ROLF SCHULTES/LINDAU NOBEL LAUREATE MEETINGS

why small companies or non-governmental organizations cannot make a big impact and significantly help the developing world.

As well as the new GMO initiative, you also signed the Mainau Declaration on climate change and campaigned in China for the release of Nobel peace laureate Liu Xiaobo. Do you consider it a responsibility to use your Nobel laureate status for the public good?

A Nobel prize is something rather special. Almost all of the laureates here in Lindau were awarded a Nobel prize because we were lucky. It is not that we are super smart or better than anybody else, but because we made a serendipitous discovery along the way. For whatever reason, when you win a Nobel prize people listen to you who never listened before. That means two things. The first is that you should use the opportunity to do good in the world, if you can. The second is that you should also be careful about what you say because you might not always be right. There are plenty of issues in which Nobel laureates could have been helpful, but they were rarely politically organized in the past. We tried to get Aung San Suu Kyi released from house arrest in Myanmar. Even though that was not successful, it showed that we laureates can come together — 225 of us signed letters that were sent to the Chinese and Burmese governments.

"Genetic engineering is just a better way of doing what we have been doing for 5,000 years."

What is the future of the Nobel prizes in the era of big collaborative science, in the light of projects such as ENCODE, the Encyclopedia of DNA Elements?

Many of the major steps forward in biology have been made by individuals or small groups of individuals. Our knowledge of biology is so limited, we are still at the starting point of understanding how organisms work and there are still terrific roles for individuals. But, in general, I am not sure science prizes are a particularly good thing. They are wonderful for the people who win them, and can be terrible for those who don't. I think they end up causing rather a lot of heartbreak. ■

This interview has been edited for length and clarity.

Gijsbert Werner is a PhD student at Vrije University Amsterdam, the Netherlands, where he studies the evolution of plant-microbe mutualisms.

Q&A Bruce Beutler

Chance encounters

Bruce Beutler is director of the Center for the Genetics of Host Defense at UT Southwestern in Dallas, Texas. He shared one half of the 2011 Nobel Prize in Physiology or Medicine with Jules Hoffmann for their work on the activation of innate immunity; the other half of the prize was awarded to Ralph Steinman. Here, Beutler talks to Christoph Thaiss about biological puzzles and intuition.

The discoveries that have resulted from your work are often referred to as the second revolution in immunology — the elucidation of how innate immunity operates — with the first revolution being adaptive immunity. Will there be a third revolution?

I hope there will be third, fourth and fifth revolutions. People always seem to overestimate what they already know, and we certainly know very little about how the immune system functions. If we think of the immune system as a machine, then we are far from even knowing all of its parts. We cannot predict the outcome of an immune response. We cannot say with confidence who will and who will not get an

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autoimmune disease. And we do not know who will and who will not respond to a vaccine. Much more remains to be discovered.

How have the main challenges in medicine changed during your career?

It is interesting that the most challenging diseases — cancer, diabetes and Alzheimer's to name a few — have not really changed since the late 1970s, when I was in medical school, with the exception of emerging infectious diseases. Some conditions are easier to address now, but the major issues remain. Autoimmunity is probably the next frontier. The majority of cases of autoimmune disease result from a complex genetic problem that has environmental influences. It is a colossal task for the immune system to maintain tolerance to self and yet be ready to react to everything in the world around us. We have some ideas about how that works, and we have developed concepts like 'central tolerance' and 'peripheral tolerance' — the two stages by which the immune system learns how to avoid attacking its own body. But when it comes to the mechanisms behind these concepts, we still know very little.

"Today, it is no longer a problem to find mutations that cause phenotypes, which used to be a bottleneck."

What made you decide to use random mutagenesis screens — chance, basically — in your research?

Chance leads to discoveries, and mutagenesis is a way to enhance one's chances of finding a surprise. Often it is the exceptional observations that lead to advances; once you understand exceptions, you understand the whole picture. We used chemically induced random mutagenesis of the mouse genome to identify genes and their functions. A mutation can create an alternative form of a phenomenon — a phenotype or trait — and we can learn a lot by seeing this alternative state. Once I saw a mouse with no eyelids. It simply had a membrane over the eyes. I found it fascinating that there is a single gene required for eyelids to develop. Similarly, one of the most interesting phenotypes I have ever seen is found in a mouse we called 'Possum'. When Possum mice are scruffed at the nape of the neck, they suddenly freeze and go into a sort of trance, for want of a better description. For a few minutes they do not seem to be conscious, but we know from electroencephalograms that they are conscious. The mutation has been identified as a defect in a single type of voltage-gated sodium channel — such a simple cause for such a complicated behavioural phenotype! And remarkably, the channel is not even located within the central nervous system. I find that really puzzling. Mutations get you thinking about how biological processes work.

Another thing I love about mutagenesis is that it is hypothesis-free. I think we can still do good science without having a prediction. If you take hypotheses out of the equation, you also take away the biases that arise because we tend to like our own ideas. If you start with a hypothesis and you find that you were correct, then you cannot really claim to have been surprised. On the other hand, if you start with a phenotype and find the gene that was damaged to create the phenotype, then you can be very much surprised by your discovery.

In that case, how does one develop an intuition for an interesting scientific question?

There is no strict algorithm to follow that leads to interesting discoveries. In my experience, scientists are guided mainly by instinct. In our case, instinct guides the design of screens. In prioritizing phenotypes for study, it helps to ask questions such as: 'Is what we observe unlike anything that has ever been seen before?' and 'Does it have implications for some important aspect of existing theory?'

I get excited by phenotypes that mimic human disease. Today, it is no longer a problem to find the mutations that cause these phenotypes, which certainly used to be the bottleneck in the whole process. Now it takes us about one hour from first seeing a phenotype to finding the causative mutation, and in my lab we usually solve about two phenotypes per day. The difficult part is to understand the mechanism, and there we have to prioritize our experiments so that we learn as much as we can with the resources available.

If there were no technical limitations, what would be your ideal experiment?

I find the speed with which we can already sequence all of an organism's protein-coding genes just magical. The team in my lab is now sequencing about 80 whole exomes — the protein-coding parts of the genome — every two weeks, and I am not sure we need to improve on that much in the future. I feel we have a surfeit of ability, so I am not crying out for new technologies in my own area. But looking more broadly, I think the great technological challenge in medicine in the long term might be in pharmaceutical development. One can envisage a time when we know the three-dimensional structure of all proteins, and that might allow us to compute the structure of drugs that would block certain biological processes without having any side effects. It is an enormous hurdle, but the day may come when computation supplants much of the screening we do presently.

If the scientific system were to be rebuilt from scratch, what do you think it should look like?

It might actually look similar to what we have today. Funding has never been a pure meritocracy, but I do not see a fairer way of doing it, practically speaking. In the area of publishing, I have flirted with the idea that someday there might be no need for peer-reviewed publication. Instead, everyone could publish their best work on their website. Over time, people would learn who the reliable sources were and apply alternative ways of ranking performance. There is a lot of objection to this approach for good reasons. Some are horrified at the prospect that shoddy work would flourish in the absence of peer review. But the model I have in mind would be somewhat similar to the way that artists are evaluated. Who peer-reviewed Bach and his complicated fugues? Imagine what we might have lost if they had been rejected.

Institutional organization is also really important. We need to maintain a mixture of people who work most effectively in small groups, as well as people who are at their best when part of large, organized efforts. Well-coordinated efforts amount to more than the sum of their parts.

If you were not an immunologist, what would you be?

I have always found enormous aesthetic enjoyment in nature. I am an amateur photographer — I take photographs of birds and I like to hike. If I were not a scientist, I might be a naturalist.

But if I were to pick some other field in science, I started out as a neurology resident, and disorders of higher cortical functions in humans still interest me. In the early 1980s, when I began seeing patients, the technology available to study neurobehavioural disease was not nearly as advanced as it is today. The opportunities to understand how the brain works are much greater now. Having a Nobel prize does give me the opportunity to broaden my horizons a bit, and I may move back into neuroscience one day.

What characteristics do you look for in students?

They need to have strong verbal abilities, both written and spoken. I find this to be a predictor of good performance in science in the long run. That may sound strange, but it is an observation I have made many times over the years. ■

This interview has been edited for length and clarity.

Christoph A. Thaiss is a PhD student in Eran Elinav's group at the Weizmann Institute of Science in Israel. He studies interactions between hosts and their microbiomes, and how these influence susceptibility to common diseases in humans.