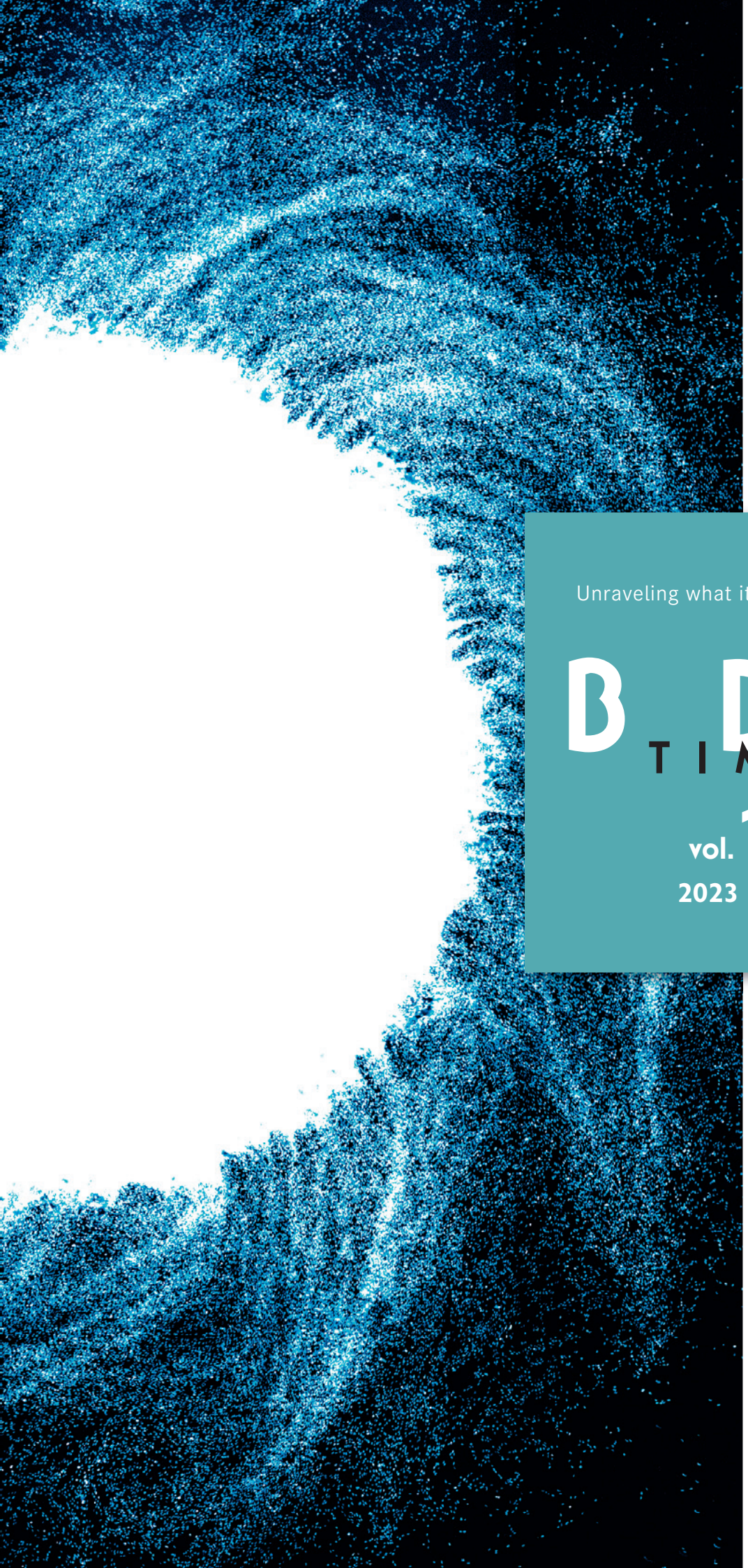

Unraveling what it means to be alive

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RIKEN Center for
Biosystems Dynamics Research

Dive into BDR's intriguing research

Taking on the World with a Unique Machine

This time we have Dr. Yousuke Ohno, who works on the design of MDGRAPE, a computer specialized for running molecular dynamics simulations. If you really think about it, the development of MDGRAPE has been going on since before 1990, which was around the time when Windows 3.1 was finally released. Looking back now, isn't it amazing to think how its development began in an era with such inefficient computers? With that in mind, let's hear more from Dr. Ohno, including about that history.

A computer specialized for simulating molecules

The "MD" in MDGRAPE stands for "molecular dynamics." That means it's a computer that simulates molecules, right?

To put it simply, it's a computer specialized for running simulations that model atoms as spheres and the forces that work between atoms as springs. It examines the shapes that molecules take, and the interactions between them. For instance, there was a simulation of the interactions between novel coronavirus (SARS-CoV-2) proteins and the drugs that bind with them.

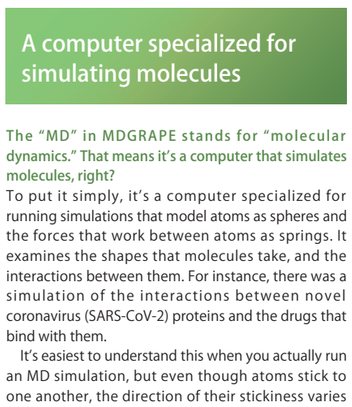
It's easiest to understand this when you actually run an MD simulation, but even though atoms stick to one another, the direction of their stickiness varies quite a bit. In the actual simulations, the atoms of every single individual amino acid are calculated.

One computational step is one femtosecond (fsec, 10^{-15} seconds or one quadrillionth of a second!), and in an 8.5-minute-long video showing the activity taking place over one microsecond (usec, 10^{-6} seconds or one millionth of a second), there were in fact about one billion calculations performed. Even still, the simulation needs to run longer in order to sufficiently simulate the behavior of the proteins.

Origins in astronomical simulation

The "GRAPE" in MDGRAPE comes from "gravity," right?

The story starts back in the 1990s, with Dr. Yoshihiro Chikada (honorary professor, National Astronomical Observatory of Japan) at the Nobeyama Radio Observatory in Nagano Prefecture. He came up with the idea that by creating a specialized machine it would be possible to run calculations related to the *n*-body problem.



Right now, all we can do for the *n*-body problem is run numerical simulations.

Newton's law of universal gravitation states that gravity has an infinite range, so if you had, say, one billion stars, there's gravity working between each pair of them, meaning you have to calculate individually the gravitational force of one billion stars × one billion pairs of stars. The actual calculation programs adopt approximation algorithms to reduce the number of calculated combinations. Therefore, even if the number of particles increases by a factor of 10 in commonly used algorithms, the computational complexity does not increase by a factor of 100, rather it is maintained within a factor of approximately 30. There was a proposal that specialized hardware would significantly speed up the calculations for galaxies and groups of stars called globular clusters. Dr. Daiichiro Sugimoto (who was then a professor at the University of Tokyo College of Arts and Sciences) took this proposal, thinking it would be useful in researching the evolution of globular clusters, and set to work on its development. The hardware was named GRAPE, since it subdivides the gravity equation, lines up the many operation circuits, and calculates them in a sort of assembly line called the pipeline architecture. At first it was only used to calculate gravitational force, but development went on to allow it to be customized for molecular dynamics simulations, which also calculate the forces that act between a pair of particles.

I see. So, on a fundamental level, the gravity problem can also be modeled with a sphere and spring.

MDGRAPE and GRAPE may calculate different phenomena, but both computers are specialized in solving the same problem.

Specialized computers and general-purpose computers

What's the difference between a computer being specialized or being general purpose?

Put simply, a specialized computer is specialized for running only certain calculations, with the ability to do other things pruned away. You could say it's a "thoroughbred."

Take the calculation of gravitational force, for example. We have the equation for Newton's law of universal gravitation. You know the one:

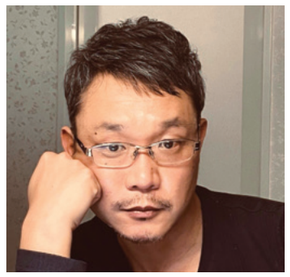
$$F = G\frac{m_1 m_2}{r^2}$$

A computer does each of these calculations one by one.

Yousuke Ohno

Senior Technical Scientist in the Laboratory for Computational Molecular Design. He holds a Ph.D. in astronomy from the University of Tokyo. He was involved in the design and production of GRAPE starting from his undergrad days, and after working on the development of specialized computers for uses such as observational astronomy, he began working on MDGRAPE. Since he began working in Osaka, he has been a fan of watching movies with surround sound.

×



Hideki Yakushiji

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

It multiplies the masses m_1 and m_2, then squares the distance r…kind of like that?

Yes, like that. In the problem we discussed earlier with one billion stars in a galaxy, it would do that calculation one billion × one billion times. Actually, the distance *r* is calculated from the coordinates *xyz* that show the positions of m_1 and m_2, so those calculations come in as well.

A general-purpose computer can do those things too, can't it?

A specialized computer has a circuit just for this calculation physically built onto its chip, and can't do any other calculations. This allows it to minimize memory use, increasing the speed of calculations.

That sounds pretty niche!

The SARS-CoV2 protein simulation I showed previously has about one million atoms, and that is not the type of problem that could make use of the supercomputer Fugaku's full system efficiently.

The first petaFLOPs machine

Both astronomy and molecules deal with so-called "astronomical numbers."

It's the combinations that are the problem. If you increase the number of spheres, the number of combinations increases by the second power.

That seems like it would require an awfully high-spec system.

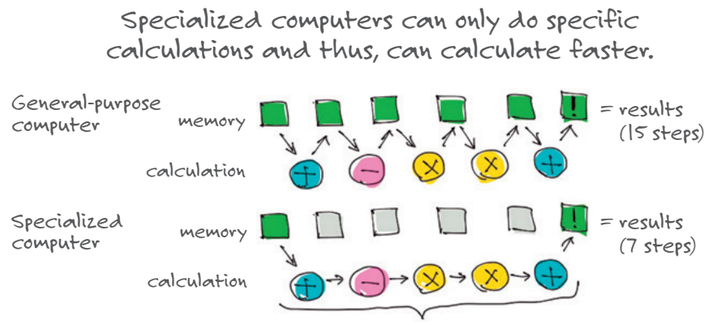
Yes, but it's okay for not every single part to be high-spec.

What do you mean by that?

As an example, if the number of particles increases by a factor of 10, the number of calculations for those combinations will increase by a factor of 100. But the computer's memory only has to retain information on the number of particles increased by 10. So, it is fine if the calculating ability of the computer is increased.

Taking that to the extreme, when MDGRAPE-3 was released, it was the first to achieve petaFLOP scale. FLOPS (floating point operations per second) are a standard for measuring computer performance, and a petaFLOP means that a computer is able to run one quadrillion (10^{15}) calculations per second. But as a specialized computer, it doesn't appear on the benchmarks for famous supercomputers, so it isn't included in TOP500 or other lists like that. Still, at that point, it was theoretically the highest performing computer in the world.

I wish more people knew this fact.



Accelerating further

In order to run longer simulations, you need to accelerate the calculations even more.

Yes, and when you do that, you run into problems with parts outside the nodes that perform the calculations.

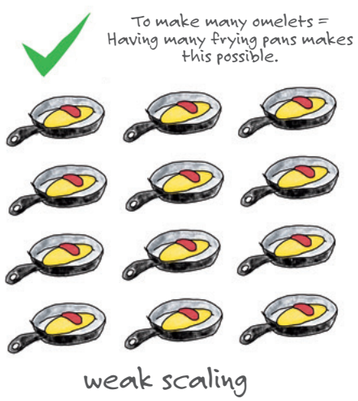
One is data transfer. The transfer of data from the nodes to memory becomes a bottleneck. As the number of calculations increases, the computer struggles to transfer the data. However, if you shrink the problem enough to let the transfer keep up, you end up just transferring data and doing no calculations. It ends up in a meaningless state for a computer to be in.

I see. You can't just speed up the calculations and leave it at that.

It's also not a matter of connecting a bunch of machines together. At this point, it turns into an argument about scaling.

Scaling?

Broadly speaking, there is an issue of strong versus weak scaling. For example, if 100 cooks use 100 frying pans, they can make 100 omelets in the same time it takes them to make one. This is called "weak scaling." But this doesn't mean that they can make an omelet any faster. By contrast, strong scaling allows you to make one omelet in one-one hundredth of the time. This requires a different approach.

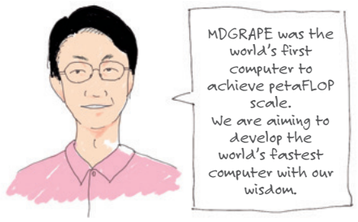


Still, even with 100 frying pans, you can't make an omelet 100 times the standard size. After you've made a frying pan that's 100 times bigger, the question of whether it works is the difference between supercomputers like Fugaku and simply connecting PCs together.

What's coming up next?

Right now, we're working on splitting calculations in a somewhat modular way, and designing the next machine as we improve the algorithms.

I really learned a lot! I hope that MDGRAPE will become the world's fastest computer again!



Postscript

After hearing Dr. Ohno's riveting explanation, I thought it was a real shame that specialized computers like MDGRAPE are relatively obscure. Manufacture of the specialized chips used in these computers is also necessary, and he also told me the struggles of that process (namely their small production lots), but the conversation got so long that we couldn't fit it into this article. How sad …

Read other interviews ▶

BDR Research Highlights

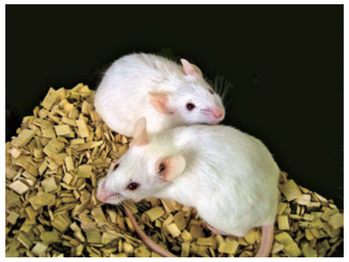
Research highlights articles and press releases between July and October 2022.
Read these and other articles on the BDR website.

01

'Cuddle hormone' oxytocin strongly affects male mice on becoming fathers

Mature male mice that have never mated often attack and even kill pups, but the same animals can become doting fathers upon the birth of their own young. The neurological basis for this transformation, which is seen in many other animals, has been a mystery. Now, in a mouse study, BDR team leader Kazunari Miyamichi (Lab for Comparative Connectomics) and his co-workers have shown that neurons that secrete oxytocin in a brain region called the paraventricular nucleus in the hypothalamus are responsible for activating the paternal instincts of new fathers. "One study has reported that human fathers who experience more skin-to-skin contact with their children tend to have elevated levels of oxytocin in their blood," says Miyamichi. "And so we speculate that oxytocin plays significant roles in human fathers as well."

Inada K, Hagihara M, Tsujimoto K, et al. *Neuron* 110, 2009-2023 (2022)

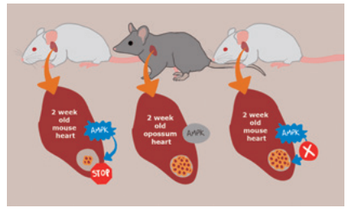


02

Harnessing the heart regeneration ability of marsupials

For humans and other mammals, damaged heart muscle—such as what occurs after a heart attack—cannot be naturally repaired because matured heart-muscle cells do not regenerate. However, unlike other mammals, marsupials such as kangaroos, koalas, and opossums are born in an underdeveloped state and many of their internal organs continue to grow after birth, including their hearts. Now, BDR team leader Wataru Kimura (Lab for Heart Regeneration) and colleagues have discovered how the hearts of newborn opossums retain the ability to regenerate for several weeks. Using this knowledge, the team was able to repair mouse hearts that were damaged a week after birth. The findings are expected to contribute to the development of regenerative heart medicines.

Nishiyama C, Saito Y, Sakaguchi A, et al. *Circulation* 146, 125-139 (2022)

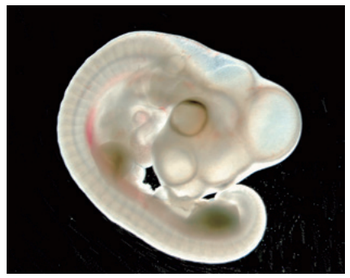


03

Mechanical sensors help coordinate cell organization during eye development

During normal development, the optic vesicle extends laterally in both directions, and two eyes ultimately form at the ends of those projections. When this process goes awry, the left and right optic vesicles fail to elongate. Instead, their tips fuse in the center of the face, forming a single eye. BDR Team Leader Yoshihiro Morishita (Lab for Developmental Morphogeometry) and colleagues set out to discover how malfunctions in a gene called *sonic hedgehog (SHH)* contribute to this 'cyclopia' birth defect. They learned that SHH signaling regulates sensing and response to physical force, guiding the direction of cell rearrangement and motion under the given stress environment within the forebrain tissue. Given the prominent role SHH plays in the development of many organs, mechanical sensing and response may be a far more important driver of tissue organization and formation than previously recognized.

Ohtsuka D, Kida N, Lee SW, et al. *Sci Adv* 8, eabn2330 (2022)

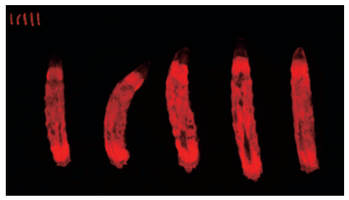


04

'Non-essential' building block proves vital to a healthy protein diet

Our brains have evolved mechanisms for sensing changes in protein building blocks in the body and adjusting the intake of protein-rich foods accordingly. Using the fruit fly as a model, BDR's Fumiaki Obata and Hina Kosakamoto (Lab for Nutritional Biology) have shown that a 'non-essential' amino acid, tyrosine, can act as a nutritional cue to guide the body's responses to a low-protein diet. The flies slow down their rate of protein metabolism and ramp up food consumption when levels of tyrosine in the diet are low. But, conversely, when tyrosine is ingested in greater amounts, the flies kick their protein metabolism into high gear. Now the team plans to corroborate the findings in mouse models. "If tyrosine plays a similar role in mammals, then we could use tyrosine restriction to control appetite, treat metabolic syndrome or even forestall aging," Obata says.

Kosakamoto H, Okamoto N, Aikawa H, et al. *Nat Metab* 4, 944-959 (2022)

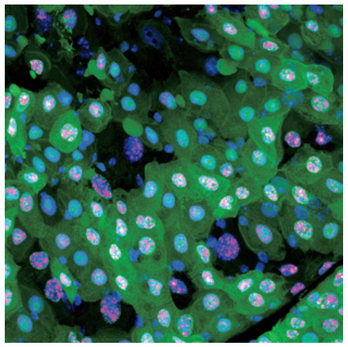


05

A finding regarding cell death changes the gut paradigm

It has long been thought that gut cells die via a well-known type of cell death called apoptosis. Now, a new cell death mechanism has been discovered by a group led by BDR team leader Sa Kan Yoo (Lab for Homeodynamics). The cells dying via this mechanism looked dark under the microscope, so the group named the phenomenon 'erebosis', based on the ancient Greek word 'erebos' meaning darkness or shadow. Erebosis appeared to be a gradual process. Because of this, the group hypothesizes that erebotic cells may be similar to skin cells, which act as a protective barrier even as they break down. This enables a continuous flux of gut tissue repair without allowing tissue integrity to be breached or arousing immune responses.

Ciesielski HM, Nishida H, Takano T, et al. *PLoS Biol* 20, e3001586 (2022)

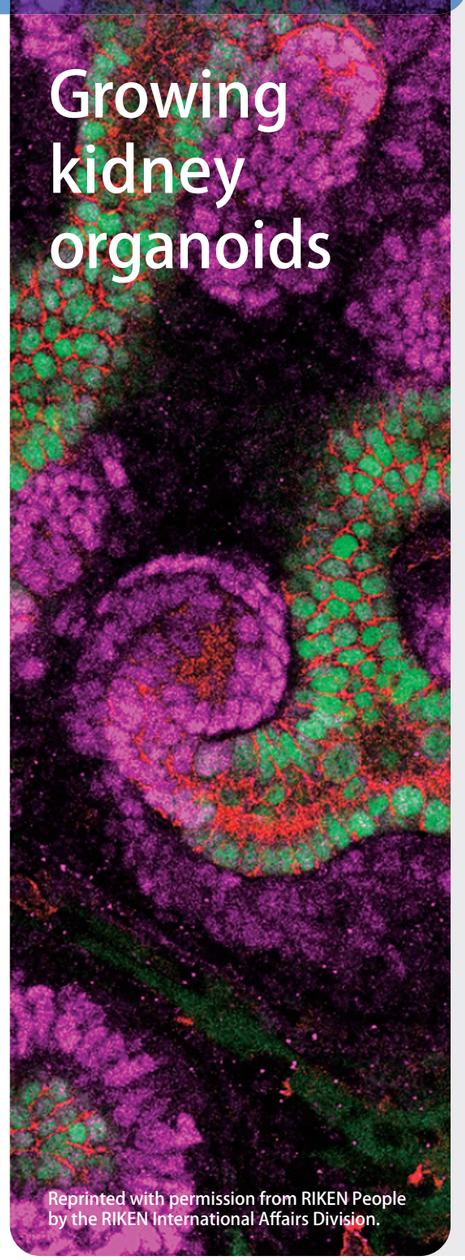


Researcher Spotlight

BDR Research Scientist

Olena Trush

Laboratory for Human Organogenesis



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Q▸Please describe your research.

A▸Each human kidney is made up of about a million filtering units called nephrons. I aim to reveal the mechanisms behind a key stage of nephron development during which a structure known as an S-shaped body (SSB) is formed. SSBs are characterized by a unique S-like folding and are critical to further looping of nephron tubules. Unfortunately, SSB structures are not easy to establish in cell cultures and we aim to improve this. I also work on another project that is trying to make pluripotent stem cell-derived kidney organoids—tiny, self-organized three-dimensional tissue cultures—for hamsters. Hamsters are short-term hibernators and we would like to induce this torpor state in the organoids and examine its unique mechanisms.

Q▸What do you think has been the most interesting discovery in your field in the last few years?

A▸In my opinion, one important recent discovery has been how to reproduce kidney formation in the lab using human pluripotent stem cells. This advance was pioneered by our team leader Minoru Takasato. We are broadly using his core kidney organoid induction protocol for our research today.

Q▸How and when did you join RIKEN?

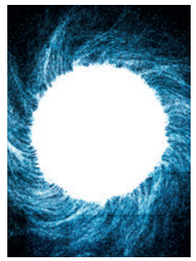
A▸I found information about my current position using a government research-career support website called the Japan Research Career Information Network (JREC-IN) Portal. I immediately contacted Takasato-sensei to discuss the opportunity. Prior to submitting the application, I had a short visit to the lab to introduce myself to the team, and then I submitted the application and went through the selection process.

Q▸What has been your most memorable experience at RIKEN?

A▸I think the most memorable part of my RIKEN experience was learning how to use the lab. I changed from developmental neuroscience to kidney development, so most of the relevant research techniques were new to me. It was an unforgettable experience to induce my first nephron-like structures from human stem cells and I had tremendous support from my colleagues during the transition.

Read full interview:

On the cover!



A blue sun?

This is an aggregate of neural stem cells and the outflow of these cells from the aggregate. At high densities, neural stem cells align their elongated shapes and radially crawl out of the aggregate. Their weak clockwise cell motility becomes accentuated at the collective migration level, resulting in the appearance of a spiral formation that is visible to the naked eye.

◎Credit:
Nonequilibrium physics of living matter RIKEN Hakubi Research Team

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