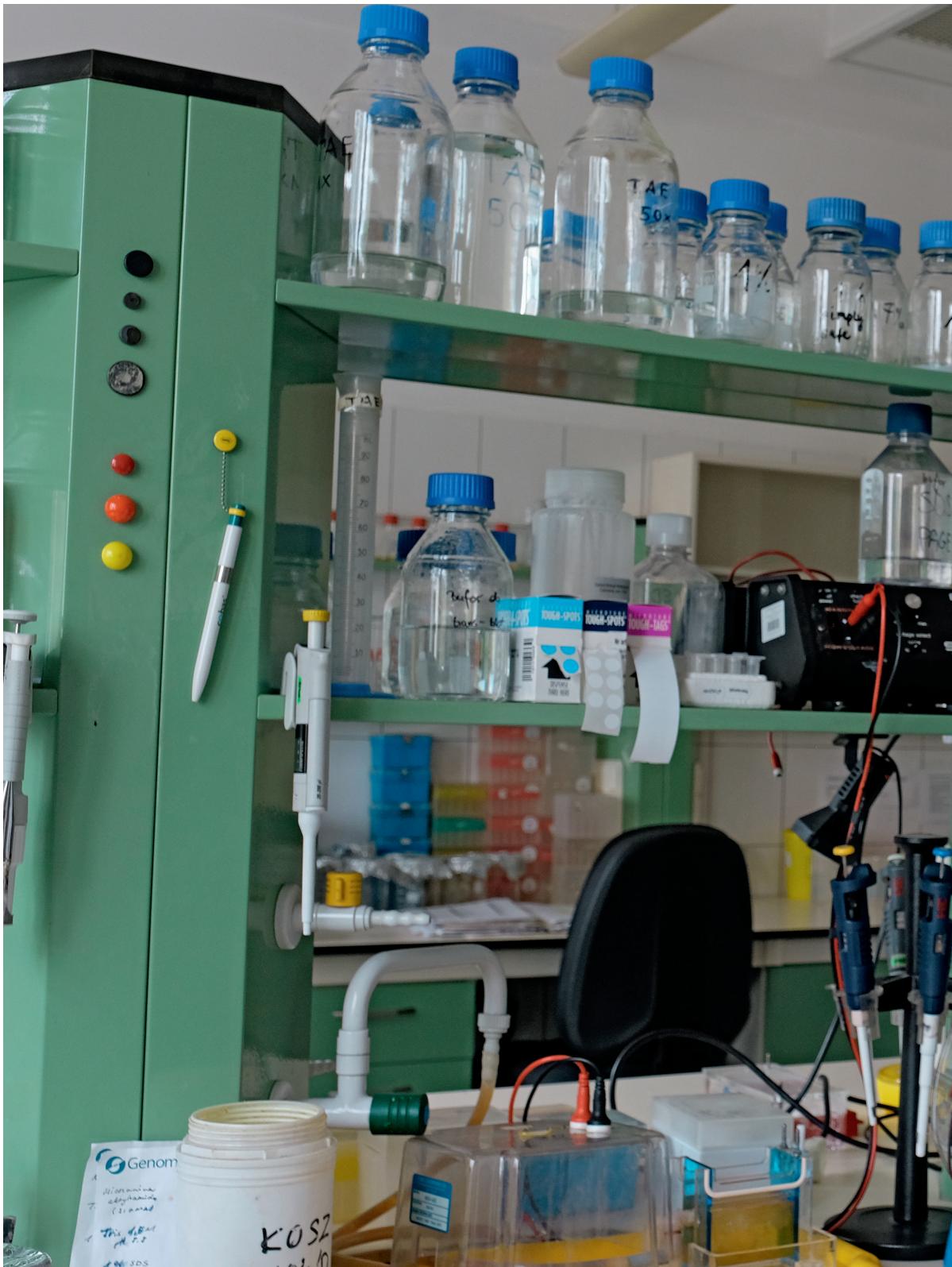
Prion-Like Proteins

Dr. Takao Ishikawa (PhD)
works as an Assistant Professor at the Department of Molecular Biology, Faculty of Biology, University of Warsaw. In his research work he studies prions, and when not at the lab he popularizes science among children and young people.
t.ishikawa@uw.edu.pl

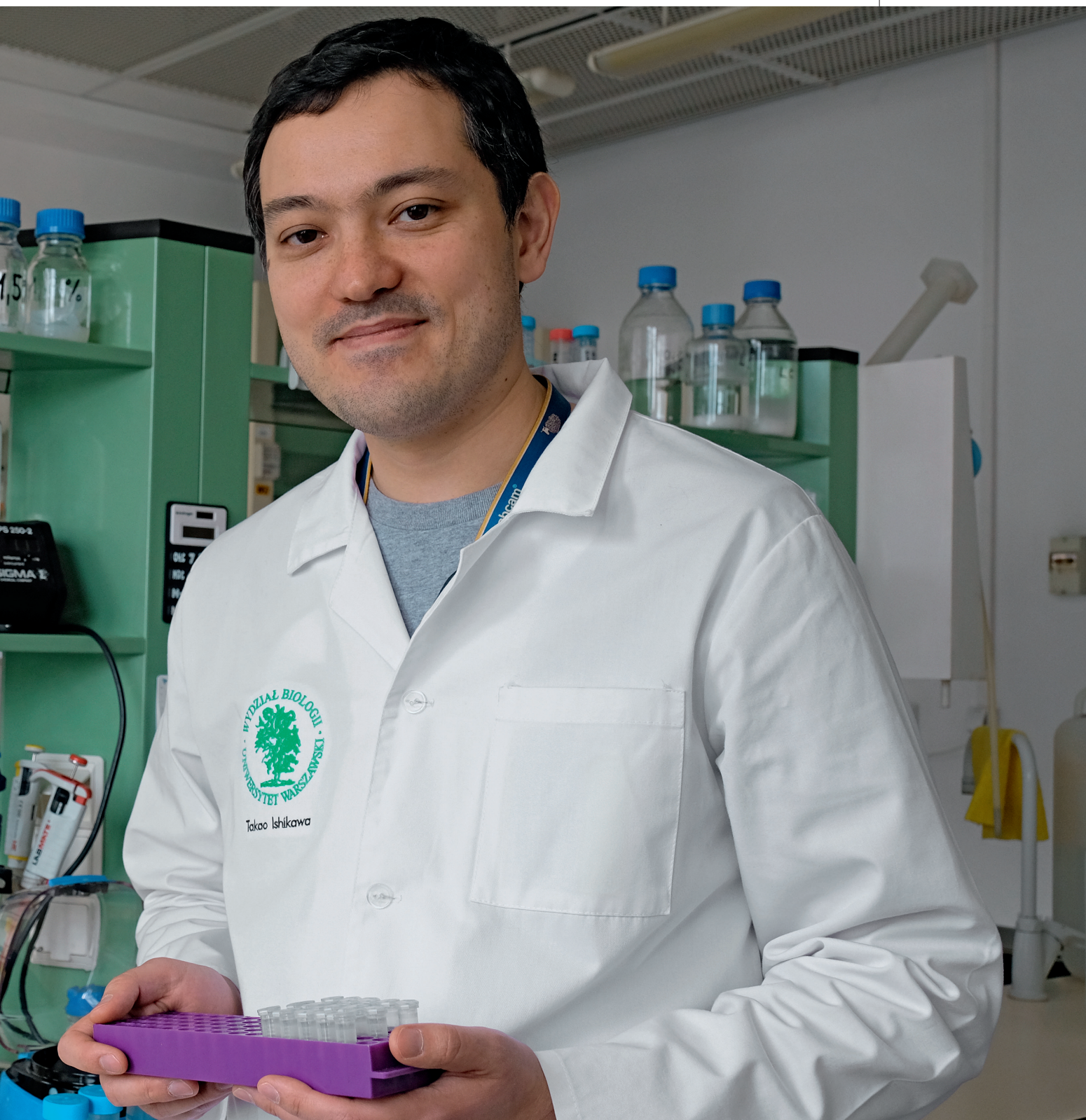


JAKUB OSTAŁOWSKI

DR. TAKAO ISHIKAWA

Dr. Takao Ishikawa from the University of Warsaw talks about why perhaps not all scientists should aim to become professors, and explains what we can learn from yeast proteins.

ACADEMIA: **You mainly study processes that occur in proteins, is that right?**
TAKAO ISHIKAWA: My research concerns the formation of artificial prion proteins in baker's yeast. They are fascinating, because they occur in two spatial forms. It's also interesting that we don't always understand the physiological role of prions – as is the case in the protein found in mammals. And they have



a specific property: they can form very regular aggregates which can reach huge sizes. They are known as amyloids. Alongside bacteria, viruses and other pathogens, they can cause infectious diseases even though they are not a life form and don't have their own genetic material. When they are transferred from one organism to another, they create centers of prions aggregation. This may cause other, healthy prions to become attached, which in turn may result in disease symptoms.

Prions are fascinating, even for scholars working in culture or the humanities. For example, the Fore people of Papua New Guinea used to practice ritual cannibalism, consuming the bodies of dead relatives, until as late as the 1960s. The population was affected by a disease caused by prions found in nerve cells. The Fore people named it *kuru* from the word "to shake," and it was also known as the "laughing sickness." It is more formally known as Creutzfeldt-Jakob disease (CJD). Its variant in cattle, bovine spongiform encephalopathy (BSE), is commonly known as "mad cow disease."

> Prions cause Creutzfeldt-Jakob disease (CJD) – its variant in cattle is commonly known as "mad cow disease."

Around thirty years ago, BSE was observed in cows in the UK, bringing concerns that people who have eaten infected meat could be affected. And in fact around 200 incidences in the early 21st century can be attributed to prions; the disease has a very long incubation period.

It turns out that baker's yeast also contains proteins with properties similar to prions, even though on structural and functional levels they are not related. However, their common feature is that they do something no other proteins do: they dramatically alter their shape and then aggregate into infectious forms. Apart from biology, I am also fascinated by engineering, so I use certain fragments of yeast proteins with prion properties to create new, fusion proteins. Such protein constructions allow us to study whether it is possible to reverse the process to return to the correct prion structure in yeast systems which are safe for researchers and cheap and easy to use. When my yeasts are "sick" because I introduced artificial prion aggregate, they require an additional amino acid in their medium to survive. Then when I apply such a "cure" compound, they regain their ability to synthesize the amino acid. In summary, based on my knowledge whether my yeasts require the given amino acid, I am able to discern chemical compounds which dissolve aggregates harmful to the cell and return proteins to their correct structure.

Does that mean that your experiments could lead to new disease treatments?

I try to select compounds which reverse the damaging effects in disease structures of prions, because if they work in yeasts, there is a chance that they will also work in mammalian prions. They will be tested on human cell cultures showing signs of prion presence, or in an animal model presenting symptoms similar to those associated with CJD.

What moment do you see as being a crucial turning point in your research?

The beginning, really. My boss asked me to deliver a short presentation at a seminar at the institute, and since I was just starting my PhD and didn't have any results yet, I asked my promotor for advice. He suggested I look at the latest research and sent me an article from *Nature* describing something which was incredible at the time: the paper said that if yeast equivalents of prions are aggregated, they are more likely to survive certain conditions than the original yeast. It was a breakthrough paper suggesting that when aggregating proteins lose their physiological activity, which is not necessarily a bad thing. I chose the topic for my seminar, and I ended up becoming fascinated by it.

At that stage, my PhD was focused on something else, so my work on prions was a sideline. But one day, I was asked by the science club from the Faculty of Chemistry to deliver a lecture. And I thought that we could combine the interests of organic chemists who aim to synthesize new compounds with a search for treatments for incurable diseases such as CJD. I talked about using yeasts in my research. After the lecture I was approached by one of the students, Kamil Lisiecki – he has a PhD of his own now – and he said that he would like to work with me to find out whether the compounds he had synthesized might have a positive effect on yeast prions. It was a really important point in my life as a scientist and as an educator. I was approached by someone I didn't know very well but who was inspired by what I said; in fact he shifted my previously Platonic interest in prions towards specific action. I wrote to researchers from all over the globe asking them to send me their yeast strains to help Kamil put his plan into action. He used the data as a basis for his undergraduate dissertation, while I learned new techniques. If we hadn't crossed paths, I probably would only be thinking occasionally about yeast prions without ever actually working on

them. We recently co-published a paper on the basis of our joint research. Additionally, I received finance for my sister project from the University Technology Transfer Centre, allowing us to develop a new version of the "yeast system."

You also work with young people to popularize biology.

I always try to raise topics I am familiar with, regardless who I am speaking to. They tend to be subjects linked with GMOs and so on. When I am invited to speak to children, I talk about how genetic engineering can help us. I try to be objective and present both sides of any problem I am discussing. I firmly believe that this technology – like any other – should not be feared, as long as it is well studied and as long as the data shows it is safe for the environment. It should be remembered, though, that biodiversity must be preserved, while unchecked production of GMOs could take us dangerously close to creating monocultures. Life on Earth is as abundant and diverse as it is because all organisms are adapted to their environment to a greater or lesser degree. If we were to replace everything by clones, it would soon lead to disaster. Look at the great famine in 19th-century Ireland, for example. The vast numbers of potatoes planted in the country were a staple food, especially among the poor. They were also clones, leaving them open to fungal infection or blight. As a direct result of massive crop failures, around a million people died and another million or so emigrated from Ireland to the US.

I also always try to listen to young people. They tend to have shorter attention spans, so instead of delivering lectures I have discussions. Children also don't have as many inhibitions as adults and they ask direct questions. For me it's as much fun as it is a challenge.

You have also worked in Japan. How do you perceive the differences in research between the two countries?

I had a scholarship in Tokyo in 2011 as part of an educational exchange program. I spent two weeks at the University of Tokyo observing how molecular biology was taught. I also have some insight into the academic world in Japan, because both my parents work at universities there. In Poland I am mainly familiar with Warsaw, so I should say that it's just a sample of the specificities of Polish academia.

The University of Warsaw is generally democratic, while Japanese universities tend to be structured in a rigid, feudal way. I grew up there so I know that this hierarchy is reflected in all aspects of everyday life. However, things are better organized and there is much more extensive administrative support. I think that this means we waste a lot of time over here.

And there is one more very notable difference. Here, in Poland, there is a powerful drive for all academics to strive to become professors. If a similar situation happened in the army, you would end up with squadrons of generals with no officers or privates. This is not how things should be. In Japan, the situation is clear: people whose personalities are well-suited for leadership rise up the ranks to make a name for themselves, to win grants, to run laboratories. But, in my view, the power of science frequently lies with mid-ranking researchers. They have a wealth of experience and they should form the heart of their laboratories, their living memory. PhD students spend four years at a lab and then tend to disappear. There is constant rotation. There is no higher doctorate (*habilitation*) process in Japan, so there are many technicians who are making vast contributions to science and research.

What's the relationship between the state and science in Japan?

Just like in Poland, Japanese researchers complain about receiving insufficient governmental funds. But the fundamental difference between Poland and Japan is the involvement of commercial enterprises. The state is very supportive and encouraging of this. But I don't want to pitch Poland and Japan against one another, especially since we are seeing significant changes in Poland. The National Centre for Research and Development provides a platform for partnership between the state, academia and business. Poland is implementing a more commercial model and we can expect positive outcomes.

> The power of science frequently lies with mid-ranking researchers, who often have a wealth of experience.

But there is another important difference. I get the impression that in Poland researchers are seen as somewhat mysterious – people don't know what they do and why. In Japan, scientists are widely respected and trusted, and the far-reaching results of their work are appreciated. The media regularly report on even minor achievements at regional universities. In Poland, for information on scientific achievement to reach the news, it has to be something truly spectacular.

INTERVIEW BY DR. **JUSTYNA ORŁOWSKA**