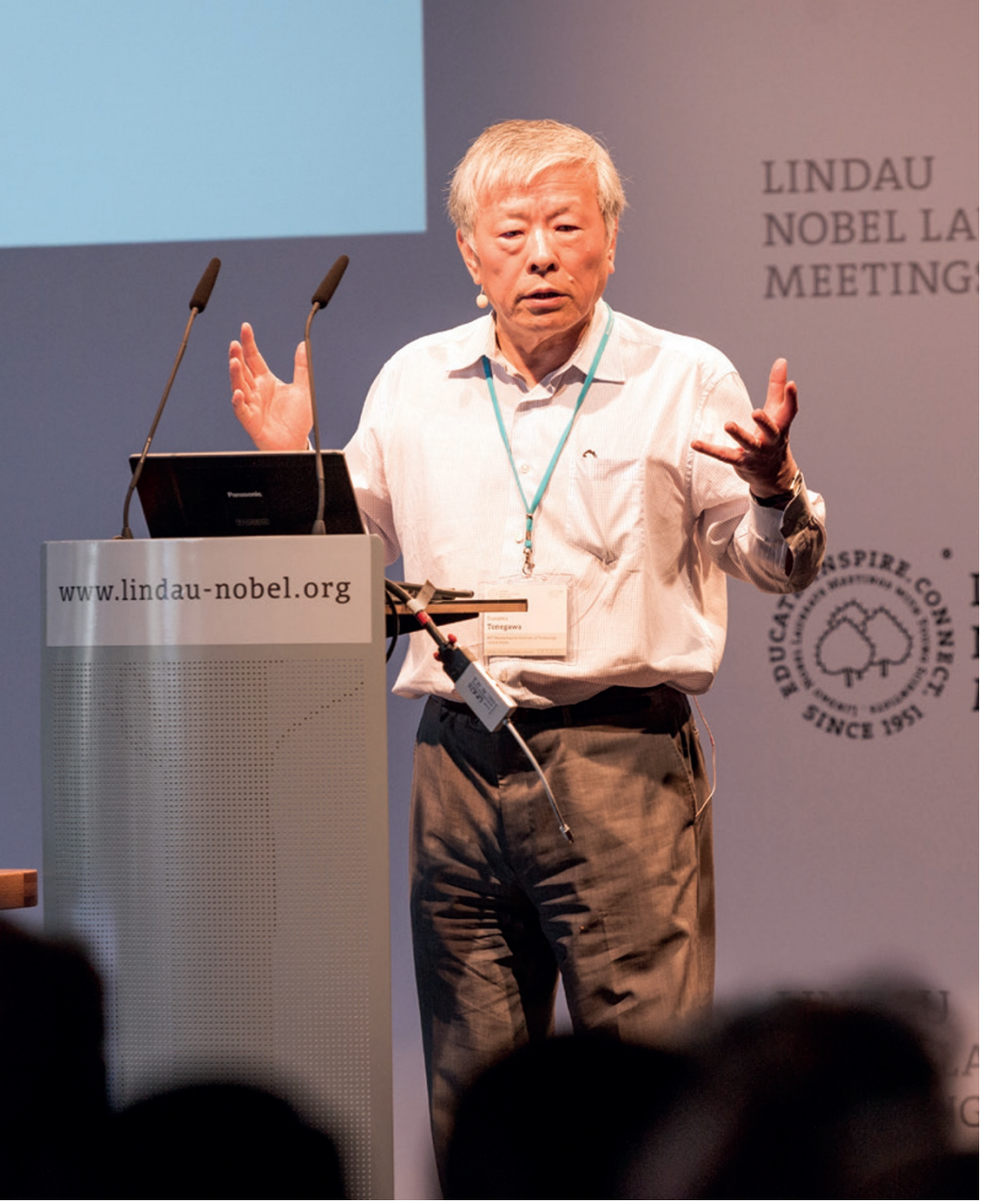


ADRIAN SCHRÖDER/LINDAU NOBEL LAUREATE MEETINGS

Q&A Susumu Tonegawa
Memory man

Susumu Tonegawa unlocked the genetic secrets behind antibodies' diverse structures, which earned him the Nobel Prize in Physiology or Medicine in 1987. Having since moved fields, he tells Keikantse Matlhagela about his latest work on the neuroscience of happy and sad memories.

You started as a chemist, then you moved into molecular biology and now you are a neuroscientist. Why change fields?
Strangely, the only people to ask me about this are journalists — my students never ask. I see myself as a scientist who is interested in what's going on inside of us. It doesn't matter whether it is chemistry or immunology or neuroscience, I just do research on what I find interesting. The switch from chemistry to immunology did not seem like a big shift when I was young, but immunology to neuroscience was. After about 15 years spent researching immunology I wanted to explore an area of science where there are still big, unresolved questions. The brain is probably the most mysterious subject there is.

Do you keep up to date with the field in which you won your Nobel prize?
I am sorry to say that I haven't been paying a lot of attention to immunology in recent years because I am preoccupied with my work on memory. I have friends, of course, from that time — very close friends. But my friends are not young. Even though they are experts, they are also retired. We tend not to talk about immunology a whole lot.

Is it helpful in neuroscience research to have a multidisciplinary background?
The brain is hugely complicated, and because it is so complicated it requires multidisciplinary research. You need mathematics to model how brain networks function. You need chemistry, molecular biology and behavioural studies of animals to answer other neuroscience questions. Neuroscience is totally multidisciplinary.

What have you learnt about the brain circuits involved in positive and negative emotions?
Imagine that a week ago you were on a vacation — you went to a Caribbean island and had a great time — and you remember the detail of what happened during your vacation. Those memories would be examples of 'episodic memory'. Sometimes episodes come with no emotional content, but often they come with a positive or negative slant — in other words, they were either pleasurable or unpleasant experiences.

My lab has been studying the part of the brain called the hippocampus to investigate its role in the formation of episodic memory, and how that varies with positive and negative emotional content. Our results indicate that there is a kind of competition between brain circuits to be able to assign a positive or a negative value to the memories. We have taken advantage of this understanding in our experiments on mice and have shown how depression can be reversed or repressed.

How do you tell if a mouse is depressed?
It is similar to the way in which you tell if a human is depressed. There are at least two symptoms. When a depressed patient encounters something difficult to resolve or improve, they give up more easily than people without depression. Another symptom is called anhedonia, which is an inability to enjoy normally pleasurable experiences. Therefore, depressed people don't seek out normally pleasurable experiences. The same goes for mice with depression.

Have you identified a target protein or group of proteins involved in mouse depression?
No. But we have found specific target cells that hold pleasurable episodic memories. They are deep inside the brain. There is an area of the brain that in male mice, for example, holds information about a specific, playful encounter with female mice. We have developed technology to identify these cells and we have genetically manipulated mice so that the cells express a light-sensitive protein. If you shine blue light onto them the cells become activated, meaning that the mouse recalls the positive experience. Going back to the depression model: if a mouse is depressed, activating these previously identified pleasure-memory cells can cure its depression. So when

NATURE.COM
To listen to the interview visit:
go.nature.com/wcwqdj

you put the mouse in a difficult situation that it would have previously given up on, it now makes an effort to solve the problem.

Have you tested this in higher animals?
Not yet. Unfortunately, the technology that we use for mice is not directly applicable to humans. But I know researchers are working on how to replicate in humans something similar to what we did in mice and eventually we can expect that this will become possible. Hopefully, one day, our findings will lead to a new kind of therapy for depression.

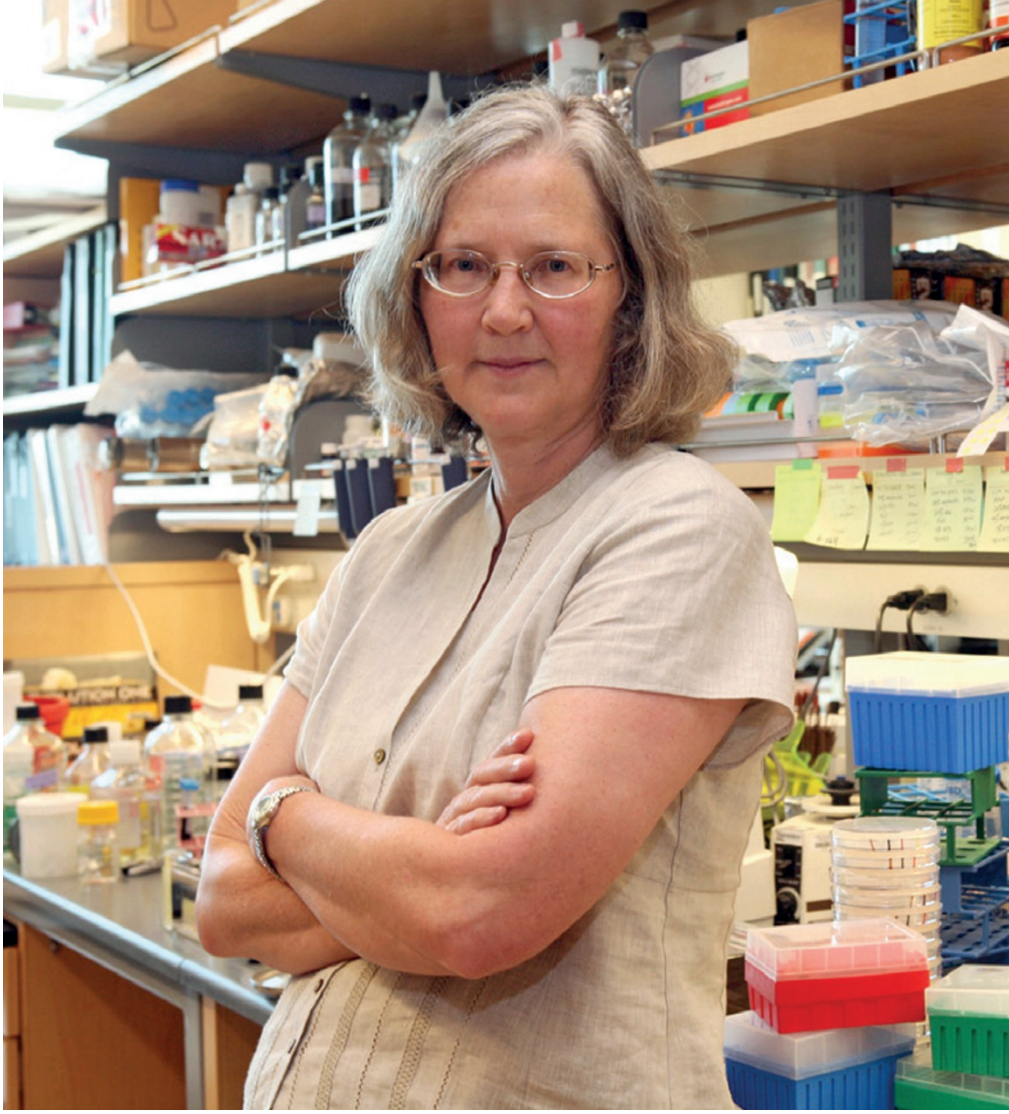
I am a researcher from southern Africa, where investment in science is low. What career advice would you give to young scientists who come from countries that are not known for their science research?
When I was a student in Japan the 1960s, I became fascinated by molecular biology. But there was no molecular biology in my country. So I had to go to graduate school abroad. I was fortunate to have the opportunity to study in the United States and I stayed abroad, including in Europe. My antibody work was entirely done in Switzerland. I didn't have much of a relationship with Japan until very recently. But now, after many years, I try to help Japanese science.

For a while, you may have to be trained outside of Africa. Since you are young, if you really want to do science I think there will be a way for you to go abroad and receive training. Then you could go back to southern Africa and try to help science in your country; if you get good training your knowledge will become useful not only to you, but eventually also to the community in which you grew up.

What are your interests outside of science?
I do not have anything that interests me as much as science. But, later in my life I was introduced to music by my wife and our children. I go to concerts with them and I enjoy it. My daughter plays the violin quite well. My younger son played cello and piano. I am not sure what I will focus on if I stop working in the lab. Once in a while I wonder what I am going to do if and when I retire. Is there such a thing as retirement for me? I can't imagine it. ■

This interview has been edited for length and clarity.

Keikantse Matlhagela is an HIV researcher and lecturer at the University of Botswana's Faculty of Medicine. Previously, she was a Fogarty Research Fellow at the Harvard School of Public Health.



Q&A Elizabeth Blackburn

End-game winner

Elizabeth Blackburn shared the 2009 Nobel Prize in Physiology or Medicine with Carol Greider and Jack Szostak for their work on telomeres — the protective caps at the end of chromosomes — and for identifying the enzyme telomerase, which maintains telomere length. Now at the University of California, San Francisco, she offers Elena Tucker an insight into her life inside and outside academia.

Why did you choose to study the ends of chromosomes?
The driver for me was wanting to understand how life works, rather than solving a particular problem that afflicts humans. When I was finishing my doctoral work at Fred Sanger's lab in Cambridge, UK, DNA-sequencing methods were embryonic. At the time, in the early 1970s, it was hard to sequence DNA except at the ends of relatively short DNA molecules. That was just what was possible. Researchers had looked at the DNA of viruses such as bacteriophages, but I wanted to know what goes on inside the nuclei of cells with real chromosomes. I heard that Joe Gall at Yale University in New Haven, Connecticut, had discovered very short, linear chromosomes in the cell nucleus of the eukaryotic protozoan *Tetrahymena*, and I thought I might be able to sequence the ends of those with the limited technology available at the time.

How did your research get off the ground?
Once at Yale I started analysing the ends of the short *Tetrahymena* chromosomes. What I found was really odd. I had expected to see something similar to the single-strand overhanging DNA observed at the ends of bacteriophage linear DNA, but telomeres were different. They consisted of tandem repeats of a short sequence, and the numbers

NATURE.COM
For an animation about Blackburn and her work visit: go.nature.com/skbuwi