Yasuki Fukita: “What I really wanted to do is the fusion of physics and biology”

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Prof. Yasuyuki Fujita, PhD, Kyoto University Graduate School of Medicine, Department of Molecular Oncology

Prof. Yasuyuki Fujita, PhD, from Kyoto University's Graduate School of Medicine, specializes in how normal epithelial cells eliminate cancer cells through competition. He first conceived this model as a student and later became the first to demonstrate it for normal vs. cancerous epithelial cells in *Nature Cell Biology* (Hogan et al., 2009). A pioneer in this field, he has authored key publications, including a review in *Cell Research* (2012), a research article in *Nature Cell Biology* (2017), and a *Nature News and Views* (2019). Born in Osaka, he studied medicine at Kyoto University and completed most of his Ph.D. at Osaka University, researching intracellular signaling under Prof. Yoshimi Takai. He then spent five years in Berlin at the Max-Delbrück-Center for Molecular Medicine, where he discovered **Hakai**, a protein involved in disrupting cell-cell adhesion (*Neuron*, 1998; *Nature Cell Biology*, 2002). From 2002 to 2011, he led a group at University College London's MRC Laboratory for Cell and Molecular Biology, focusing on epithelial cell competition. Since then, he has continued this research at Hokkaido University and, since 2020, at Kyoto University. Beyond academia, Prof. Fujita is known for his engaging personality, love for storytelling, and interests in socializing and sports. He also spent three months volunteering in Uganda, helping establish a clinic for patients with malnutrition and infectious diseases.

- **What exactly is cell competition?**

Cell competition is a process in which cells with different properties compete for survival or space. Often, abnormal, or aberrant cells are identified and eliminated by other cells, maintaining tissue health. This process also plays a role in the early stages of cancer. When oncogenic mutations occur in a single cell, neighboring cells can recognize and eliminate them, acting as a natural cancer-prevention mechanism.

Miguel Torres was the first to demonstrate that cell competition occurs during mouse embryonic development, showing that abnormal cells are eliminated to ensure proper body formation. His 2013 study published in *Nature* had a significant impact on the field. I started working on cell competition in 2009, and after being impressed by his findings, I invited him to Japan for a talk. Since then, we have maintained a strong connection, discussing cell competition mechanisms despite our different research focuses.

Spain is a strong hub for cell competition research—Ginés Morata, based at a cancer center, first discovered cell competition in *Drosophila*, making him the "father" of the field. Japan is also advancing rapidly in this area, and today, both countries are at the forefront of cell competition research. We frequently invite Ginés and Miguel to our conferences in Japan, including a major international meeting last summer.

- **How does cell competition help prevent cancer in our bodies?**

Although not yet fully demonstrated, our research using mouse models suggests that when cancerous cells emerge, they can be eliminated through cell competition. This phenomenon is observed across multiple species, including *Drosophila* and zebrafish, indicating it is a conserved biological mechanism.

We also found that various environmental factors, such as chronic inflammation and high-fat diets, can weaken cell competition. For example, in obese mice, cell competition decreases. This suggests that lifestyle choices may influence our body's ability to eliminate early-stage cancer cells.

- **Does this mean our diet and lifestyle can influence how well our healthy cells fight against cancer?**

While we do not yet fully understand how cells recognize abnormal ones, this is a major question in the field. Miguel and I are actively investigating potential triggers that enhance or suppress cell

- **Why do some cancer cells evade the immune system while others do not?**

The immune system typically responds at later stages of cancer development. In the very early stages, normal cells may act as the first line of defense, eliminating abnormal cells before the immune system is involved. This highlights the potential importance of cell competition as a protective mechanism in early cancer prevention.

- **How close are we to using your findings to develop cancer treatments?**

If we can fully understand the mechanisms behind cell competition, it could be applied to cancer prevention. Our research indicates that a low-glucose diet—achieved through intermittent fasting or a ketogenic diet—can enhance cell competition in mice and promote the elimination of cancer cells. However, we still need more detailed studies to determine how this can be translated into practical applications.

Additionally, we have identified a drug that promotes cell competition, which could be another potential avenue for treatment. While cell competition may not be applicable to advanced malignancies, it could be valuable for early-stage cancer prevention.

- **Could we one day train healthy cells, like the immune system, to better fight cancer?**

That is one of our key goals. Since we know that low glucose promotes cell competition, modifying environmental conditions or cell behavior could enhance our body's natural defenses against cancer. However, we must first clarify the underlying mechanisms before developing a viable treatment.

- **Could future treatments involve creating "super healthy cells" through diet, drugs, and lifestyle adjustments?**

Advances in genetic sequencing allow us to identify individuals at higher risk for certain cancers, such as pancreatic or colon cancer. In the future, we might tailor interventions to strengthen specific organs' defenses against cancer. We know that certain individuals may have a higher predisposition to diseases like pancreatic or colon cancer. With the increasing accumulation of sequencing data, it’s possible that in the future, by analyzing DNA, we could gain a deeper understanding of these tendencies. This could guide us in identifying individuals at higher risk for certain cancers, such as pancreatic cancer. In turn, we could explore ways to boost the pancreas’ defense mechanisms to reduce the risk. This kind of tailored approach might become possible as sequencing data continues to advance. However, we are still in the early stages of understanding how to fully utilize this information. One thing we’ve found is that cell competition, which can influence cancer development, behaves differently across tissues. For example, when we compare the lung, intestine, and pancreas, we observe that cell competition is very active in the intestine. But in the lung, cell competition may be less pronounced, and sometimes cells can escape from this competition, potentially leading to tumorigenesis. However, we still don’t fully understand why cell competition occurs differently in various tissues. Understanding why competition differs between tissues is an important area of research.

- **Immunotherapy is becoming a standard treatment for many cancers. Could it be combined with cell competition research to find a cure?**

I’m not entirely sure whether cell competition can be applied to highly malignant cells. What we have shown so far is that cell competition seems to occur at earlier stages of cancer. So, while I'm uncertain if cell competition research could directly lead to cancer treatments, it may offer insights into prevention strategies.

Currently, there are no drugs proven to truly prevent cancer. The closest example is anti-inflammatory drugs, like aspirin, which have been shown to reduce the risk of colon cancer, but that's about it. So, cancer prevention could be a major focus in the future. Cell competition, in particular, could play a role in such preventive approaches, and that is my ultimate goal.

The biggest challenge is proving that a drug can effectively prevent cancer. Typically, this requires studying large populations—millions of people with and without the drug—to observe long-term outcomes. However, many researchers worldwide are working on developing diagnostics for precancerous conditions. Once these diagnostic tools are available, the effects of cancer-preventive drugs can be scientifically assessed. By monitoring the progression of pre-cancerous cells—whether they evolve into malignant ones or disappear—prevention strategies can be better understood. If such diagnostic methods are developed, we could see significant progress in preventive medicine.

- **Did you always want to study basic science?**

My background is in medicine, so I have always been interested in applying research to real-world problems. In addition to cell competition, I work on cancer diagnostics, aiming to combine prevention and early detection.

- **You trained in Japan and later moved to Europe for your postdoctoral work. What differences did you notice in research culture?**

I did my postdoc in Berlin for six years, then became a principal investigator (PI) in the UK for eight and a half years before returning to Japan as a professor.

Cultural differences are significant. In Japan, we are trained to prioritize societal needs and adapt to collective expectations. In Europe, individuals tend to be more self-oriented. This philosophical difference influences research dynamics—for example, junior scientists in Japan often defer to senior colleagues, while European labs tend to be more egalitarian.

In a way, we are eager to keep things clean, like picking up dust from the street. Traditionally, we've been educated to think this way—though it may be changing now. In the laboratory, this translates to younger or junior people often taking the lead from senior colleagues.

- **How do you manage a diverse team in your lab?**

My lab has 23 members, with about 40% coming from countries like Egypt, Korea, China, and Taiwan. Having led a lab in London with mostly non-Japanese researchers, I have learned to respect different cultural perspectives. I have to mention that when I was a PI in London, most of my lab members were not Japanese. At that time, I struggled quite a bit. However, what's really important is respecting each lab member's philosophy and culture. For example, I had a Spanish postdoc whose approach to work was quite different from mine. I'm the type of person who's very hardworking and focused on work, as you might expect from a Japanese perspective. But she values work-life balance and enjoys life outside the lab. Sometimes I felt frustrated, especially when we were about to submit a paper, as I wanted her to be more involved in the process. But for her, maintaining a balance between work and personal life was especially important. Over time, I came to understand her perspective more, and I realized that I couldn't impose my way of doing things on her. She has her own lifestyle. Once I accepted that, it became easier for me, and I wasn't frustrated anymore.

Japanese researchers often work long hours—I stay until 10 p.m., and some students work past midnight. However, I do not enforce this; it is simply a cultural norm. I also try to respect work-life balance differences, particularly with international researchers.

- **You admire the philosophy of the samurai Ryoma Sakamoto. How does that**

influence your approach to research?

For a long time, Japan was governed by the samurai, especially during the Edo era. During this time, the social structure became very rigid, with little flexibility and a strong emphasis on hierarchy. This system limited Japan's development, and the country didn't progress much because of the solid hierarchy. Additionally, there was increasing pressure from European countries to open up trade, and if Japan had continued on this path, it might have become a colony of European powers, particularly the UK.

In response, some samurai made great efforts to change the system. They fought against the government, leading to civil wars. Sakamoto was one of the most active figures in this movement. He worked hard to reform the social structure because he deeply understood Japan's situation. I admire his philosophy, which emphasized having a big dream and a clear goal in life. He believed that when you're born, you should aim for something big and always strive toward that goal. It's a simple philosophy, but I really like it because it's about being ambitious. This mindset has had an influence on my own philosophy, and it's something I value deeply.

- **If you had unlimited time and resources, what would you study?**

What I really wanted to do, but haven't yet achieved, is the fusion of physics and biology. My background is in medicine, but I became interested in science when I was around 18 or 19. At that time, I wanted to pursue something revolutionary, something that no one had tried before. I realized that there are three major fields in science: physics, chemistry, and biology. The fusion of chemistry and biology has already been explored, as has the fusion of physics and chemistry. But there hasn't been as much focus on the fusion of physics and biology.

Physics offers vast topics like electric and magnetic fields, but very few have explored how these concepts intersect with biology. There are also other areas in physics, like waves, which I think could form a new research area. While fields like mechanobiology and mechanical sensing have made progress in merging physics and biology, there are still many untapped areas in physics that could be applied to biology.

If I had more time, I would definitely explore this area more. But I'm not sure if I have unlimited time for research. You're still young, so perhaps you could pursue physics in your own research. For me, I feel that without a complete understanding of physics, it's hard to produce truly original ideas. I've tried to find time to study physics, but it hasn't been enough.

- **What is your opinion about the CNIC?**

This center primarily focuses on cardiovascular diseases, whereas my main research area is cancer. However, there is some overlap—Miguel [Torres] is working on cell composition, and I study cell competition, so we share a similar research interest. The key difference is that he focuses on embryonic development and cardiomyocyte differentiation, while I concentrate on cancer. Although I am not heavily involved in stem cell research, we both explore the basic phenomenon of cell competition, which connects our work.

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