RIKEN Center for
Biosystems Dynamics Research

Unraveling what it means to be alive

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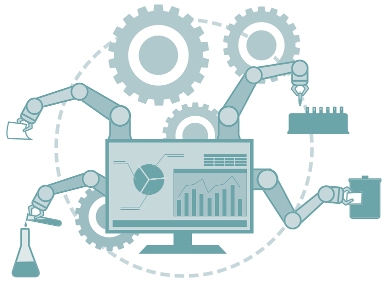
Dive into BDR's intriguing research

The Future Beyond Automation



Dr. Atsushi Shibai, who studied at the National Institute of Technology (KOSEN) before coming to BDR to pursue automation research, introduced me to a fellow KOSEN graduate Dr. Nobuyuki Tanaka. I had met Dr. Tanaka on a different occasion when he had shown me a device to measure "wettability". As soon as I arrived at Dr. Tanaka's office this time, he said to me, "Let's go to the microfabrication cleanroom."

A microfabrication cleanroom for biology?

Tanaka (T) ▶ Please change into the gown before entering. We are trying to prevent dust from entering the room, which houses equipment and tools for microfabrication and precise measurement. The most obvious equipment being microscopes, specifically, digital microscopes used to measure surface topography. And this atomic force microscope is used to observe protein structures or biomolecular dynamics.

Yakushiji (Y) ▶ What is this instrument that looks like a vacuum chamber?

T ▶ That is a lithography system. It creates patterns on the surface of materials by exposing them to light and electron beams. Light has a diffraction limit, and this means that it cannot produce objects smaller than its wavelength, so we generally use electron beams to make any object smaller than one micrometer.

Y ▶ What kind of small objects are you making?

T ▶ We are making devices that allow us to control the placement of cells, such as confining a single cell, lining cells up in a row or creating a cell sheet.

Y ▶ So in this room, you build experimental apparatuses and verify that they have been properly fabricated using precision measurement devices.

T ▶ Yes. But the scale is extremely small. So factors like dust, temperature, and humidity become extremely important and is why we use a cleanroom. There is also a camera and a sensor for sound.

Y ▶ I can understand why you have a camera installed, but why a sound sensor?

T ▶ We are not in the room 24 hours a day, and we need a way to know when the alarm sounds due to errors or troubles with one of the equipment.

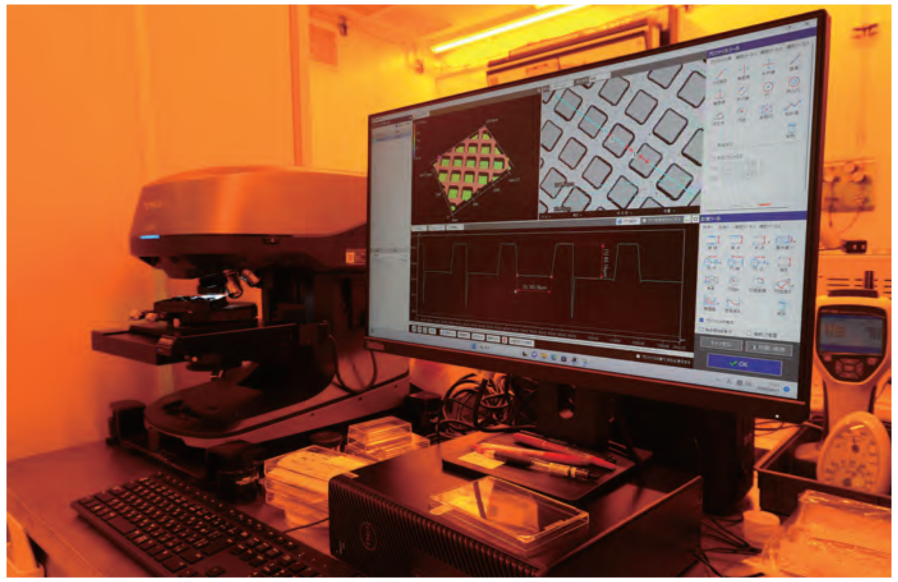
Y ▶ I see.

T ▶ Let's move to the next room.

It's like something made in a small-scale factory in Osaka!

T ▶ Research automation is also another topic of research in the lab, and in this room we have a robots for experimental automation.

This is a 'sealer' robot that sticks adhesive film on top of 96-well plates to seal them up. And this is a robot that removes that adhesive film, also known as a 'peeler.' Next to that is an automated centrifuge. When you place the plate here, it is whisked into the machine and then it is automatically centrifuged.



Lithography system, which uses light and electron beams to make fine patterns.

Dr. Nobuyuki Tanaka

Senior Technical Scientist in the Laboratory for Biologically Inspired Computing. He has had a love for machinery since childhood and enrolled in Suzuka KOSEN because he wanted to build robots. After earning his PhD from the Department of Mechanical Engineering at Osaka University, he moved to the Institute of Advanced Biomedical Engineering and Science at the Tokyo Women's Medical University, following the trend of interdisciplinary collaborations between medicine and engineering. He has been approaching biology from an engineering perspective, such as developing a device that measures "cell wettability" from his research on surface properties. His hobbies are running and mountain climbing. He can run a full marathon in under three hours and is a collector of *tenugui* hand towels.

Y ▶ These robots each have their own specific functions, so will another robot be moving the plate between these robots?

T ▶ Yes. We are currently doing some preparations to link the different robots together. We have a student from Osaka University, who is a strong programmer, helping us to develop control software. The plan is to control the robots through digital commands and we are currently devising a digital communication protocol that will allow us to do this.

Y ▶ I did not know that there were robots for sticking and removing adhesive films. I am especially curious about how they remove the film. If it is not done right, I imagine that it will be like when opening a bag of potato chips goes wrong and the bag tears.

T ▶ It's genius actually. This [robot] has a roll of adhesive tape-like film that is used to remove the sealed film. When the sealed plate is inserted into the robot, the adhesive tape-like film is adhered to the top of the surface of the film you want to remove. The robot then peels the film off the plate by rolling the film horizontally away from the plate.

Y ▶ Smart. Kind of like a packing-tape system.

T ▶ These robots do not have a typical robotic form and are specialized for a specific function or role, but there are of course robots with robot-like arms.

Y ▶ This is cute!

T ▶ It is, isn't it? This robot also works very energetically. It's not only cute, but I think this robotic arm is optimally designed for mass production. The manufacturer of this robot is likely targeting its use in factories where several hundred units are installed for use.

Y ▶ Like car manufacturers?

T ▶ In Japan, it would be the manufacturing industry. However, in the Americas and Europe, the so-called mega pharmas have already been incorporating experimental automation for quite some time. Thus, this has led to advances in development of automated devices and robots for the life sciences. In Japan, there is what is referred to as a "drug lag" where there is a time lag between approval for use of new drugs overseas and when it becomes available for patients in Japan, which in some cases are due to "laboratory automation lag."

Y ▶ I think those 'sealer' and 'peeler' robots we saw earlier were manufactured overseas. The idea for those robots seems like something that small-scale factories in Osaka would come up with.

T ▶ With Higashiosaka's technical capabilities, they would be able to make those robots. But those manufacturers do not realize the large potential for this market, particularly at the global scale because this sector in Japan is quite small as compared with the car industry.

Y ▶ They can of course produce one if they have the go ahead, but it's not like they can sell large numbers of them afterward. It would just end up being a one-of-a-kind robot.

T ▶ When using a foreign manufactured device, it can be challenging because we have to figure out on our own how to integrate it into our system.

Y ▶ I guess there are a lot of device manufacturers. But you need to be able to link them together to advance automation.

T ▶ We need to contact people in other countries if we have any questions, and that means there are inevitably delays in our current situation. There is also an issue of standards.

Cute robotic arm

Y ▶ You are referring to a common protocol between different robots?

T ▶ There is a wide variety of devices and robots, and also many labs working on their development. We need to acknowledge this diversity but work to establish standards that allow the smooth integration of all of these efforts.

Automation will lead to new biology

Y ▶ Do you engage in a lot of research collaborations?

T ▶ Yes, I do. We did a survey [on automation] in one project, and we received a lot of feedback saying, "I know there is automation technology available, but I don't know how to use them" or "I don't understand the merits of automation."

Y ▶ Yes, I can see how it could be difficult to envision.

T ▶ So we asked about their scientific interests and they problems they had, to which we proposed effective automation solutions for. I used to work in a robotics lab and then went to the medical university as part of a collaboration between medicine and engineering, and I am now at a life science research center. So, I am hoping to be able to serve as a bridge between science and technology.

Y ▶ There is probably a lot of different things you can propose when you know both sides.

T ▶ In the life sciences, technology is often used as a tool, so I generally talk frankly with the researchers about the assets available and what I know. But I also think there is another side to automation.

Y ▶ Another side?

T ▶ For example, in biological experiments, you conduct your experiments by planning on what day to do this and what day to do that. But which day is a unit of time decided by humans.

Y ▶ I guess it is not something that directly concerns a cell. It could just be one step within a workflow, just to ensure that a task does not fall on a weekend.

T ▶ Cells function in a way that if a certain gene is expressed, they advance to the next step regardless of whether this happens on a weekend. Cells also do not have a set of defined rules for this process, and many things unfold autonomously and spontaneously. This is likely their natural state.

Y ▶ And its humans who are trying to explain it on our terms.

T ▶ It is conceivable that human intervention is actually producing results that differ from the natural state. I think it is possible that through automation or autonomy, experiments can be conducted in more natural conditions.

Y ▶ Automation is not just a way to increase productivity, but to generate a new interpretation of biology as well.

Postscript

Living organisms can adapt to many things, and likewise, cells used in experiments also adapt to the feed, like media and growth factors, given to them, which you could say is making them domesticated. It brings to mind a vague memory of being told in a physics class I took long ago that "observation itself is already an act of intervention." Our talk made me ponder about how observation of nature should be carried out if human intervention is already considered disrupting natural states.

BDR Research Highlights

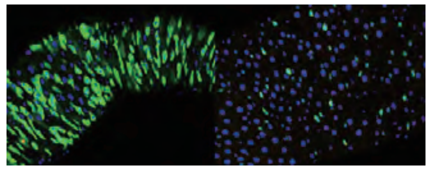
Research Highlights articles and press releases between August 2024 and March 2025.
Read these and other articles on the BDR and RIKEN websites.

01

How aging affects stem cells: A fly's tale

Sa Kan Yoo and his colleagues in the Lab for Homeodynamics have identified key changes to both chromosome structure and gene expression that affect stem cell function during aging. Using fruit flies, they found that these changes led to stem cell exhaustion, which prevents stem cells from multiplying. The findings provide the first evidence of an independent exhaustion signal and enhance our understanding of how the delicate balance between stem cell exhaustion and proliferation is disrupted in normal aging.

Tomita-Naito S, Sulekh S, Yoo SK. *iScience* 27, 110793 (2024)

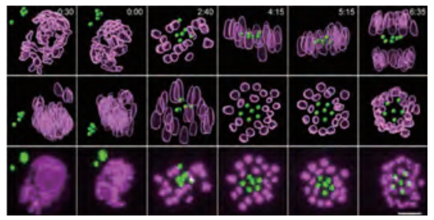


02

Synthetic beads mimic critical process in cell division, opening new paths for biomachines

Kinetochores are elaborate machines with dozens of proteins organized into layers—some interacting with the fibers that pull apart during cell division, others linking to the chromosomal DNA. A team led by Tomoya Kitajima (Lab for Chromosome Segregation) has engineered artificial kinetochore beads that performed just like their natural counterparts, joining the cellular tug-of-war and maintaining the critical tension needed to ensure accurate chromosome alignment. This demonstration could lead to future innovations in synthetic biology and disease prevention.

Asai K, Zhou Y, Takenouchi O, Kitajima TS. *Science* 385, 1366–1375 (2024)



03

DNA copying hits a snag in early embryos

A team of BDR researchers led by Ichiro Hiratani and Tomoya Kitajima have uncovered a surprising period of genomic instability in embryonic development in mice. They found that at the 1- and 2-cell stage, relatively uniform copying of DNA occurs in embryos. But for a brief window around the 4-cell stage, mouse embryos hit a chaotic period where DNA replication suddenly becomes messy and prone to mistakes. From the 8-cell stage onward, the timing of replication followed a predictable pattern similar to that seen in adult cells. Their findings could inform practices in reproductive medicine clinics, potentially leading to improved outcomes in fertility treatments.

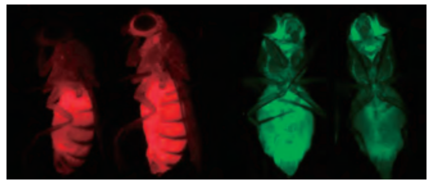
Takahashi S, Kyogoku H, Hayakawa T, et al. *Nature* 633, 686–694 (2024)

04

Limiting intake of a non-essential amino acid brings surprising benefits to flies

Amino acids are classed as non-essential if the body can make them or as essential if they can only be obtained from food. Research by Fumiaki Obata and co-workers in the Lab for Nutritional Biology have found that feeding female fruit flies a diet low in tyrosine, one of the non-essential amino acids, improves their ability to endure food shortage, reduces their reproductive output, and causes them to live longer. The findings could have implications for how diet affects human longevity and reproduction.

Kosakamoto H, Sakuma C, Okada R, et al. *Sci Adv* 10, eadn7167 (2024)

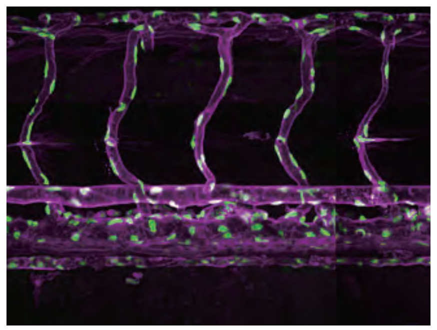


05

Water gives cells a push in blood vessel formation

During development, blood vessels sprout new branches to supply blood to new areas. Tumors hijack this process to syphon off resources to support their proliferation. New branches form through special cells at the leading edges of blood vessels—endothelial tip cells—migrating to new locations driven by a process known as actin polymerization. A team led by Li-Kun Phng (Lab for Vascular Morphogenesis) has discovered another mechanism is also at work—they showed that water flow also assists endothelial tip cells to migrate in zebrafish.

Kondrychyn I, Wint H, He L, Betsholtz C, Phng LK. *eLife* 13, RP98612 (2024)



06

Vulnerable neurons linked to social dysfunction in autistic mice

Neurodevelopmental disorders such as autism spectrum disorder have been widely studied, but the molecular mechanisms that underlie them remain largely unknown. Now, a team led by Kazunari Miyamichi in the Lab for Comparative Connectomics have found that oxytocin-secreting neurons—known for their key role in establishing and maintaining social bonds—are selectively disrupted in neurodevelopmental disorder model mice associated with atypical social traits. Remarkably, a single activation of affected neurons during the neonatal stage had a lasting effect, improving social behaviors into young adulthood.

Tsurutani M, Goto T, Hagihara M, et al. *Nat Commun* 15, 8661 (2024)

07

Investigating the link between genes and vertebrae in tetrapods

The number of vertebrae in each region of the spine varies between species; it is known as the vertebral formula. For example, nearly all mammals have seven neck vertebrae. In contrast, birds have anywhere between 9 and 25. By analyzing the arrangement of vertebrae in the spines of nearly 400 species of tetrapods including mammals, reptiles, birds, amphibians, and extinct dinosaurs, a trio of BDR researchers, Rory Cerbus, Kyogo Kawaguchi and Ichiro Hiratani, have found some follow a predicted pattern, whereas others do not. Their approach may uncover further vertebral patterning and provide clues for understanding the evolutionary and developmental factors which produced them.

Cerbus RT, Hiratani I, Kawaguchi K. *Proc Natl Acad Sci U S A* 121, e2411421121 (2024)

08

Monkey brain map reveals the importance of sight

The network of blood vessels in the brain supplies the various brain regions with oxygen and nutrients. A team led by Joonas Autio and Takuya Hayashi (Lab for Brain Connectomics Imaging) have developed a detailed cortical layer map of the blood vessels that weave through the brain of macaque monkeys. It reveals how blood supply is finely tuned to fuel critical functions such as perception and cognition. A better understanding of how blood flow is distributed across different brain regions and layers could help unravel how vascular dysfunction impacts disorders linked to neurodegeneration and aging.

Autio JA, Kimura I, Ose T, et al. *eLife* 13, RP99940 (2024)

Peek-a-LABoo

Team Director Ryoichiro Kageyama heads the Laboratory for Neural Stem Cell Research* and also leads the Center for Biosystems Dynamics Research (BDR) as the Center's second Director. When asked for some words of wisdom for researchers at BDR, he shared, "Keep challenging yourself. It is when you are facing difficulties that you are more likely to make unexpected discoveries." *Moved from RIKEN Center for Brain Science (CBS) in April 2025.

Laboratory for Neural Stem Cell Research

Q Before establishing your laboratory at RIKEN, where and what kind of research were you doing?

A Before RIKEN, I was carrying out research on developmental rhythms at the Institute for Frontier Life and Medical Sciences, Kyoto University. Gene expression is generally considered to be regulated by two major types of rhythms. Following birth, the circadian clock generates changes in gene expression levels in an approximately 24-hour cycle to regulate day and night activities. In contrast, the circadian clock does not function during the embryonic period before birth, and there is a species-specific developmental rhythm. In mice, this is a two-hour cycle and in humans, it is a five-hour cycle. The somites from which vertebrae, ribs, and skeletal muscles are derived form in pairs from the anterior to posterior direction according to this developmental cycle. A similar rhythm has been found to be important for neural stem cell proliferation. We were conducting research to uncover the underlying mechanism and role of this developmental rhythm.

Q What kind of research are you aiming to conduct at RIKEN?

A Neural stem cells can be found in the adult brain, but many of them are in a quiescent state and cannot readily generate new neurons. While the developmental rhythm does not function in these adult brain neural stem cells, we have previously shown in experiments using aged mice that when this rhythm is artificially induced in these neural stem cells, they begin to actively generate neurons and show improvement in cognitive function and memory. We are planning to advance research into the clinical applications of this technology. Additionally, we are planning to investigate the mechanisms of developmental rhythm and its role as there is still much that remains unknown.

Q What is the composition of your lab members like?

A There are four research scientists, four graduate students, two international exchange students, one agency staff, and an assistant. Our team's strength lies in our unique techniques such as live imaging of gene expression displaying short-periodical rhythms and optogenetic induction of short-periodical gene expression rhythms.

Q Is there anything that you have been hooked on lately?

A Brisk walking. It has been reported that walking at a fast pace can activate adult brain neurogenesis and improve memory and cognitive function.

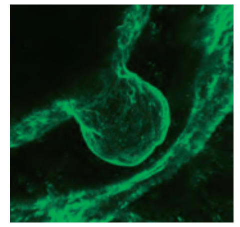
Q Is there anything that you enjoy or that surprised you coming to Kobe?

A Kobe is a fashionable and pleasant city to live in. It's fun to walk around Kobe with both the sea and the mountains being close by and the many different stores around the city.

Q What type of people do you want to join your lab? Please give us a few words to those who would like to join the lab.

A Research is a succession of failure, but those are times that can lead to unexpected findings. It's important to have the mindset to continue pursuing challenges without being discouraged by failure.

On the cover!



Luminous moss?

This is an image of the skin of a mouse embryo with the basal membrane, a scaffold for cells, labeled with green fluorescent protein. The hair follicle, which produces hair, is seen forming a round, bud-like structure that elongates downward from the skin surface.

Credit: Lab for Tissue Microenvironment

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