Unraveling what it means to be alive

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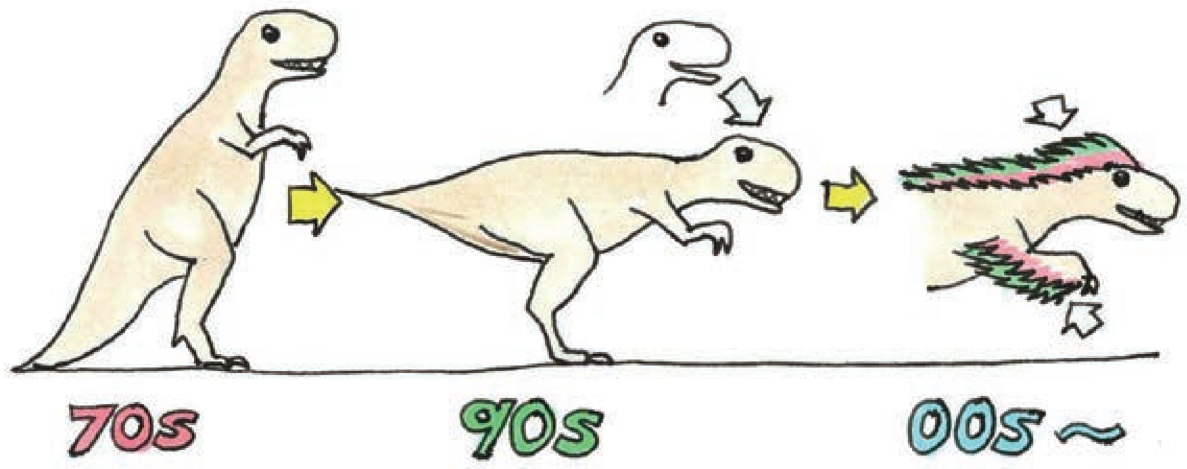
Dive into BDR's intriguing research

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.

Applying Embryology to Dinosaur Studies

We are going to interview Dr. Egawa who is a dinosaur researcher.
I can't wait! But, why dinosaur research not at a museum but at RIKEN?
Since RIKEN BDR is a biological research institute, rather than a geological one, I'm curious to find out what kind of research he is doing...



How long have scientists believed that birds are descendants of dinosaurs?

Yakushiji (HY) ▶ I was excited to hear that there is someone who's doing research on dinosaurs at BDR. I was particularly looking forward to this interview. Do you specialize in a certain species?

Egawa (SE) ▶ I'd say I focus more on the ones that eventually evolved to become modern birds such as theropods like Tyrannosaurus. Since dinosaurs are extinct, we can't analyze them from a biological perspective. Therefore, it is easier to discuss the lineages that left their descendants today since they provide more clues to us. In other words, we can learn a lot about theropods by looking for clues in birds, which are their direct descendants. In a nutshell, I'm doing research on dinosaurs through birds.

HY ▶ I remember about 20 years ago or so that it was just speculation to say that the birds are descendants of dinosaurs. But now it's accepted as a fact. When was it confirmed as a fact in the academic world?

SE ▶ Before the end of the 20th century, the debate had basically ended and it was accepted as a fact in the academic world. Having said that, it's not that I witnessed the debate personally so I'm just following the whig historiography (the attitude that views history as the story told by the winners of the debates).

HY ▶ Oh, it wasn't as recent as I thought!

SE ▶ The connection between birds and dinosaurs was first suggested by Thomas Henry Huxley, who was called Darwin's Bulldog.

In the 20th century, the wrist joints became the center of focus because those joints bend differently between lizards and birds. And it was pointed out that some dinosaurs had the joints that bend the same direction as that of birds.

HY ▶ I can see how the hand of Deinonychus resembles that of birds.

Reconstruction images constantly change

HY ▶ It seems to me that the reconstruction images change every time I look at it. For example, I used to see Spinosaurus standing on four legs but I now see it standing with two legs.

SE ▶ You mean the opposite—it's now depicted to walk on four legs. There have been some recent publications on this topic, too.

HY ▶ Is it true that it does change a lot?

SE ▶ It definitely does. These days, Tyrannosaurus is even depicted with fluffy fur.

I'm gonna diverge a little bit here, but personally, I love the reconstruction images of dinosaurs because it's like a snapshot of the popular theories of each era during which they were created. I can see what ideas were trending among researchers throughout history by looking at the reconstruction images. This is fascinating to me.

HY ▶ It's interesting to me that even the idea of whether Spinosaurus stood with four legs or two legs can be up for debate. It would seem that debates like that can be settled by looking at the skeletons which have a defined structure, unlike features like the color or texture of the skin which require some speculation.

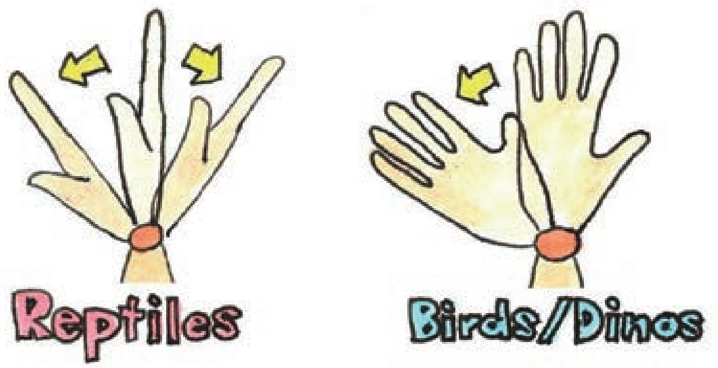
SE ▶ That's because complete skeletons are unrealistically rare. A lot of them are reconstructed from only about ten percent of the bones of an entire skeleton.

HY ▶ That is definitely impressive! That means that you can even reconstruct a dinosaur from a single bone. It seems impossible to me, but how is it done?

SE ▶ We use closely related species as a guide. That also means that those images are drawn only when we have a known relative species.

HY ▶ How do you determine which species are related?

SE ▶ If there is a specific feature that's unique to a lineage, then we can group them together. Since it's not possible to analyze the genome of fossils, we have to rely on their morphology to draw a phylogenetic tree. In simpler terms, to draw a phylogenetic tree, we first look for a feature that we don't see in any of the ancestors or that is found in only a few species, and those species sharing the novel feature are grouped together. We basically keep grouping based on the shared traits and features to create the phylogenetic tree. If we find an animal with the same unique feature as a known species, we categorize it into that group.



Shiro Egawa

Special Postdoctoral Researcher in the Laboratory for Evolutionary Morphology. He specializes in the evolutionary morphology of vertebrates. He's most fascinated by the biological aspect of dinosaurs. After earning his PhD at Tohoku University, he moved onto a postdoctoral fellowship at the Peabody Museum of Natural History at Yale University, before taking up his current position. His research attitude is rooted in judo and music since his school years.

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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.

Fossilized proteins?

HY ▶ These days, a lot of phylogenetic trees are drawn based on genome sequences, but I suppose it's not that simple for dinosaurs.

SE ▶ Right. It's not feasible for dinosaurs.

Even though genetic information can be traced back several hundred thousand years, it's still not that simple. However, proteins can remain for a very long time.

HY ▶ You mean re-construct a DNA sequence from an amino acid one?

SE ▶ Well, it's difficult to do that from an amino acid sequence, but there has been an interesting study recently. It appears that proteins can preserve their three-dimensional structure, replacing the amino acid molecules making up that protein.

HY ▶ Do you mind elaborating?

SE ▶ Sure. It's really just like a fossil. When bones become fossilized, it means that the calcium phosphate and collagen of the bones are mineralized. The same basic thing appears to happen with proteins—the protein shape remains while its contents are replaced. There is a method called immunostaining, which uses antigen-antibody reactions to detect proteins with a certain shape. Because protein structures are preserved, there have been studies in recent years showing that this method is applicable to fossils, too. So these days, we can use immunostaining on the Tyrannosaurus. Having said that, it's only been several years that this has been going on, so there is also a possibility that it'll be disproved. The story about the discovery of DNA sequences in dinosaurs was also disproved after a few years, too.

HY ▶ I didn't realize that there was such a discovery.

SE ▶ Therefore, likewise we need to carefully monitor fossil immunostaining research, although I think it's possible that the data may really have biological significance.

HY ▶ That'd be interesting, but I guess we can't just take this at face value...

Embryology for Dinosaurs

HY ▶ What comes to mind when I think of dinosaurs is science museums and such. But, why did you choose to come to RIKEN?

SE ▶ Because the information we can obtain from dinosaur fossils are limited to their morphology, discoveries about dinosaur evolution have been mainly made based on such morphological data. Therefore, I figured it's easier to do research based on their morphology even if I'm doing biological research without fossils. As an undergrad, my thinking process for my future was dinosaur studies based on morphology; I prefer biology, especially anatomy, over geology; I want to learn something more related to their life sciences; and how and where can I use my strengths? I eventually concluded that the answer was developmental biology of birds. I came to RIKEN almost as an extension of that path. When studying developmental biology, it helps a lot to have the proper experimental environment set up with the proper equipment.

HY ▶ In speaking of developmental biology, it's easy to understand when you are studying existing living creatures today, how do you link that story to talk about it for creatures that went extinct millions of years ago?

SE ▶ It requires a certain amount of logic when we are debating on things that old. Incidentally, what drew me to RIKEN was that I could have discussions on evolution and development, which also requires having a bit of philosophical mindset about science.

If we take birds as an example, they display unique traits and features that differ from reptiles and mammals. Those traits and features were acquired at different times in history and accumulated over time. If we apply developmental biology to some features of birds that appeared further back in the past, we can infer on what kind of developmental changes occurred during the dinosaur era.

HY ▶ Let me see if I understand this. For example, if there is a three-legged bird like Yatagarasu and you find another species from 80 million years ago with similar traits, then you can trace back in evolutionary history to find when they became three-legged. Is it something like that?

SE ▶ Basically, yes. Suppose we were to compare the developmental processes of two-legged and three-legged birds that are alive today, and discover embryologically why and how the Yatagarasu develop three legs. Then, looking at the fossil record, we might find a point in the evolutionary history when the bird acquired a three-leg morphology, from which we can infer that the developmental process for three legs was acquired around this point in evolution. That's the kind of logic my research is based on and it's the most basic and naive way of thinking in evolutionary developmental biology. The relationship between development and evolution is probably more complex and there's even more evolutionary phenomena involved. What I'm working on right now takes it a step forward from this.

Research goes on from skeletons to muscles

HY ▶ What plans do you have now to expand your research?

SE ▶ Up until now, I've been focusing my research on the thigh bone of birds and dinosaurs where it bends into the L-shape. I'd next like to study the muscles that move the thigh bone.

HY ▶ Right. Without muscles, you can't move the bones...

SE ▶ When we broaden our perspective to include muscles, we can start to think about functionality instead of just forms. Since the law of physics such as gravity is the same in the dinosaur era as it is today, we can use the mechanical simulations to speculate the way the muscles might have moved.

HY ▶ It seems that as the technology develops further, restoration illustrations will be more realistic.

SE ▶ I think the animation of dinosaurs, in particular, might become much more realistic. The approach is a bit different but I sometimes wonder if I'm aiming for the same thing as dinosaur illustrators or movie artists.

HY ▶ I remember when Tyrannosaurus used to be depicted as being heavy and stalking like Godzilla, but now it seems quite agile despite its size.

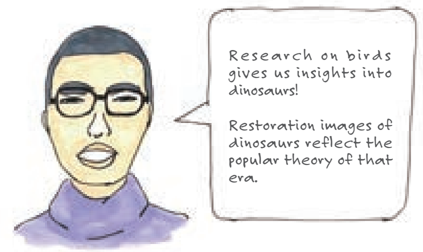
SE ▶ Oh, that's probably from the period when the Jurassic Park movie came out. By the 2000s, there were some theories saying that they couldn't even run...

HY ▶ It might be interesting to see this history organized chronically.

SE ▶ There might be such books. I'm not sure...

HY ▶ I'd love for you to write that book!

SE ▶ OK. I'll do that when I'm about 40.



Postscript

Since the topic was dinosaurs, I was excited as I listened to him speak. The reconstruction images in the museums and movies are so different now compared to what I used to remember seeing when I was growing up, since they just reflected the changes in the theories in the academic world. Regardless, the dinosaurs these days are so colorful. I'm curious to see what they are seen to look like 30 years from now.

Read other interviews ▶

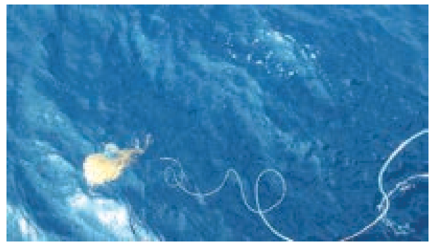
BDR Research Highlights

Research highlights articles and press releases between December 2020 to February 2021.
Read these and other articles on the BDR website.

01
Can sting rays and electric rays help us map the ocean floor?

The ocean floor is a big place full of natural resources, but many are hidden away in places we have yet to find. Ocean exploration is therefore necessary, and currently, automated vehicles, sonar, and satellites are used for this purpose. A team led by Yo Tanaka of the Lab for Integrated Biodevice is developing a completely different system for exploration that relies on the natural swimming behavior of benthic sting rays and electric rays. They first confirmed that rays spend much of their time skimming slowly around the ocean floor. Then by attaching pingers, devices that emit ultrasonic sound, to the rays and lowering them into the ocean from a large boat outfitted with several receivers that pick up the pinger's sound, they could calculate the position of the ray. By comparing their data with an existing seabed map of the same area, they were able to demonstrate the proof-of-concept and feasibility of using the ray's position to map the seabed.

Funano S, Tanaka N, Amaya S, et al. *SN Applied Sciences* 2, 2142 (2020)



02
Hijacking hibernation

In the last few years, scientists have been able to clarify the energy-saving mechanisms at work in hibernation, culminating in two important papers published in June 2020. But what does this mean for human hibernation? BDR's Genshiro Sunagawa, who co-led the study of one of the papers, explains how a small subset of neurons in mice regulate this metabolic phenomenon of hibernation and how it affects the heart rate, oxygen consumption, respiration rate, and other physiological functions. His long-term goal is to apply their findings to medicine. Slowing metabolic processes in critically ill patients will buy time to transport them to the hospital, and reducing metabolism in organ transplants will extend their viability. Moreover, long-term hibernation in humans may lead us to space travel.

Takahashi TM, Sunagawa GA, Soya S, et al. *Nature* 583, 109–114 (2020)

03
Changes in nutrient storage and metabolism help fruit flies reach maturity

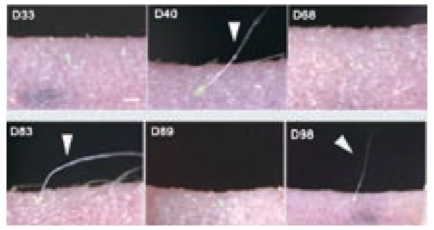
Although organisms generally can survive by consuming stored nutrient sources in the event of starvation, it was not known whether such a survival strategy is always employed in the actual life history of an organism. Through mathematical modeling, Takashi Nishimura (former Lab for Growth Control Signaling), Yoshihiro Morishita (Lab for Developmental Morphogeometry) and their colleagues simulated nutrient management in developing fruit flies. They show that flies shift their response to starvation from consumption to conservation of nutrient stores during the transition from growth (early larval stages) to maturity (late larval stages) to optimally maximize their adaptation for future survival and reproduction.

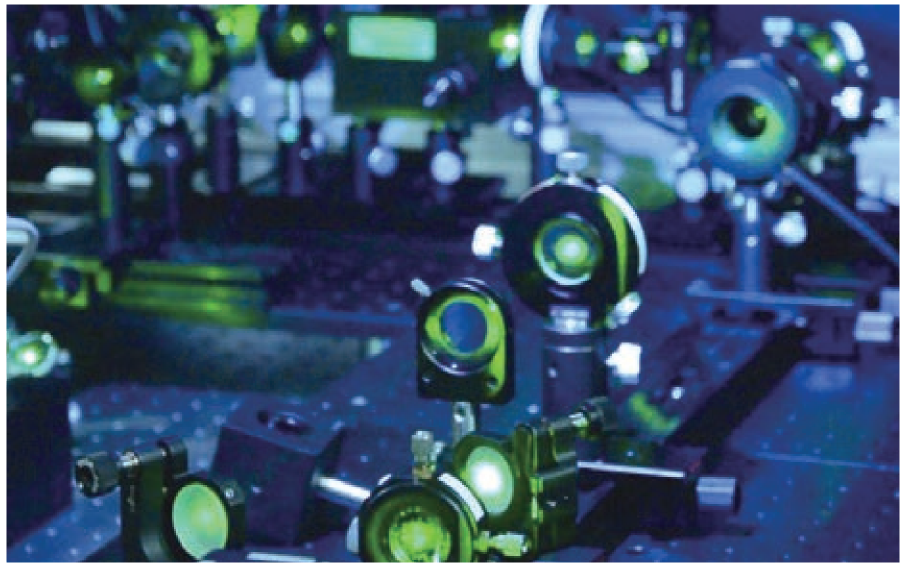
Yamada T, Hironaka KI, Habara O, et al. *Nat Metab* 2, 1096-1112 (2020)

04
A recipe for cyclical regeneration of bioengineered hair

Mammalian hair growth is a continuous cyclical process in which hairs grow, fall out, and grow back. The hair follicle contains several types of epithelial stem cells, but the cell populations that enable long-term cyclical regeneration of hair follicles have long remained unknown. A study by Makoto Takeo, Takashi Tsuji (Lab for Organ Regeneration) and their collaborators now reports the establishment of a culture method to amplify hair follicle stem cells in vitro while maintaining the ability to regenerate hair follicles. In addition, they identified the stem cell population that was critical for ensuring long-term cyclic hair follicle regeneration.

Takeo M, Asakawa K, Toyoshima KE, et al. *Sci Rep* 11, 1173 (2021)





05
Raman spectroscopy provides non-invasive way to track cell reprogramming

Induced pluripotent stem cells (iPS cells), which are produced by reprogramming differentiated cells to revert to an undifferentiated state, have the ability to produce all cell types of an organism, and are considered to hold promising applications for regenerative medicine. To gain a better understanding of the cell dynamics during the reprogramming process, Arno Germond, Tomonobu Watanabe (Lab for Comprehensive Bioimaging) and colleagues used an analytical technique known as Raman spectroscopy to monitor chemical changes in cells. Raman spectroscopy uses a laser beam to measure the signature molecular vibrations of each chemical group and does not require labeling samples, making it less invasive, faster and less expensive than existing methods. The team uncovered evidence that Raman spectroscopy provides spectral biomarkers that indicate the progression of reprogramming.

Germond A, Panina Y, Shiga M, et al. *Anal Chem* 92, 14915-14923 (2020)

Peek-a-LABoo

The RIKEN Hakubi Fellows program offers outstanding and talented early-career scientists the opportunity to lead an independent team to pursue creative and ambitious research with the potential for high scientific and societal impact. This time, we introduce the Nonequilibrium Physics of Living Matter RIKEN Hakubi Research Team led by Hakubi Team leader Kyogo Kawaguchi who was appointed in 2018 in the first round of recruitment for the program. Trained as a nonequilibrium physicist but with an interest in biological concepts, Kawaguchi applies mathematics and physics approaches to understand the fundamental principles governing living systems.

Nonequilibrium Physics of Living Matter RIKEN Hakubi Research Team

What are the main research themes of the laboratory?

We are investigating the unique phenomena that arise when cells assemble together (collective cell behavior) and the molecular mechanisms involved in cell differentiation from a physics-based perspective.

How many people are in the laboratory?

There are a total of six people—two technical staff with a biology background, three research scientists with a physics background, and the principal investigator.

What is remarkably unique about the laboratory?

We do not have a particular technology to boast about, but perhaps one unique aspect of the lab is that we do (at least try to do) everything within our reach, regardless of whether it is experimental or theoretical. We do wet lab experiments involving chromatin reconstitution, single molecule microscopy, and long time-lapse imaging of cultured cells. In the same lab but in the dry area, we do machine learning, numerical simulation-based research, and pure theoretical physics.

How has the COVID-19 pandemic affected the research activities of the laboratory?

We did experience some difficulties in performing experimental work. There were also delays in obtaining specific parts from vendors that we needed to set up our microscope system. But we overcame these obstacles by shifting our focus during this time to more desk work-based tasks such as theoretical research and analyses of data we had already collected.

Read past Peek-a-LABoo columns

On the cover!

Different fly species?

These are in fact all the same fruit fly species, Drosophila melanogaster. Their different appearances are due to one or multiple genetic mutations, which lead to black bodies, white eyes, etc. There is one wild-type (normal) fly and mutant flies with 20 different phenotypes. Can you identify them all?

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Hanna Ciesielski, Lab for Homeodynamics

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