHT: Advances in imaging technologies powered high-throughput drug screening with physiologically relevant 3D models.

The CellPathfinder, a comprehensive image-analysis software suite supporting morphology characterization, visualization, and 3D quantification. It specifically addresses the need for automated, reproducible quantification of complex brightfield and fluorescence multi-well experiments.

In Lukonin's lab today, this type of dual microlensed spinning disk–based technology serves as the workhorse for high-throughput organoid screening assays. "We need systems that tick all the boxes for us in terms of imaging quality, reliability, hands-off execution of workflows, and data format," he said.

A shared vision

2020s–present

Organoids matured into more accurate representations of human tissues in the 2020s. Researchers developed vascularized organoids that form their own blood vessels and sophisticated brain organoids with basic learning-related activity (10,11). Bioengineered organoid-on-chip systems improved physiological control, while patient-derived organoids combined with gene editing made personalized therapy testing more feasible (12).

These advances helped drive a major shift in how new medicines are developed. In 2025, the US Food and Drug Administration took further steps to reduce reliance on animal testing, recognizing advanced in vitro systems referred to as new approach methods— including organoids — as viable alternatives in certain drug development stages.

As organoids became more lifelike, they placed greater demands on imaging. To support these needs, Yokogawa introduced the CellVoyager CQ3000 in 2024, with Yokoyama leading hardware design.

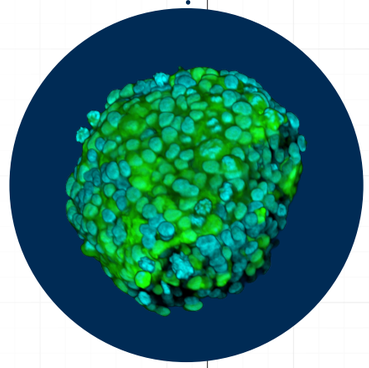
The CQ3000 brings advanced capabilities — including water-immersion optics for high-quality imaging deep inside 3D tissues and flexible multi-camera configurations for increased throughput — into a more compact, updated system.

Yokoyama's team also tackled automation reliability. In high-throughput screening, he explained, "microplate jamming and clashing often occurred even if using an accurate robot." To prevent this, they added new clamp mechanisms and sensors that ensure precise, repeatable microplate positioning, enabling smoother, faster imaging runs.

These days, Yokoyama enjoys working with researchers as they explore new investigations the system can support. "I'm so happy that CQ3000s have started to be used around the world," he said.

Looking ahead, the alliance between organoids and imaging will only grow stronger. Together, they are making preclinical research more human-relevant, predictive, and scalable. "This would allow us, down the line, to bring more novel medicines to patients more quickly," Lukonin said.

CREDIT: YASUNORI YOKOYAMA, YOKOGAWA



CREDIT: YASUNORI YOKOYAMA, YOKOGAWA

TOP IMAGE: The CQ3000 enhances uniform illumination and automated precision, supporting advanced long-term 3D biology studies. RIGHT: Modern imaging tools enable detailed analysis of complex 3D tissues, bringing drug development closer to human biology.

REFERENCES

1. 横河電機初のバイオ分野のイノベーション、秘訣は「ジレンマ超越」だった. ビジネス+IT at <https://www.sbbit.jp/article/cont1/99330>
2. Martin, G. R. Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proceedings of the National Academy of Sciences* 78, 7634–7638 (1981).
3. Thomson, J. A. *et al.* Embryonic Stem Cell Lines Derived from Human Blastocysts. *Science* 282, 1145–1147 (1998).
4. Eiraku, M. *et al.* Self-Organized Formation of Polarized Cortical Tissues from ESCs and Its Active Manipulation by Extrinsic Signals. *Cell Stem Cell* 3, 519–532 (2008).
5. Sato, T. *et al.* Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature* 459, 262–265 (2009).
6. Corrò, C., Novellasdemunt, L. & Li, V. S. W. A brief history of organoids. *American Journal of Physiology-Cell Physiology* 319, C151–C165 (2020).
7. Yang, H., Sun, L., Liu, M. & Mao, Y. Patient-derived organoids: a promising model for personalized cancer treatment. *Gastroenterol Rep* (Oxf) 6, 243–245 (2018).
8. Method of the Year 2017: Organoids. Nat Methods 15, 1–1 (2018).
9. Lukonin, I. *et al.* Phenotypic landscape of intestinal organoid regeneration. *Nature* 586, 275–280 (2020).
10. Zhou, R. *et al.* Vascularised organoids: Recent advances and applications in cancer research. *Clinical and Translational Medicine* 15, e70258 (2025).
11. Birtele, M., Lancaster, M. & Quadrato, G. Modelling human brain development and disease with organoids. *Nat Rev Mol Cell Biol* 26, 389–412 (2025).
12. Singh, D., Thakur, A., Rakesh & Kumar, A. Advancements in Organoid-Based Drug Discovery: Revolutionizing Precision Medicine and Pharmacology. *Drug Development Research* 86, e70121 (2025).

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