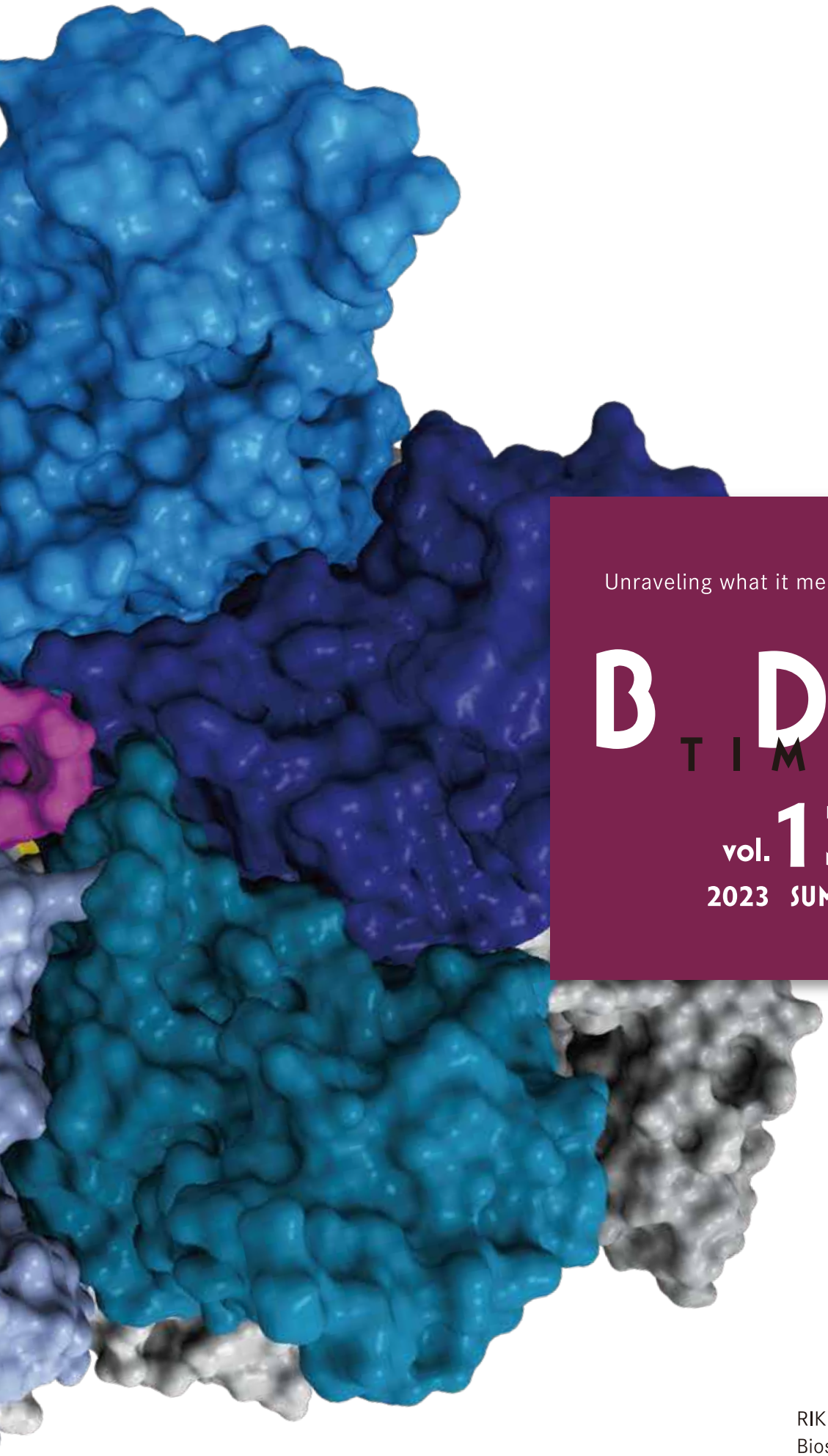

Unraveling what it means to be alive

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RIKEN Center for
Biosystems Dynamics Research

Dive into BDR's intriguing research

A physicist contemplating the origins of living things

Dr. Yousuke Ohno, who I previously interviewed about MDGRAPE, had told me that he had been intrigued by a recent Japanese press release suggesting that amino acids could be generated even without nitrogen, so I went straight to the horse's mouth and talked to Dr. Tomonori Fukuchi who was involved in that study.

After 5,000 years, half of them will be amino acids?

Yakushiji (HY) ▶ My interest was peaked by your recent Japanese press release, "Amino acids can still be produced without nitrogen—new possibilities for the origin of the amino acids (translation)," hence why I am here to talk to you today.

Fukuchi(TF) ▶ Thank you very much. I hope you don't mind if my talk will be something not really biologically oriented…

HY ▶ That's fine! The press release explained that by using the phenomenon of radioactive decay, it may be possible to make amino acids from compounds that do not contain nitrogen, to which I thought, "Yes, that certainly may be possible." How did you come up with this idea?

TF ▶ At BDR, I usually work on the development of devices for positron emission tomography (PET). PET is an imaging technology that generates images by using light from the beta particles emitted by radioactive decay of tracers or radionuclides. In addition to PET, I was also developing instruments to detect and measure beta particles directly. I was searching for a good tracer to test this instrument I was developing, and carbon 14 (^{14}C) matched the criteria I had in mind in terms of its availability, half-life, and energy.

I realized that the energy of the beta particles emitted by ^{14}C (decay) is low. If the energy of the beta particles is high, the atom could become dislodged in a process called recoil from the energy produced by beta particle emission. But then, I thought if the recoil energy is low as seen in ^{14}C decay, perhaps the atom won't become dislodged. In that case, it's possible that carboxylic acids could become amino acids. Since ^{14}C becomes nitrogen (^{14}N) when it decays, I speculated that it may turn into a new molecule that includes ^{14}N.

Propionic acid includes three carbon atoms linked together and contains a carboxyl group on one side and a methyl group on the other. If the carbon of this methyl group turns into nitrogen to become an amino group, we have an amino acid with a carboxyl group and an amino group—in this case glycine.

HY ▶ Ah, I see. Nothing will come of it if the carboxyl group becomes separated when ^{14}C decays, but if it remains attached, it's glycine.

TF ▶ So, I simulated the probability of glycine formation and found that, even if we accounted for some degree of molecular instability, glycine could be produced at least one-third of the time.

HY ▶ That's a reasonable likelihood! Now that you've explained it, I can see what you are saying. That never occurred to me before. There may be many things that can be made in a similar way.

TF ▶ Since this was a simulation, we still need to confirm this experimentally. If you consider the half-life of ^{14}C, it would be ideal to make propionic acid, leave it alone and then check back on it after 5,000 years, but that of course means I can't confirm it myself (laughing). But the half-life refers to the probability of decay, so if you use the latest analytical equipment to measure trace amounts of the molecule, you should be able to confirm it in a much shorter time frame.

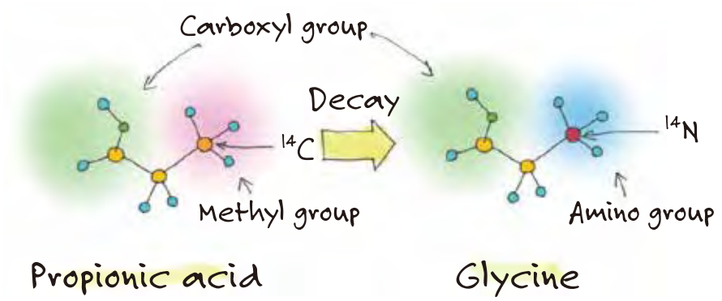
HY ▶ Even if it is a trace amount in a short period of time, when you look at it from the scale of the Earth's time and physical quantity, it may be sufficiently accumulated. In the field of the origins of life, there are ongoing debates about how amino acids and nucleic acids materialized. Was that something you were interested in?

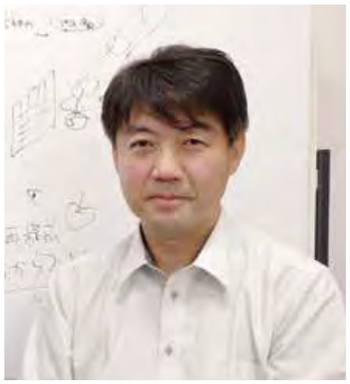
TF ▶ Actually, I am also working on using PET for fossil imaging, so I did quite a bit of studying around that topic. As a result, I was aware that there is a lot we don't know about the origins of life.

TF ▶ Another big mystery in relation to amino acids is the existence of optical isomers.

HY ▶ For reasons unknown, life on Earth uses only left-handed or L-amino acids, right? I know there have been many speculations, but there is no definitive theory yet for this either.

TF ▶ I believe there is a reason for this. In physics, forces are categorized into four types—gravitational force, electromagnetic force, strong nuclear force and weak nuclear force. Only the weak nuclear force is actually asymmetrical, while the others are symmetrical.



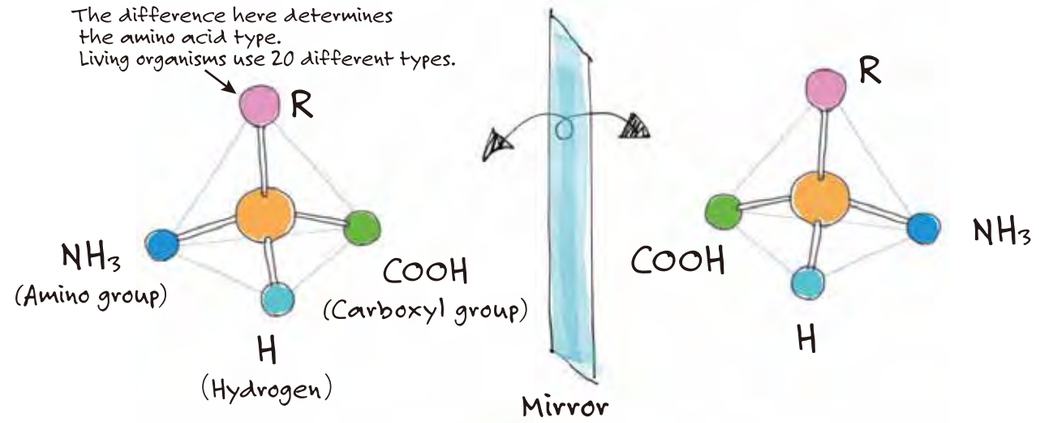


Tomonori Fukuchi

Research Scientist in the Laboratory for Health and Pathophysiological Science (at the time when interviewed). He holds a Ph.D. from Kyushu University in nuclear physics. During his university days, he was a trumpet player and played in a brass band as well as an orchestra. He is skilled at playing billiards. In addition to being the coach of a baseball team made up of RIKEN staff, he is also currently working on a novel.

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.



Development of applications lead to new ideas

HY ▶ You mentioned in passing earlier about fossil imaging, but what do you mean by that?

TF ▶ When developing a device, it's also important to think about applications of the final product. That is when I came up with the idea of fossil imaging.

HY ▶ Why fossil imaging?

TF ▶ I was vaguely thinking that it would be interesting to measure something that normal people wouldn't measure, and then I had the opportunity to listen to a talk by an earth and planetary scientist.

HY ▶ It is indeed quite difficult to see inside fossils. Though, lately, we do see stories about CT scans of mummies and such.

TF ▶ That's right. So, I thought that I might be able to see something with the device I was developing.

HY ▶ How? With PET, you inject a probe with a radionuclide attached to it into the body and detect where it disperses. In the case of cancer diagnosis using PET, you use something like ^{18}FDG (glucose with ^{18}F attached to it), right? But with fossils, it's impossible to inject something in the first place.

TF ▶ We need to change our thinking and switch the order of how normal PET imaging is done. If we bombard the stable nuclides dispersed in the fossil with a beam of gamma rays from the outside, certain elements will be converted into radionuclides that can then be detected with PET.

HY ▶ I see. So, it works because gamma rays are highly penetrative.

TF ▶ Proton beams are fine as well, but gamma rays can penetrate easier into the rock (i.e. fossil).

HY ▶ So basically, if the stable nuclides became radionuclides that can be detected with PET, they can then be used for imaging. If this is successful, it would mean one would be able to see the internal structures of fossils in three-dimension, right? That would be interesting.

TF ▶ Right? I did a lot of studying while I was considering all the possibilities for my device, and that's when I came up with the idea of creating the amino acids we were talking about at the beginning.

HY ▶ So that's the connection.

All roads lead to nuclear physics?

TF ▶ Somehow, I think everything that I have worked on thus far is all connected.

HY ▶ Incidentally, my impression of you was someone working on the development of PET, but what is your background?

TF ▶ Nuclear physics. Particularly, on the experimental side. The number of protons determines what the element is and isotopes of an element have different numbers of neutrons. When the number of protons and neutrons changes, the structure of the atomic nuclei also changes. You may have had an image of the atomic nucleus being roundish, but it can also become oblong.

HY ▶ Whoa, really? I didn't know that.

TF ▶ I think that you know about the K-shell or L-shell. That is referring to the orbit of electrons, but the atomic nucleus can be understood in a similar way. In the case of electrons, there are eight electrons in the L-shell, right? Well, the atomic nucleus also has similar shell structures, which are determined by how full the shell is. Shells with a good balance of proton and neutron numbers are stable, while those that are imbalanced are prone to decaying. There is also something called magic numbers, and when the proton or neutron numbers reach these numbers, their stability increases even if they are situated in unstable regions. When stable, the shell shape is fairly round, whereas when it is unstable, the shell shape deforms. Likewise, when the atomic nucleus is excited, the shape will change again and the excited state will also have a lifespan.

HY ▶ How do you study the shape and properties of atomic nuclei?

TF ▶ When electrons are excited and then return to the ground state, they emit X-rays; when protons and neutrons are excited and return to the ground state, they emit gamma rays.

HY ▶ Wasn't there a specific wavelength region for X-rays and gamma rays within the electromagnetic spectrum?

TF ▶ This is often done for convenience when representing them in diagrams, but the original definitions are different. X-rays are emitted from molecules, and gamma rays are emitted from atomic nuclei.

HY ▶ I see. I didn't know that.

TF ▶ So, I was first doing research measuring those gamma rays to determine the structure of atomic nuclei.

HY ▶ Wow, that story all connected nicely!

Postscript

The name of Center for Biosystems Dynamics Research suggests that it is a research center studying the functions of living systems, but our conversation was primarily centered around physics. However, biomolecules are molecules and molecules are made up of atoms, so when you get down to it, I guess it naturally becomes a story about physics. I was left astounded by the depth and profoundness of the life sciences as well as the research at BDR.

BDR Research Highlights

Research highlights articles and press releases between November 2022 to April 2023.
Read these and other articles on the BDR website.

01

Inducing hibernation-like state in mice can protect organs during heart surgery

Hidetoshi Masumoto (iPS cell-based Cardiovascular Medical Research) and Genshiro Sunagawa (Lab for Hibernation Biology) have developed and demonstrated a new method which slows metabolism down to a hibernation-like state to protect organs during heart and aortic surgery when blood circulation has to be blocked.

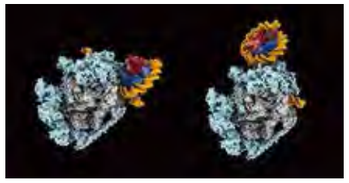
Kyo S, Murata K, Kawatou M, et al. *JTCVS Open* 12, 201-210 (2022)

02

Gene-reading enzyme razes and rebuilds DNA-winding structures in its path

The Lab for Transcription Structural Biology has shown using cryo-electron microscopy that RNA polymerase II first takes apart nucleosomes and then puts them back together again during DNA transcription. This process allows the enzyme to access genomic sequences while ensuring that epigenetic details in the structures are not lost.

Ehara H, Kujirai T, Shirouzu M, et al. *Science* 377, eabp9466 (2022)



03

A nifty trick to help plants thrive in iron-poor soils

Some plants have evolved a unique strategy to capture iron, which is important for plant growth, yield, and overall health, by releasing compounds called mugineic acids into the soil. They bind with iron to form a complex that can be absorbed via a specific transporter system in the root. Atsushi Yamagata in the Lab for Protein Functional and Structural Biology and others have now determined the structure of the transporter protein for the first time using cryo-electron microscopy. This research is now guiding work to develop derivatives of mugineic acids, which could become a new generation of highly effective fertilizers for alkaline soils.

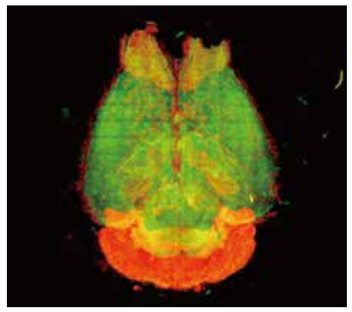
Yamagata A, Murata Y, Namba K, et al. *Nat Commun* 13, 7180 (2022)

04

Phosphate tags on brain enzyme govern sleep dynamics in mice

Sleep-promoting proteins whose activity could be modulated by phosphate tags was previously identified by the Lab for Synthetic Biology. Now the researchers in the same lab have shown how different phosphorylation patterns on one sleep-promoting protein—a neuronal enzyme called CaMKIIß—in mice can control different sleep induction and maintenance processes in their brains.

Tone D, Ode KL, Zhang Q, et al. *PLoS Biol* 20, e3001813 (2022)

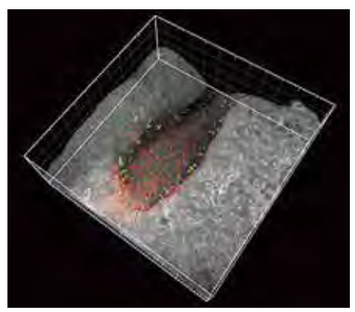


05

How mouse embryos determine left from right

During early embryonic development in mice, the motile cilia of a group of cells at the node gyrate clockwise, setting up a leftward flow in the surrounding fluid. This fluid flow is then sensed by immotile cilia located to the left and right of the moving cilia and causes the left and right sides of the embryo to develop differently. Hiroshi Hamada and Takanobu Katoh (Lab for Organismal Patterning) and co-workers have now shown that the immotile cilia in mice embryos sense this fluid flow mechanically, resolving a two-decade debate.

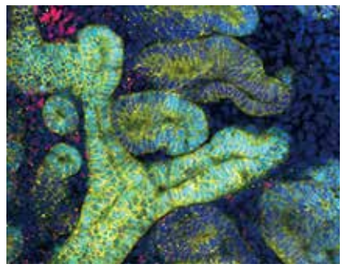
Katoh TA, Omori T, Mizuno K, et al. *Science* 379, 66-71 (2023)



06

The next milestones in generating artificial organs

Organoids are developed from stem cells and cultured on 3D frameworks, where they self-organize into functional tissue. However, the largest organoids available today are only a few millimeters across. "Once we discover how to grow them at scales comparable to real organs, we could create artificial organs derived from a patient's own stem cells," says BDR team leader Minoru Takasato. He is involved in a consortium that brings together RIKEN researchers and external collaborators to tackle organoid challenges and find real-world applications.

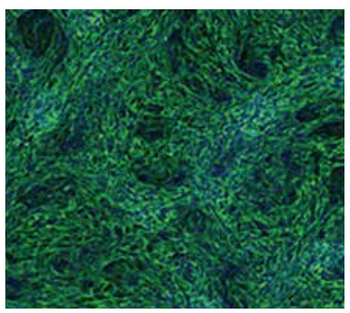


07

An experimental strategy for recreating organ formation in the lab

Researchers in the Lab for Lung Development and Regeneration and their collaborators at Cincinnati Children's Hospital have developed a laboratory protocol that selectively activates certain signaling pathways to convert human stem cells into various mesenchymal lineages, which support the formation of the liver, gut and other organs. In addition to shedding light on organ development, this could eventually enable doctors to provide treatments tailored to individual patients.

Kishimoto K, Iwasawa K, Sorel A, et al. *Nat Protoc* 17, 2699-2719 (2022)



BDR Photo Tour

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

View from the eighth floor of the Integrated Innovation Building (Kobe Campus)

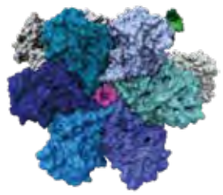
Towers of giraffes in the morning sun?

▲ The sunrise over Osaka Bay viewed from the east side of the top floor of the RIKEN Integrated Innovation Building (IIB), which is located on Port Island, an artificial island. Silhouettes of the gantry cranes along the wharf emerging in the morning sun.

◀ Looking out from the south side of the IIB. In the far distance, behind the airplane taking off from Kobe Airport, you can see the faint outline of the mountains of the Kii Peninsula.

▲ The Port Liner's Iryo Center Station seen from the west side of the IIB. Many RIKEN staff get on and off here and at the neighboring Keisan Kagaku Center Station.

On the cover!



A six-winged pinwheel?

This is the transcription termination factor Rho. It is a ring-shaped structure consisting of a hexamer that forms a tunnel in the center for the RNA (magenta) to pass through. When Rho attaches to the RNA polymerase (white and gray) during transcription, it uses this tunnel to pull the RNA out and terminate transcription at the appropriate time.

◎Credit:
Lab for Transcription
Structural Biology

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