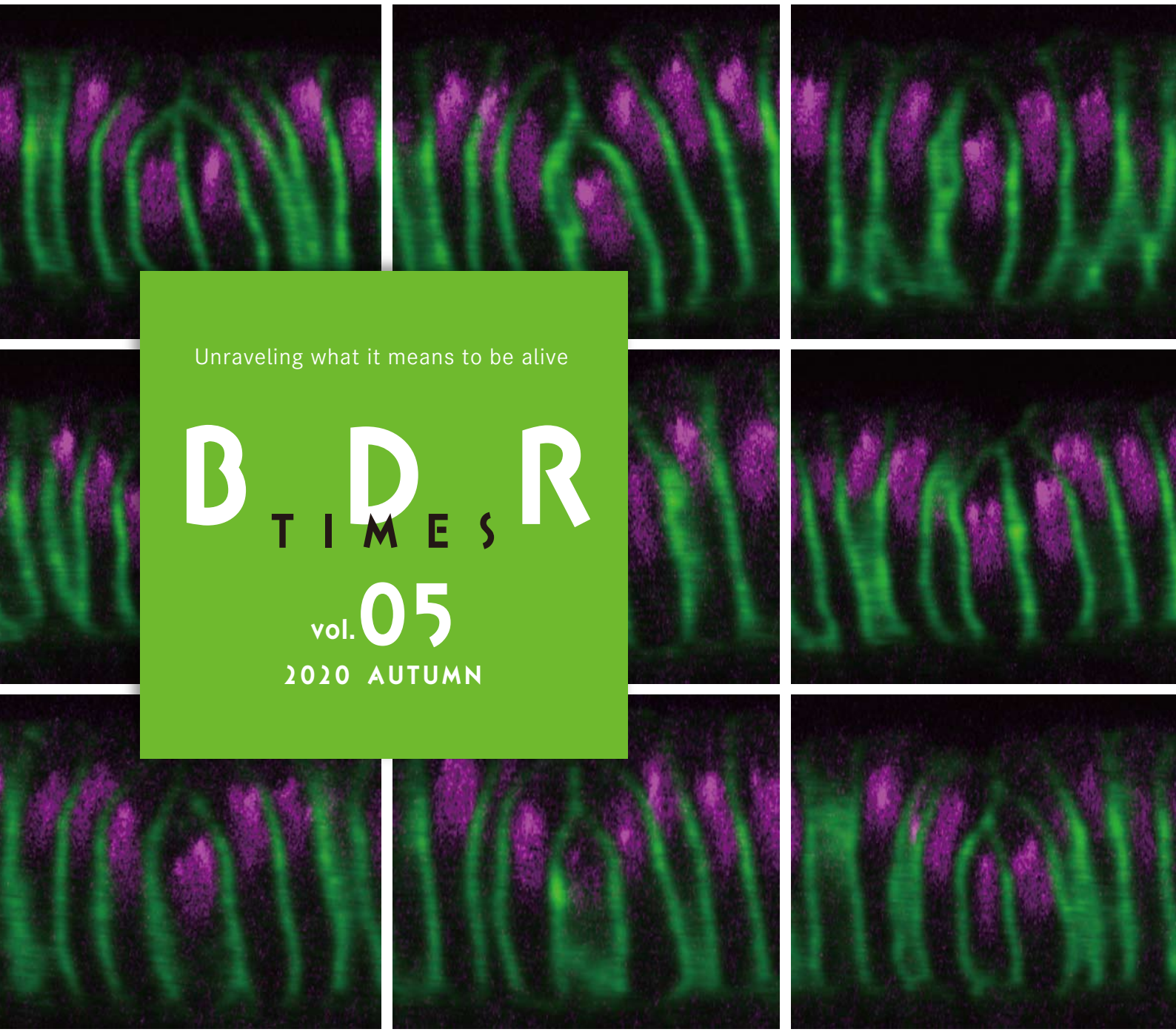

Unraveling what it means to be alive

B D R TIMES

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RIKEN Center for
Biosystems Dynamics Research

Dive into BDR's intriguing research

RIKEN BDR researchers are carrying out many intriguing and interesting research projects, but it can sometimes be difficult to understand what they are actually doing. Hideki Yakushiji meets with researchers to delve behind the scenes of their research.

Behind the scenes of cutting-edge research

Today's guest is Dr. Mika Yoshimura. She's an expert on bioinformatics who analyzes a huge amount of data from a NGS (Next Generation Sequencing). Her role does not usually get a lot of attention but as a woman who works in the male dominated field of information systems, she sparks my curiosity more than usual…

Single cell analysis

Yakushiji (HY) ▸So jumping right in, based on the fact that you belong to the Laboratory for Bioinformatics Research, would you say that you prefer to work in a "dry" lab environment doing bioinformatics such as data analysis, rather than in a "wet" lab doing experiments?

Yoshimura (MY) ▸Yeah, that's true that I don't do any "wet" lab experiments at all. My team mainly works on developing the technology for high-throughput single cell RNA sequencing (single cell RNA-seq). This is the technology that analyzes RNA transcribed from DNA in each single cell using a device called a next-generation sequencer. Our lab often collaborates with other labs using this technology and my role is to analyze the data based on the joint effort.

Of course, there are dry lab researchers with their own research themes who develop algorithms and analytical methods. Although my role is within the "dry" lab environment, I find myself supporting the "wet" lab researchers quite often.

HY▸There seems to be a lot of collaborative research, why do you think single cell is such a hot topic right now?

MY▸I think it's because it makes it easier to understand a cell population when each of them is already analyzed individually.

In the past, the bulk RNA-seq was the mainstream method in which all cells were processed together for expression analysis, but by using single cell RNA-seq, the characteristics of individual cells in a cell population can be analyzed. For instance, we can even observe the difference between the state of each cell during the process where iPS cells become another type of cell.

In addition to that, in my opinion, by expressing the data in a matrix format, mathematical formulae can be used to analyze them which, in turn, allows us to examine them from various angles.

I didn't think research was for me

HY▸Have you always done this kind of work before you came to RIKEN?

MY▸In both undergraduate and graduate school, I was doing research in a "wet" lab. Even my PhD thesis was based on the data I collected from the experiments that I conducted myself, so I wasn't familiar with computers at all. But for some reason, I got a job at an IT company after graduate school.

HY▸Oh? Why? (laughing)

MY▸There were various reasons, but one of the main reasons is that I didn't think research was for me.

First of all, I got a job as a fresh graduate at a system integrator company and then I moved to a software package development company and finally came to RIKEN.

HY▸That's a great career. What made you decide to return to academia?

MY▸There were various reasons again. The job at the software package development company was pretty demanding and it affected my health. There is a trend in the IT industry to switch jobs in one's mid-thirties. Since I couldn't see a long-term career vision at that company, I wondered what to do. I found an internship at a company in the scientific education field. While I was there, I became acquainted with researchers from RIKEN and heard that they were hiring not only researchers but also engineers with a science background. That position was at the laboratory where I currently work.

Mika Yoshimura

Expert Technician,
Laboratory for Bioinformatics Research
After earning a Ph.D. from Tokyo Medical and Dental University, she worked at an IT company several years until an internship opportunity brought her back to academic research. Currently, she is working on constructing a workflow for single cell analysis as well as analyzing data from joint research. Her hobby is apparently gaming.

Hideki Yakushiji

Business developer based in Kobe. He has a broad background in areas such as analytical chemistry, optics, biotechnology and IT. He is involved in a widerange of activities to assist in commercializing technologies and ideas born from academia, including setting up opportunities for idea sharing, finding investors, and strategic planning.

HY▸That's why joint research is so common.

MY▸Exactly. I really hope that the collaborators are happy with the work I do...

Working with cutting-edge technology can be challenging

HY▸Are you worried if they're happy with you? Why?

MY▸I don't think I have the same depth of background and foundational knowledge of data analysis that would allow me to think outside the box like industry experts. I know sometimes discoveries are made in a eureka moment in the researcher's mind based on their experience and knowledge. I'm not confident that my level of knowledge would lead me to that kind of discovery. I usually consult with my boss and the researchers in the lab so that I can receive a thorough review before submitting the results.

HY▸It may be difficult to analyze without some knowledge of the biological phenomenon.

MY▸There are various cases. It is relatively smooth when I'm verifying the hypotheses that are already fairly well established. On the other hand, it can be difficult in the case of finding something new by looking at the results from single cell analysis. I try to slice the data in a number of ways, but I still get feedback from "wet" lab researchers where they point out what's missing from their point of view. Then I go back to analyzing the same data, this time, based on their feedback. It's a process of trial and error.

HY▸When seeking new findings, it sounds difficult to judge whether the analysis result is good or bad.

MY▸That's right. Also, there is always a new analytics tool coming out, so I feel pressured to keep up to date, otherwise I'm afraid we won't be able to produce good results. I constantly feel that there is a more efficient way than what I'm doing right now.

Also, it's natural but it's still tough to be one of a very few people who do this kind of work.

HY▸I see, that means that job is less likely to get standardized.

We need to keep updating...

MY▸Well, technology is advancing rapidly. "Wet" lab researchers are quite smart so they are capable of learning some level of coding skills. Some of them can write codes that can analyze the data to a certain degree. Currently, we have a package that is close to becoming the global standard for single cell RNA-seq analysis, which is written in R that is often used in the field of statistical processing. While R is used for economics, it allows us to create various charts that are useful for our research.

HY▸R. I'll check it out later.

MY▸R makes it easier to draw graphs and diagrams.

R doesn't require much programming knowledge to do a little analysis or drawing charts. In fact, there was a researcher who was able to start writing in R on their own while we were working together.

HY▸I see, then you have to keep ahead of the game ... But how did you learn that at first?

MY▸There weren't many books available back then, so I studied the code written in R by other researchers. I could follow most of it because I was trying to do almost the same thing with my code. When I didn't understand the algorithm in their code, I read the technical books.

HY▸Your brain seems to be wired like an engineer's…

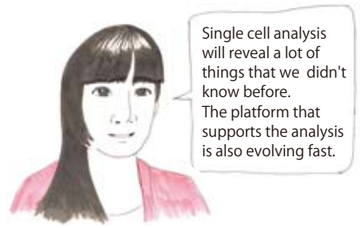
MY▸It's like learning by reading the code. There are many good books now.

In fact, we accept students as interns. When we train them, we ask them to read the books as well as to actually write it for themselves.

HY▸I think it would be nice if you could do a workshop on that. It would be fun.

MY▸I once hosted a training session with other researchers where "wet" lab researchers could feel comfortable participating. I'd like to do that again when I have more time.

HY▸I'm looking forward to it!

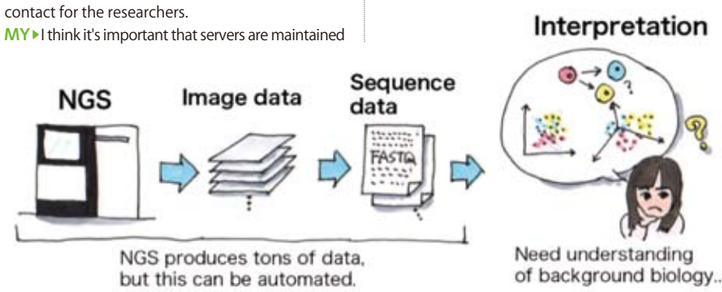


Bulk analysis

Since cells are processed together in one tube, the data obtained is just an average of those cells.

Single cell analysis

Data for individual cells can be obtained since cells are processed respectively.



POSTSCRIPT

This interview felt to me as if I was getting a look behind the scenes of the exciting world of single cell analysis. I'm sure there are many things I didn't quite understand but I feel a renewed appreciation for the people who support such cutting-edge research even though they are not in the spotlight.

Read other interviews

BDR Research Highlights

Research highlights articles from RIKEN Research and press releases between March to July 2020. Read these and other articles on the BDR website.

01

Stem cells exert tight control over the timing of brain development

Brain stem cells, or radial glia, give rise to all the neurons in the cerebral cortex, and are stretched between the apical and basal membrane surfaces. The transition of some radial glia from symmetrical to asymmetrical division that later leads to brain expansion has been thought to be governed by changes in the mitotic spindle orientation in radial glia relative to the apical surface. But a new study by Fumio Matsuzaki and Ikumi Fujita in the Lab for Cell Asymmetry showed that while manipulating spindle orientation of early-stage radial glia did cause the radial glia to detach from the apical surface, it did not necessarily lead to their migration. Instead, early-stage radial glia can extend 'endfeet' that reattach to the apical surface allowing symmetric division to proceed. This discovery could also shed new insights into our understanding of mammalian brain evolution.

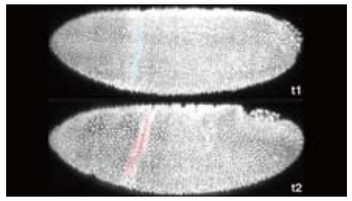
Fujita I, Shitamukai A, Kusumoto F, et al. *Nat Cell Biol* 22, 26-37 (2020)

02

Mechanical forces shape animal "origami" precisely despite "noise"

The reproducibility of form, shape, and characteristic appearance is a key feature of our development that is made possible because their instructions are coded in our DNA. What is perplexing, however, is how this reproducibility is achieved despite genetic variation and developmental "noise" resulting from environmental, physical and chemical fluctuations. An international team led by Yu-Chiun Wang (Lab for Epithelial Morphogenesis) discovered that a genetic "blueprint" for tissue bending, despite specific instructions down to the single-cell level, is insufficient to explain developmental consistency. The mechanical forces that sculpt the embryo turn out to be the noise-producing culprit, and unexpectedly, play a previously overlooked role that ensures the precision in tissue bending – a true double-edged sword!

Eritano AS, Bromley CL, Bolea Albero A, et al. *Dev Cell* 53, 212-228.e12 (2020)



03

Exploring the molecular dynamics of the new coronavirus

Makoto Taiji and his colleagues in the Lab for Computational Molecular Design used the MDGRAPE-4A dedicated drug discovery supercomputer to analyze the structural dynamics of the main protease of SARS-CoV-2, the virus that causes the new coronavirus disease, COVID-19. The raw data of the ten microsecond-long simulation has been published on Mendeley Data (doi:10.17632/vpps4vhryg.2) for use by researchers around the world.

04

RIKEN group leads world in single-cell transcriptome profiling

Single-cell RNA sequencing (scRNA-seq), a technique used to characterize the transcriptome of individual cells in a sample, is currently a focus of intense research. Many scRNA-seq protocols are now available, but as they all have marked differences in standards an international group has benchmarked 13 different methods using a unified reference sample resource. The group, led by Holger Heyn of the Centro Nacional de Análisis Genómico in Spain, found that the Quartz-seq2 method, developed by Itoshi Nikaido's Lab for Bioinformatics Research, was overall the best method developed to sequence single-cell RNA.

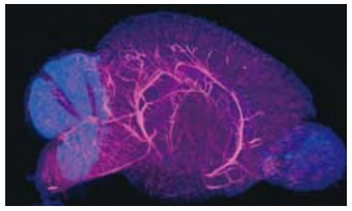
Mereu E, Lafzi A, Moutinho C, et al. *Nat Biotechnol* 38, 747-755 (2020)

05

New staining technique visualizes whole organs and bodies

Hiroki Ueda, Etsuo Susaki and colleagues from the Lab for Synthetic Biology have established an optimized three-dimensional (3D) tissue-staining and observation technique, named CUBIC-HistoVIsion, based on existing tissue clearing technology the lab previously developed. Their recent study details how the new technique can be used to stain tissue and label cells in mouse brains, human brains, and whole marmoset bodies. This technique will allow detailed anatomical analysis and whole-organ comparisons between species at the cellular level.

Susaki EA, Shimizu C, Kuno A, et al. *Nat Commun* 11, 1982 (2020)



06

Finding more chromosome structures by assuming less

Some talk to people in their neighborhood, while others talk to people outside their communities but still in the same city. Likewise, chromosomes possess different types of structural features—closely interacting structures on a small scale are called TADs and longer range interacting structures on a larger scale are called compartments. Now, Yuichi Taniguchi, Vipin Kumar and Simon Leclerc in the Lab for Cell Systems Control have developed a new clustering technique for analyzing data derived from Hi-C experiments that allow them to identify multiple structural features at different scales at once and to associate them with a hierarchical tree.

Kumar V, Leclerc S, Taniguchi Y. *Nucleic Acids Res* 48, e26 (2020)

07

A new biomarker for the aging brain

Toshihiko Aso, deputy team leader of Lab for Brain Connectomics Imaging and his collaborators have identified changes in the aging brain related to blood circulation. In their study, they found that natural age-related enlargement of the ventricles, a condition called ventriculomegaly, was associated with a lag in blood drainage from a specific deep region of the brain. The lag can be detected easily with magnetic resonance imaging (MRI), making it a potential biomarker for predicting ventriculomegaly and the aging brain, which can then be treated quickly.

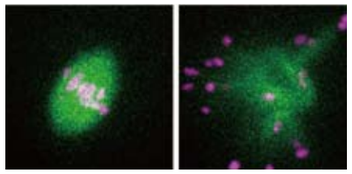
Aso T, Sugihara G, Murai T, et al. *Brain* 143, 1843-1856 (2020)

08

Mice need kinetochores rich in a microtubule crosslinker to achieve error-free oocyte division

Animal oocytes are susceptible to errors during the segregation of genetic material. These errors can result in miscarriages and congenital disorders such as Down syndrome. Tomoya Kitajima and Shuhei Yoshida from the Lab for Chromosome Segregation and collaborators have found that mice need kinetochores (the main point of attachment for spindle microtubules) rich in the microtubule crosslinker Prc1 to achieve error-free formation of spindles during oocyte cell division. Significantly, the team found that kinetochores in humans are not rich in Prc1. This difference between mouse and human oocytes could go a long way to explaining why oocyte division in humans is more error prone than that in mice.

Yoshida S, Nishiyama S, Lister L, et al. *Nat Commun* 11, 2652 (2020)



BDR Photo Tour

Introducing interesting research equipment and devices as well as favorite spots at BDR campuses in Kobe, Osaka, Yokohama, and Hiroshima.

Molecular Imaging Facility (MI R&D Center Building, Kobe Campus)

We can observe what is going on inside the body without causing damage or harm, and visualize tissue organization, cell function, and molecular dynamics.

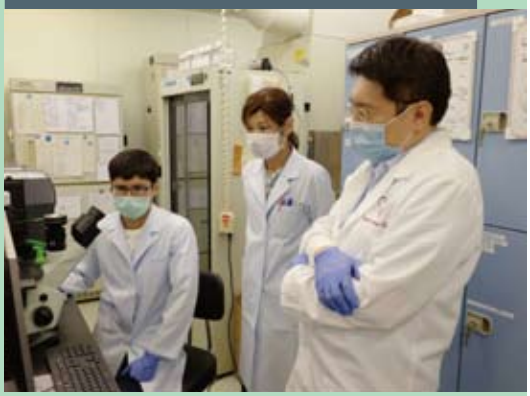
◀The world's first connectome scanner for primates, which is based on high magnetic field MRI (magnetic resonance imaging), is a powerful tool for dissecting function, architecture and connectivity of the human and non-human brain. The wall illustrations are designed to create a calming atmosphere for human (and animal?) subjects.

▲View of the MI R&D Center Building from the Port-liner's Iryo Center Station. "MI" is short for molecular imaging. To the right of the building is the RIKEN Integrated Innovation Building (IIB).

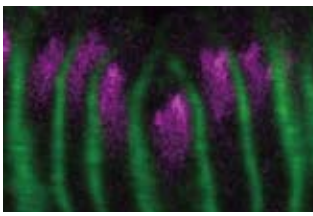
◀PET/CT scanner for animals. We are carrying out basic research on the use of positron emission tomography (PET) not only for diagnosing cancers—already commonly used in hospitals—but also for diagnosing various other diseases and for drug discovery.

Peek-a-LABoo

The BDR's Clinical Translational Research Program aims to merge demands of clinical settings with cutting-edge basic research. Two researchers with clinical knowledge and experience are leading respective teams under this program with the goal of advancing our understanding of diseases as well as developing applications for regenerative medicine. We will introduce these two labs here.

Hematopoietic Stem Cell Research Miyanishi Lab		iPSC-based Cardiovascular Medical Research Masumoto Lab
		
Senior scientist Masanori Miyanishi, who is the research leader, two graduate students, two technical staff and two visiting scientists.	How many members are in the laboratory?	Senior scientist Hidetoshi Masumoto, who is the research leader, one visiting scientist, one technical staff and one student trainee.
We are involved in a wide range of research from basic to applied research to understand the biological characteristics of hematopoietic stem cells (HSCs), which produce all blood cell types in the body, and maximize their potential for uses in clinical settings.	What kind of research is the laboratory conducting?	We are striving to generate heart tissue from induced pluripotent stem cells (iPSCs) and replicate the function of the heart in a culture system for uses in regenerative medicine and drug discovery research with the goal to create new medical treatments.
We have established the world's best method for identifying, purifying and analyzing HSCs, which are surprisingly scarce with only one found among 100,000 blood cells, with high reproducibility. We also have expertise in functional screening to identify genes involved in homeostasis of the hematopoietic system.	What is remarkably unique about the laboratory?	We have established techniques for generating the different types of cells that comprise the heart from human iPSCs, and have also integrated these techniques with cell engineering technology to generate 3D artificial tissues.
It is important to determine the best direction for research and development by accurately understanding the needs of the clinical field and the patients. We are working in collaboration with many different researchers with the desire to deliver new technology to the clinical field as quickly as possible.	What is important to keep in mind in clinical translational research?	For example, being able to transplant a heart generated by iPSCs would be the ultimate goal of basic research, but this is still expected to take a long time to achieve. Besides pursuing basic research, it is therefore necessary to determine which research and developments made so far can be used clinically, and to make an effort to bring these benefits to the clinic.
The research instruments and facilities and technical support available is outstanding. Being located in the Kobe Biomedical Innovation Cluster facilitates networking and collaborations with people working in nearby hospitals.	What are the advantages of doing clinical translational research at BDR?	There are researchers working in various research fields at BDR, and it is easy to engage with them in collaborative research.

On the cover!



Meadow of flowers in full bloom?

The initiation of cephalic furrow in the *Drosophila* embryo. This enigmatic structure appears only transiently and yet precisely during development. Its function remains unclear. Green marks the cell membrane and magenta is the cell nucleus.

◎Image: Lab for Epithelial Morphogenesis

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