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MEDICAL RESEARCH MASTERCLASS

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MEDICAL RESEARCH MASTERCLASS

16 October 2014 / Vol 514 / Issue No 7522

Cover art: Nils-Petter Ekwall

It is no exaggeration to say that the annual Lindau Nobel Laureate Meetings can be a life-changing experience for many of the 600 or so young scientists who attend. Researchers, all aged under 35, are selected from thousands of applicants from more than 80 countries and, this year, some were lost for words when asked to sum up the experience of what it meant to spend a week mingling with their scientific heroes on the German island of Lindau.

After all, where else can you rub shoulders with the discoverer of HIV, the person who uncovered the genetic foundations of cancer, or the scientist who risked his life to prove that stomach ulcers are caused by a bacterium?

This year's Lindau meeting, the 64th held since 1951, was themed physiology or medicine and took place between 29 June and 4 July, with 37 laureates in attendance. For the first time, there were more female young researchers than male.

Some laureates were familiar faces, such as Werner Arber, for whom it was his 26th visit. Others, including Michael Bishop, Jules Hoffmann and Barry Marshall, were new to the experience. Despite a busy schedule, the laureates clearly enjoyed exchanging ideas with the next generation.

Taking inspiration from the opening lecture by Randy Schekman, who shared the 2013 Nobel prize for work on the cell's internal transport systems, we report on the part played by autophagy in conditions such as cancer and Alzheimer's disease (page S2). There are discussions — initiated by *Nature Video* and available at www.nature.com/lindau/2014 — between young researchers and laureates on the science and ethics of ageing (S14) as well as Q&As with six laureates, conducted and written by young scientists (S5).

We are pleased to acknowledge the financial support from Mars, Incorporated in producing this Outlook. As always, *Nature* has sole responsibility for all editorial content.

Matthew Chalmers
Contributing Editor

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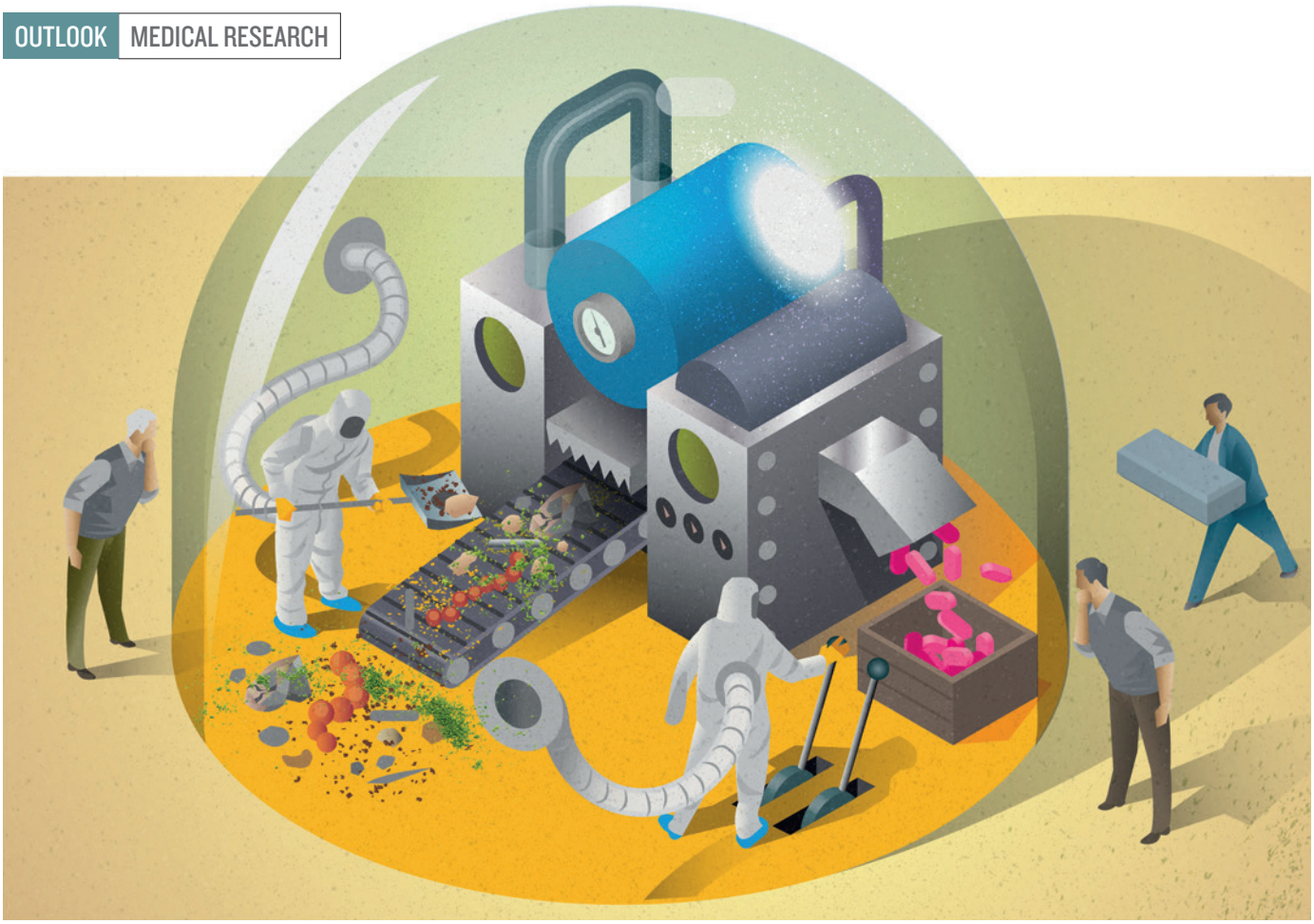


NILS-PETTER EKWALL

MOLECULAR BIOLOGY

Remove, reuse, recycle

Waste removal is not usually described as sexy, but the once-neglected field of autophagy — which plays a part in cancer and other diseases — is a hot topic in biomedical research.

BY MICHAEL EISENSTEIN

When Ana María Cuervo began researching her thesis in autophagy — a cellular recycling mechanism — little did she know that two decades later she would be working in one of the most dynamic fields of medical research. Randy Schekman, winner of last year's Nobel Prize in Physiology or Medicine, even chose to talk about autophagy in his opening address to the 37 laureates and 600 young scientists at this year's meeting instead of cellular trafficking — his prizewinning work. Cuervo is accustomed to this rise in interest. "I did my thesis on autophagy in the early 1990s when autophagy wasn't cool," says Cuervo, who is now co-director of the Einstein Institute for Aging Research at the Albert Einstein College of Medicine in New York City. "When I finished, everybody told me to change fields because autophagy was a dead end," she confesses. Studies have proved this prediction to be spectacularly wrong.

Autophagy was once considered to be little more than a cellular recycling bin — a process by which cells break down unwanted biomolecules into raw materials. But more recent research has revealed that autophagy is, in fact, a nexus for the cellular stress response and a failure point for many diseases. In the past ten years, researchers have made connections between autophagy and the immune response, cancer, neurodegeneration and ageing, says Daniel Klionsky of the University of Michigan in the United States. "The field just exploded."

A PROMOTION FROM HOUSEKEEPING

There are different types of autophagy, but the best-understood pathway is known as 'macroautophagy' — a bulk mechanism for gathering up and degrading proteins, organelles and other cellular materials. The process begins with the formation of a double-membrane structure known as a phagophore, which elongates and engulfs nearby cellular components (see 'Eating up the cell').

Autophagy was discovered in the 1960s, based on microscopic observations of selective degradation of cellular material within the lysosome (see 'A history of autophagy'). Over time, scientists accumulated evidence that this process helped cells to deal with nutrient-poor conditions, to eliminate excess proteins and even to remove entire mitochondria — the cell's metabolic power plants. However, most functions seemed to fall under the umbrella of basic maintenance, and autophagy research remained a niche field.

The turning point that showed autophagy was not simply cellular housekeeping came in the mid-1990s, when a number of proteins (now known as Atg proteins) that collectively mediate the formation and maturation of the phagophore were reported. Since then it has become clear that the Atg machinery intersects with physiological processes underlying an array of disorders, but scientists are still struggling to figure out the conditions that autophagy prevents or promotes.

CANCER CONTROVERSY

Autophagy seems to provide a crucial bulwark against genetic and biochemical damage — for example, by eliminating damaged mitochondria that would otherwise leak toxic molecules into the cell. As such, it is perhaps unsurprising that cancer was the first disease to be linked with autophagy. However, current evidence suggests that autophagy can act as both an enabler of and a protector against tumour growth, creating some debate in the field.

In 1999, Beth Levine and her colleagues at Columbia University, New York, showed that a protein called beclin-1 suppresses tumour activity in humans and promotes early formation of the phagophore[1]. The group also found that several cellular pathways that drive tumour growth inhibit autophagy, either by preventing activation of beclin-1 or by interfering with other Atg proteins. Levine is waiting for proof before declaring that autophagy failure itself drives tumour growth, but she believes it makes for a compelling hypothesis. "The general view is that autophagy plays a protective role against the development of cancer," she says.

However, some scientists believe that autophagy can also help advanced tumours to thrive by allowing cancerous cells to cope with the stress associated with competing for limited nutrients and oxygen, not to mention the toxicity caused by radiation or chemotherapy. Autophagy inhibitors could, therefore, render established cancers more vulnerable to treatment, says oncologist Ravi Amaravadi at the University of Pennsylvania in Philadelphia. "The overarching theme is that autophagy is an adaptive stress response that protects the cancer cell in advanced disease," he says.

KEEPING A CLEAR MIND

But it is not only cancer that is linked to the failure of autophagy — it also seems to play a key part in neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. These conditions are characterized by the formation of dense protein aggregates, which point to some sort of failure in cellular housekeeping, but disruptions vary considerably between the conditions.

For example, neurons in Alzheimer's patients exhibit increased numbers of autophagosomes, the membranes that enclose the cell components before they are broken down, yet they can no longer fuse effectively with the lysosome.

Although the roots of Alzheimer's pathology remain unclear, with toxicity linked to accumulation of two proteins called tau and amyloid-β (Aβ), autophagic failure could provide a reasonable explanation for either pathway. "At late stages of disease you get what looks like an autophagy blockade that might compromise the whole process," says neuroscientist David Rubinsztein at the University of Cambridge, UK. "That's going to affect not only tau and Aβ clearance but also removal of damaged mitochondria and other processes."

By contrast, some forms of Parkinson's are associated with disruptions in a parallel autophagy pathway called chaperone-mediated autophagy in which specific proteins are delivered directly to the lysosome for degradation by means of a protein called LAMP2A without involvement of the autophagosome.

One of the proteins normally removed by this process is α-synuclein, the plaque-forming protein associated with Parkinson's. Mutant forms of the protein or an excessive production of it can gum up the system and cause a gradual but steady decline in neuronal health. "Chaperone-mediated autophagy cannot remove the molecules at the normal rate, and the protein begins to accumulate," says Cuervo. The normal autophagic process can compensate to a certain extent. However, as Rubinsztein and others have observed, α-synuclein can also exacerbate the condition.

CONSTRUCTIVE FEEDBACK

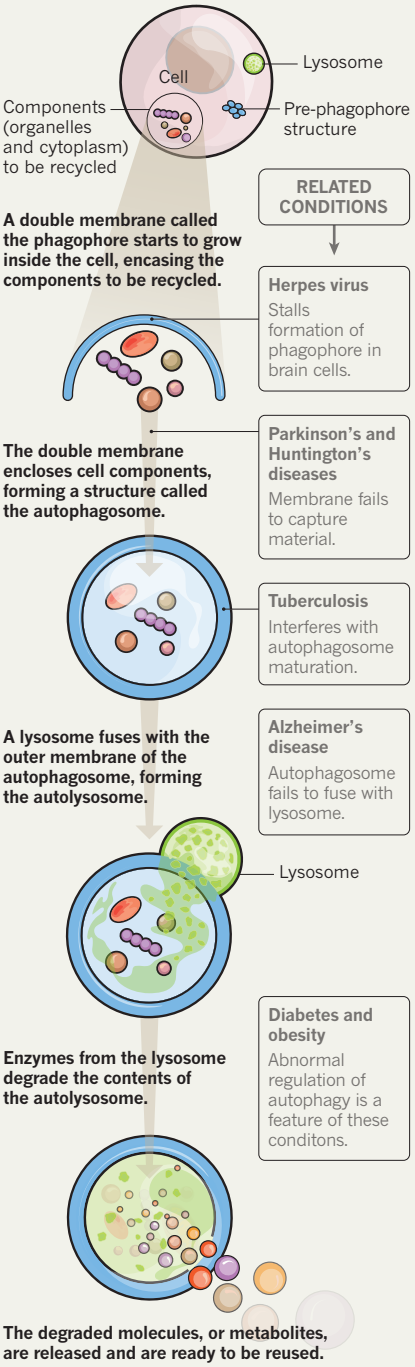
The impact of autophagy goes beyond the confines of an individual cell — this process is also used to regulate metabolic function throughout the entire body. Cuervo and her team recently found[2] that the liver helps to manage metabolism by using chaperone-mediated autophagy to selectively destroy the enzymes that convert sugar into energy. This is crucial, says Cuervo, because otherwise the liver becomes a "selfish organ" that uses all the glucose for itself at the expense of other tissues. Along with her colleague Rajat Singh, she has also found[3] that nutrient-sensing functions mediated by autophagy help the brain to convey that it is time to eat by switching on appetite signals and switching off those that indicate satiety.

Elements of the autophagy machinery also act as a line of defence against viruses and bacteria by diverting would-be cell hijackers to the lysosome for destruction. Microbiologist Vojo Deretic at the University of New Mexico in Albuquerque hypothesizes that the autophagy machinery may have served as a primordial form of immunity in early evolutionary history, by helping the body to distinguish between molecular signatures that represent foreign threats and those that are indicators of 'self' and should be ignored.

Many pathogens have evolved strategies that can sabotage autophagy, which Deretic first encountered while attempting to understand how *Mycobacterium tuberculosis* lives inside immune cells. He found[4] that the bacteria were escaping destruction by selectively attacking a molecule that would otherwise transport them to the lysosome. Likewise, Levine has observed[5] that the herpes virus thwarts autophagy to survive within neurons. "It has a protein that binds to the beclin-1 protein and blocks its function," she says. "This is not necessary for viral replication *in vitro* but is essential for replication in neurons, and this meant that viral evasion of autophagy was necessary for disease."

EATING UP THE CELL

Autophagy is part of a cell's normal function, removing proteins, damaged organelles and other unwanted material. Failure of the system is implicated in a number of conditions and ageing.



With so many crucial processes seemingly converging on a single cellular pathway, the expectation is that failures in autophagy have far-reaching consequences throughout the body. The evidence now strongly suggests that ageing is associated with a decline in autophagy, and some researchers are intrigued by the striking overlap among conditions that are associated with both ageing and autophagy, such as

diabetes, cancer and neurodegenerative disease. Cuervo and her colleagues have found evidence that chaperone-mediated autophagy might be an important factor in healthy human ageing. For instance, her team learned that the receptor in this pathway (LAMP2A) normally decreases with age, and therefore reduces the cell's ability to degrade proteins, which Cuervo believes could increase the risk of metabolic diseases. This initiates a vicious circle, whereby failure to control enzymes that break down sugar and fat leads to their steady accumulation in the body which, in turn, further suppresses autophagy. The inability of the cell to maintain its internal environment could be linked to other ageing-associated disorders, too. "It's like my mother used to say: in a clean house, everything works better," says Cuervo.

Conversely, other tricks to boost longevity seem to demand healthy autophagic function. For example, caloric restriction — in which subjects greatly reduce their food consumption without crossing the line into malnutrition — has been strongly linked with increased lifespan in many animal models. These same physiological conditions also stimulate autophagy, offering tantalizing evidence that these two processes — autophagy and the longevity gains associated with restricted caloric intake — may be linked. Research from Levine's group has also shown that exercise can stimulate autophagy, and she speculates that our well-fed and sedentary contemporary lifestyles may suppress our capacity to maintain the high level of autophagy that helped to keep our ancestors healthy.

HUNGRY FOR NEW THERAPEUTICS

The potential link between increased autophagy and better health could be good news from a therapeutic perspective. The Levine group has developed a promising molecule that can stimulate autophagy, protecting mice against otherwise-lethal viral infections and blocking the accumulation of proteins associated with neurodegenerative disease in cultured cells.

Rubinsztein's team has obtained promising preliminary results in mice with an autophagy-stimulating drug called rilmenidine, which has already been approved for treating high blood pressure in the United States and Europe. The drug is being tested in an ongoing clinical trial for safety in patients with Huntington's disease, and Rubinsztein hopes to move towards efficacy trials in patients with early stage neurodegenerative disease — an area where many clinical researchers see the greatest promise in autophagy-targeting therapeutics.

Several pharmaceutical companies, including Novartis, Pfizer and Millennium, are testing the waters, primarily focusing on inhibiting autophagy to make cancers more susceptible to chemotherapy treatment. In August 2014, Amaravadi and his colleagues published half a dozen phase I trials in which they paired different cancer treatments with hydroxychloroquine, an antimalarial drug that also impairs lysosomal degradation. Although the results were ambiguous in terms of efficacy, the safety profile seems favourable. Amaravadi also reported evidence of stalled autophagy in blood cells and tumour tissue from patients treated with the highest doses of hydroxychloroquine, suggesting that this drug or a related compound might be able to thwart a mechanism by which cancer eludes destruction.

Given the ambiguous role of autophagy in helping or hindering cancer, experts have expressed concern that the genetic heterogeneity found within a typical tumour could make cancer too challenging a target for such a broad therapeutic approach. "I'm not optimistic that this pro-survival function of autophagy is going to be a good therapeutic in all or even most cancers," says Levine. At least one study[6] suggests that inhibiting autophagy might instead provoke more aggressive tumour growth, although another study[7] has contested those findings. For now, this remains a topic of considerable debate, and Amaravadi hopes to gain deeper insights in an upcoming phase II trial in patients with pancreatic cancer. "This is very important because it's randomized, so if there's a signal we'll know that it's due to the hydroxychloroquine," he says.

From a therapeutic perspective, hitting the wrong target could have dire consequences. "If you're having problems with autophagosome clearance, as has been shown with Alzheimer's, then a drug that promotes autophagosome formation will just create more vesicles that aren't going anywhere and make a bad traffic jam worse," says Cuervo. Furthermore, some viruses actually make use of the autophagy machinery to assist in replication, so the same drug that thwarts, say, herpes might encourage poliovirus proliferation and release.

Additionally, many of the drugs being tested affect autophagy either incidentally or in conjunction with other cellular pathways, making it harder to determine whether autophagy is the culprit or the cure for a given condition.

BACK TO BASICS

Deretic has obtained promising early data from a compound that may help to contain the proliferation of HIV by means of autophagy, but wants to get a better insight into how the molecule works before getting too excited. "We have to be very careful about how we interpret the data and what we expect to see before we even start the experiment," he says. "Is it an inducer or an inhibitor, and is it driving the whole process or just half of it? A lot of screening data stop short of answering these questions."

These questions become even harder to answer in the clinical setting, where researchers often rely on proxy indicators to glean static snapshots of a highly dynamic process. Klionsky has worked with many of the field's top researchers to devise best practices for studying autophagy, but it can still be fiendishly difficult to determine how a given experimental manipulation is altering the process — especially when one is targeting cells deep within the brain or liver.

For this reason, some of the most important near-term studies in autophagy will be basic research efforts that monitor the nuts and bolts of the process. "We need to understand how autophagosomes are built, what regulates the way they form and what regulates their itinerary within the cell and fusion with lysosomes," says Rubinsztein. "Having that toolkit expanded will give us more potential insights into links with different types of disease." ■

Michael Eisenstein *is a freelance journalist based in Philadelphia, Pennsylvania.*

BACK IN TIME

A history of autophagy

The story of autophagy begins with Belgian cell biologist Christian de Duve, who shared the Nobel prize in 1974 for his exploration of the structural and functional organization of the cell. De Duve discovered the lysosome, an acidic membrane within the cell that is loaded with enzymes that can digest biomolecules. In the 1960s, scientists learned that proteins and structures called organelles within cells were being scooped up from the cytoplasm and delivered to the lysosome for destruction and recycling. De Duve coined the term 'autophagy' to describe such cellular self-cannibalization.

Early studies linked autophagy to the body's ability to sense nutrients, suggesting that the process enables cells to obtain raw materials during starvation. Once this model was established, interest in the subject waned. Things changed in the mid-1990s when researchers began to untangle the mechanisms that drive autophagy. From studies in simple organisms, such as yeast, scientists built genetic and functional maps of the machinery used in autophagy. It became clear that autophagy was conserved throughout evolution and served a more crucial purpose than just providing emergency rations to cells. **M.E.**

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CHRISTIAN FLEMMING/LINDAU NOBEL LAUREATE MEETINGS

Q&A Jules Hoffmann
Fighting fit

Jules Hoffmann shared the 2011 Nobel prize in Physiology or Medicine for discoveries in the activation of innate immunity against bacteria and fungi in fruit flies. Now based at the Institute of Molecular and Cellular Biology at Strasbourg University in France, Hoffmann talks to Ádám and Dávid Tárnoki about how to use the immune system to kill cancer cells.

What is our biggest health threat today?
One of the most important discoveries in medicine was probably vaccination. For most of human history, people died from infections. This is now largely under control and average life expectancy has doubled in the past 100 years or so. However, we still do not have vaccines against a number of very important pathogens, such as HIV or *Plasmodium*, the agent of malaria, and we also have some vaccines against established pathogens that do not fully protect people. With resistance against antibiotics becoming an increasing problem, vaccination has to be improved accordingly. In addition, we now face the problem of an ageing population in which cancer, neurodegeneration, stroke and cardiovascular diseases are the major killers. Obesity is another key issue. Finally, we have to be careful about the effect of new materials or environmental toxins on our physiology in general, including our immune system, but we do not have to panic about this.

Will we eventually be able to stimulate the immune system to kill cancer cells?
This is a very important emerging field, and there is great hope that we will understand what induces an immune response against cancer cells. When you kill cancer cells using chemotherapy, those cells leak large numbers of molecules, some of which are thought to induce antibody formation against cancer cells. The immune system has checkpoints — proteins or inhibitory pathways — that prevent lymphocytes from overreacting and attacking normal tissue. The rationale here is that alleviating or inhibiting their functions in tumours will make reactions of the immune cells more aggressive and efficient. Indeed, clinical trials are underway indicating that this can be a promising avenue in curing some cancers.

What is the secret to conducting Nobel prizewinning science?
Science is a very stressful job because you have to choose the right field, get good results and then publish those results before your competitors. It demands full engagement and an enormous amount of work, so it is healthy to have other cultural interests and also a nice family life. I met my future wife when she was hired to work in our laboratory by my thesis advisor. It is very good when you have a partner who understands and shares your commitment.

Intellectual freedom is also crucial. From very basic, curiosity-driven research we ended up doing things that eventually turned out to be interesting for medicine. But we did not anticipate this when we set out. Basic science makes you ask questions and find results that suddenly open up to something that nobody knew before.

What advice do you give to your students?
I advise young students to choose a good subject and a good supervisor. In addition, I encourage them to be aware of all the progress in their field, particularly regarding techniques. For example, in our research we had to immunize 100,000 flies individually in order to identify one inducible antifungal peptide, drosomycin, whereas today 20 would be enough because the technique has evolved so dramatically. Also, I tell them not to stick to the established techniques in their field: be open and interact with other fields. I was trained as a humble zoologist, but we had to get involved with cellular biology, biochemistry, analytical chemistry, molecular biology and molecular genetics in order to achieve our research goals. Finally: work hard. My grandparents were butchers on one side and farmers on the other, and they worked very hard indeed.

Do you always think and behave scientifically?
I recently met some researchers at the Dead Sea in Israel, who had interesting results: they had cured three people with psoriasis and they wanted my opinion on it. I cautioned that because they did not have a full cohort showing the way the volunteers had been treated in the salty environment of the Dead Sea compared with a control group, they could not be sure of the reasons why the subjects were cured because of their work. This is scientific thinking, and it certainly influences the way I behave, but it's not something you have to do all of the time. Some things I do don't make much scientific sense. I choose not to drink alcohol at lunchtime, for instance, but in the evening will enjoy a good French wine. ■

SANDOR VARSZEGI

Ádám and Dávid Tárnoki are identical twins working in the Department of Radiology and Oncotherapy at Semmelweis University in Budapest. They revived the Hungarian twin registry and perform twin studies in areas that include atherosclerosis, respiratory diseases and anthropometric traits to try to understand the epigenetic background of these diseases.

CHRISTIAN FLEMMING/LINDAU NOBEL LAUREATE MEETINGS

Q&A Barry Marshall
A bold experiment

Laureate Barry Marshall, professor of clinical microbiology at the University of Western Australia in Perth, tells Meghan Azad why he risked his health to prove his theory about the link between stomach ulcers and bacteria. He shared the 2005 Nobel prize with Robin Warren for discovering the stomach-dwelling bacterium Helicobacter pylori *and for proving that it is this microorganism, not stress, that causes most peptic ulcers.*

What sparked your interest in science and medicine?

From the first day I ever saw a book I was very keen to read. My father was a tradesman, so I read about motor mechanics, electrical equipment and even thermodynamics, and my mother was a nurse, so she had anatomy and physiology books. Finding out how things worked was always a natural thing. I didn't intend to go into research but it was part of my medical training. I could have worked on lots of things besides the bacterium *Helicobacter pylori,* but that was the one that really took off.

What drew you to ulcers and *H. pylori*?

The conventional wisdom was that people developed ulcers because they were suffering from stress, which was thought to increase gastric-acid secretion to the point at which the stomach lining breaks down and a peptic ulcer forms. I was sceptical that stress caused physical diseases, and I certainly was not prepared to lie to patients by telling them that. So I looked for a more evidence-based cause. Every medical and microbiology textbook at the time stated that the stomach was sterile, so nobody had thought of doing a culture or looking for bacteria with a simple Gram stain, a laboratory technique used to identify species of bacterium. If they had, they would have found *H. pylori* in five minutes! There were a few paradoxical things that made *H. pylori* hard to find — for example, it is often not detectable in the vicinity of an ulcer. In fact, we had cultured the bacterium months before we realized that the species was important in the formation of ulcers.

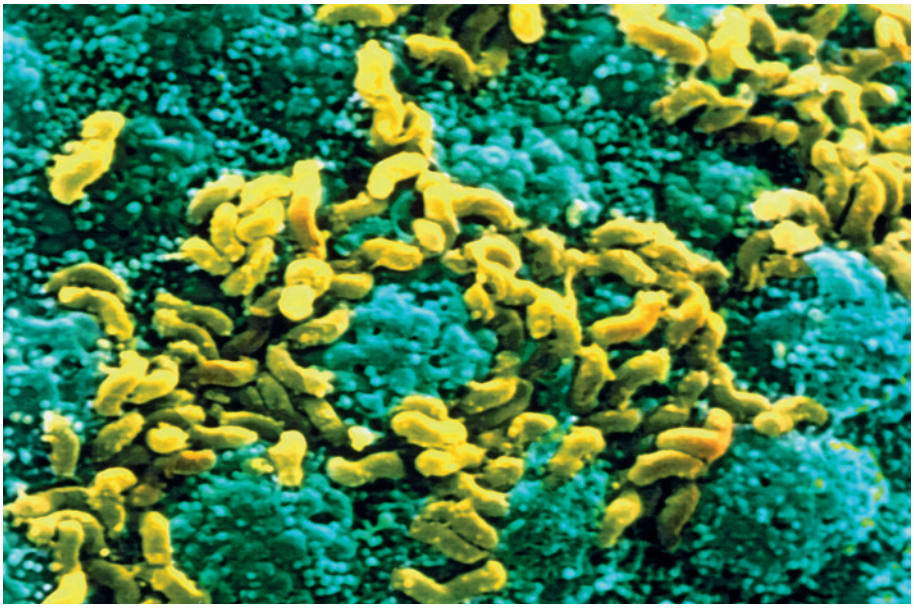
When did you realize your work might be worthy of a Nobel prize?

Robin Warren and I were jointly awarded the Nobel prize. We first identified the association between bacteria and ulcers in late 1982, and this was followed by a period of hypothesis testing and extrapolation. In April 1983, we carried out an experiment to prove that we could kill *Helicobacter* with ulcer drugs and I knew then that we were almost certainly on the right track. Then we had our first paper published in *The Lancet* and we went out to celebrate. Robin's wife said that we might win the Nobel prize and we joked that it might happen within a couple of years, but I am glad it didn't. It would be difficult to have won a Nobel so early in your career — I think you would develop a big inferiority complex.

You swallowed a culture of *H. pylori* to prove your hypothesis. What led you to do this, and what did your family and colleagues think?

I was becoming increasingly frustrated because I was successfully treating stomach-ulcer patients with antibiotics but couldn't convince other doctors to use this approach without solid experimental evidence. I tried to infect piglets for six months, but piglets grow quickly, so it was a tough experiment to do.

P. MOTTA/SAPIENZA UNIV. ROME/SPL



Stomach cells (stained blue) and Helicobacter pylori (yellow), a bacterium that causes peptic ulcers.

Without data proving that I could reproduce an ulcer by infecting an animal with *H. pylori*, a human experiment was the only option. When I decided to drink the *Helicobacter* culture I felt a bit embarrassed, and I didn't really discuss it with my bosses in case they forbade me to do it. But I suspect they knew. I had an endoscopy beforehand to check that my stomach was normal and to establish a baseline, and my boss said: "Barry, I'm not sure why you asked me to do this endoscopy, and I don't want you to tell me." I did not expect to develop any symptoms, but I did become ill with vomiting and bad breath. A further endoscopy revealed the infection, proving that a healthy person could be infected by *Helicobacter*. Of course, there are plenty of things that can go wrong in a single self-experiment, and it is very doubtful that such a study would get published these days — even back then it was a bit of a stretch.

"When I decided to drink Helicobacter, I didn't tell my bosses."

Even after your self-experiment, the medical community remained sceptical that *H. pylori* was connected to stomach ulcers. How did you finally convince them?

We were keen to present our data and announce that we had discovered the cause of ulcers, so we submitted our paper to the Australian Gastroenterology meeting in 1983. It was rejected. Fortunately, my boss at the time had some experience with *Campylobacter*, which was becoming a popular explanation for infectious colitis, or inflammation of the colon. *Helicobacter* looked similar, so I spoke to a *Campylobacter* expert in Britain and we sent him some cultures. He grew them and became excited about it, too. Then, in 1984, we went to a meeting of microbiologists, who are always interested in any new microbe, and things really took off after that. It took a few more years to gain support from gastroenterologists.

There a growing body of evidence that infection with *H. pylori* during childhood may protect against immune diseases such as asthma and allergies. What is your take on this?

For the past 30 years we have had the hygiene hypothesis, which states that a lack of early childhood exposure to microorganisms disrupts the natural development of the immune system. We know that hygiene levels have increased significantly during the past century and that allergic diseases are on the rise, but linking these trends is difficult. We know that parasitic worms, which are still common in Africa but no longer in developed countries, suppress the immune system. Infection with *Helicobacter* used to be common, but since the twentieth century that has been declining in developed countries. Finnish populations show decreased immunoglobulin E, the antibody linked to allergies, in people with *Helicobacter*, and in New York City, studies have found that children with *Helicobacter* have a lower risk of developing asthma, eczema or any kind of allergic disorder. These results are tantalizing, but other studies have not necessarily found the same thing.

Stomach ulcers were once firmly believed to be non-infectious diseases, but you proved that a microbe was responsible. Will other long-term diseases turn out to have an infectious cause?

As far as I am concerned, everything is environmental until you convince me that it is genetic. Take rheumatoid arthritis: we do not know the aetiology of it but we have got expensive treatments similar to the way we used to prescribe acid blockers for ulcers. Eventually we will figure out the actual mechanism that triggers this cascade of immune problems in rheumatoid arthritis — maybe it is a viral infection. Genomic and microbiological studies are extremely powerful here. For example, when my grandchildren first started mixing with other children at playgroups, they were taking home a new virus every week. We need to collect samples and ask what those viruses are so that 20 years from now, when some of those kids develop serious illness, we can look back at their microbiologic history. There are a lot of data that need to be collected and there are fantastic research opportunities that will help to solve those problems.

I understand that you are developing an edible vaccine made from *H. pylori*.

Yes, although it has been harder than we thought. The idea is that you engineer an *H. pylori* strain that is deficient in some way and cannot give you permanent colonization. Then you clone some extra DNA into it, so that it could produce a useful peptide analogous to, for example, an influenza vaccine antigen. I expect that one day such oral vaccines will be available as food products in the supermarket, rather than requiring a needle. We are also working on probiotics related to *H. pylori* in clinical trials, and I have co-authored a paper looking at the migration of humans around the world based on variations in the *H. pylori* genome. Show me your *H. pylori* and I can tell you where you came from!

What advice do you have for young scientists?

First, do what you like to do, because turning up every day for a job you do not enjoy feels like a death sentence. Second, do not be afraid to sacrifice salary to do something that you are interested in. Third, keep some balance in your life — most of your papers are going to get rejected initially, and occasionally you're going to feel down, so it is good to have a partner with an objective perspective.

If you had to be a microbe, which one would you be and why?

Helicobacter pylori, because I would have no competition! ■

Meghan Azad is an assistant professor at the University of Manitoba and Manitoba Institute of Child Health in Winnipeg, Canada. Her research with the Canadian Healthy Infant Longitudinal Development (CHILD) study is focused on the early-life origins of chronic diseases and the gut microbiome.

CHRISTIAN FLEMMING/LINDAU NOBEL LAUREATE MEETINGS

Q&A Françoise Barré-Sinoussi
HIV adversary

Françoise Barré-Sinoussi and Luc Montagnier were jointly awarded the 2008 Nobel prize in Physiology or Medicine for their discovery of HIV in 1983. Three decades on, Barré-Sinoussi is director of the Retroviral Infections unit at the Pasteur Institute in Paris. Here, she tells Iria Gomez-Touriño about the latest strategies to combat the virus.

HIV was discovered more than 30 years ago. How far have we come since then?
The main achievement after the discovery of HIV was the diagnostic test, which meant that we could prevent transmission of the virus by blood and blood derivatives. The next big steps were the prevention of mother-to-child transmission using the antiretroviral treatment AZT in 1994 and the advent of potent combinations of antiretroviral therapies in 1996. These are both good examples of what we call translational science, whereby basic knowledge is used to develop tests and treatments for the benefit of patients.

It is estimated that for every HIV-infected person starting therapy two individuals are newly infected. What are we doing wrong?
People are still really scared about being tested for HIV, even if they know that there is a treatment for it. In my experience, people worry that others could think they are drug users or sex workers and are afraid about being rejected by society. Unfortunately, this stigma still exists not only in resource-limited countries but also in countries such as France.

Does the solution lie in better education or further research into treatments?
Education is part of prevention, care and treatment. We can't say prevention is more important than treatment or vice versa. If we do not treat the 35 million people who are already infected, the epidemic will continue. The treatment itself is also prevention, as we can reduce the transmission to others. We should also campaign for the use of existing preventative tools, such as the condom, but also for the development of new ones. Earlier this year there were some encouraging preliminary results based on a single injection of long-lasting antiretrovirals, monthly. This kind of technology could certainly be a breakthrough.

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To what extent is religion the cause of more people becoming infected?
Religion is one of many factors, but it is an important one. When Pope Benedict XVI claimed [in 2005] that condoms are not the solution for HIV, this had a really bad impact on African Catholic countries and this is really a shame. We also have some countries drawing up homophobic legislation under the influence of religious dogma, but such measures will not reduce HIV infection. However, I have been in many places where local religious leaders are doing a remarkable job informing people about the risks and encouraging them to protect themselves.

What is the most promising route towards a cure for HIV infection?
In my opinion, remission, which means that the virus is still present in a patient's body but controlled so it does not replicate, is more likely to be achievable than a complete eradication. We already have examples in which very early treatment after the infection has led to such remission.

The VISCONTI patients [a group of 14 patients in France who were all given antiretroviral drugs soon after becoming infected] maintained a tight control of HIV replication several years after treatment was stopped. Also, the 'Mississippi baby' [an infant treated immediately after she was born with HIV] was able to maintain virological control of her infection for more than two years after the medication was stopped. Sadly, in this case the infection rebounded recently. We need to develop better tools to detect and measure the persistent virus.

Why is a vaccine for HIV proving so elusive?
There are lots of reasons. One is that the development of broadly neutralizing antibodies is very slow. Being highly variable, the virus can escape easily from the control of the immune system and the infection is very rapid, resulting in abnormal alteration of the immune defence. Vaccines are efficient and very often you still have very low levels of replication, which is good because it re-stimulates the immune system. In the case of the HIV antigen, re-stimulation can also be bad because trace amounts of antigens that are harmful to the immune system will prevent the vaccine from working. We have a list of antigens that can be harmful, but we don't know which antigens initiate the abnormal signalling in immune cells.

A real breakthrough was the use of an SIV [simian immunodeficiency virus — the non-human primate equivalent of HIV] vaccine candidate using cytomegalovirus (CMV) as a vector. This CMV-based SIV vaccine is able to induce very efficient immune responses and to clear SIV infection in macaques. Recent results also show that a cocktail of broadly neutralizing antibodies in mice and macaques can efficiently suppress HIV plasma viraemia and reduce proviral DNA.

In 2012 the International AIDS Society published seven priorities for HIV research. What has been the impact of this strategy?
We decided to launch the Towards an HIV Cure initiative to stimulate and coordinate international efforts, and also to advocate for more research in the area. Several consortiums in the United States have been established to develop a cure for HIV, with experts coming from fields such as immunology, genetics, virology and also the private sector. Our knowledge of HIV persistence under antiretroviral treatment has progressed in past years. Strategies being investigated include reactivating the latent virus to flush it out of the cells and then to kill the virus with immune agents or a vaccine. Gene therapy to make cells resistant to HIV infection is also being explored.

"If we do not treat the 35 million people who are already infected, the epidemic will continue."

For the first time, this year's Lindau meeting boasts more female young researchers than male. How can more women be encouraged to take scientific posts?
When I first started work in the 1970s at the Institut Pasteur in Paris, France, there were no more than five female professors; today, the same institution has close to 50% female professors, which is wonderful. One way forward is to better recognize the work of women, although I think that this is already progressing. Another issue is children. I made the choice not to have children because I thought it was too difficult at that time to have a career and a family — although it might not be the best solution and many other women scientists do choose to have a family. Certainly we can better organize research institutions to offer childcare, for instance. While we all can agree that equity is a good thing, women shouldn't be selected just because they are women. ■

Iria Gomez-Touriño completed her PhD in biology at the University of Santiago de Compostela, Spain, and is a Marie Curie postdoctoral fellow in the immunobiology department of King's College London, where she focuses on identifying the T-cell receptors of autoreactive T cells in type 1 diabetes.

CHRISTIAN FLEMMING/LINDAU NOBEL LAUREATE MEETINGS

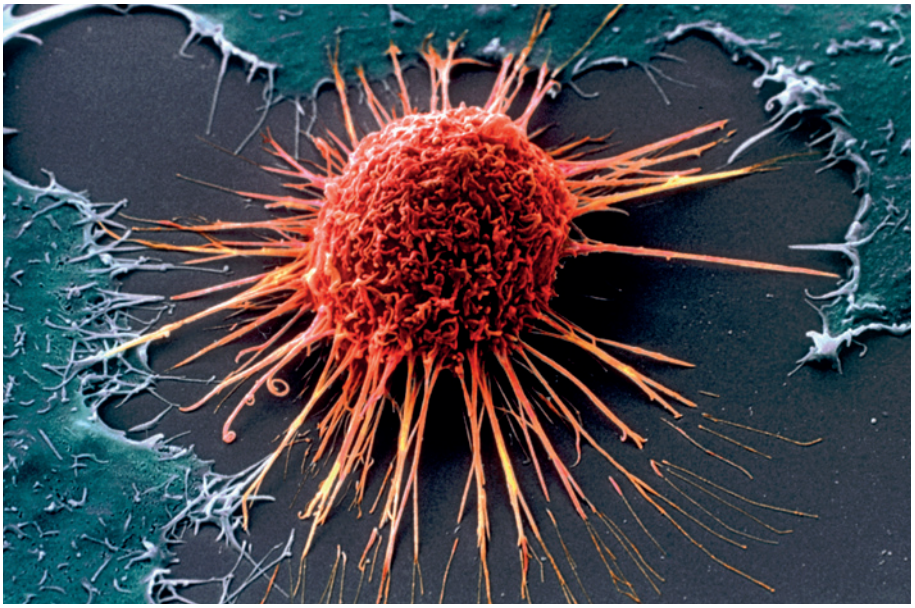
Q&A Michael Bishop
Free thinker

Michael Bishop and Harold Varmus proved that genetic changes could drive the formation of tumours. They were awarded the 1989 Nobel prize in Physiology or Medicine for discovering the origin of retroviral oncogenes. Bishop — now director of the GW Hooper Foundation at the University of California, San Francisco — tells Kipp Weiskopf about 40 years in cancer research.

What first drew you to science, and to biomedical research in particular?
My first scientific hero was Arrowsmith — the main character in the 1925 novel of the same name by Sinclair Lewis, which almost every medical student of my generation read. It is about an idealistic young man who starts out as a family physician but is not satisfied and wants to be a medical scientist who cures diseases. I identified with him because I grew up in rural Pennsylvania wanting to be a doctor but I was not very sophisticated. When I went to medical school at Harvard in Boston, Massachusetts, I had never seen the inside of a research laboratory, so I immediately took up with classmates who had undergraduate research experience and I credit them with my decision to try research.

What has been the most exciting stage of your career?
I had a great time working on polio in my early years in the lab. But I switched to retroviruses just before the discovery of reverse transcriptase, which was essential to the biotechnology revolution. We found ourselves at the cutting edge of an absolutely new field in which things were moving extremely rapidly. Every young scientist's objective should be to start something new because that's when things are really fun. If I were beginning my scientific career today I would study neuroscience, which has fascinated me ever since I encountered it during my first year at Harvard Medical School and which still has thrilling frontiers.

Has working in the San Francisco Bay Area been a particular influence?
When I arrived in 1968 it was in the middle of the Haight-Ashbury 'hippie heaven' era [named after a district in San Francisco], and a degree of openness also pervaded the academic community. I had other offers from institutes on the East Coast, but I disliked their academic pyramid structures. So I went to the University of California, San Francisco



STEVE GSCHMEISSNER/SPL

A cervical cancer cell — many cases of this form of the disease are caused by the human papillomavirus.

(UCSF), which at the time was of no consequence whatsoever. That did not bother me in the least because I was working on a very humble problem and having a wonderful time. There was an atmosphere that made it okay to explore any research direction. It was also a lively political environment. I flirted with the Peace and Freedom Party for a while, and it was the time of the Free Speech movement. There was an open spirit that I had never quite encountered before.

In more than 40 years of cancer research, what hits have we scored?

Two success stories are slam dunks. First, recognition of the fundamental role of the genome in cancer has completely transformed the way we think about every aspect of cancer. Consider the issue of what causes cancer. I view this as the most challenging unsolved problem in cancer research. Genome science may help solve this problem, because the nature of the damage in tumour DNA often represents the chemical signature of the causative agent. This is clearly seen in skin cancers caused by exposure to sunlight, and there are genomic clues for other cancers, such as breast cancer. Or consider early detection of cancer. It seems only a matter of time before either molecular cytology on excretions or circulating DNA help us to detect stealth tumours, such as pancreatic and ovarian cancer. And of course, the implications for therapy are profound.

"The fact that we have allowed the tobacco industry to continue to control the agenda is a public disgrace."

The second big hit has been in public health — specifically, the substantial drop in lung cancer in the United States that is attributable to the dramatic decline in smoking. Unfortunately, we are not doing as well in some other realms, such as obesity, or immunization against the papillomavirus, which causes cervical cancer.

Will we find a cure for cancer?

It seems unlikely to me that there will ever be a single cure for cancer. The disease is just too heterogeneous for that. Instead, I would like to emphasize that if we are ever going to conquer this disease, it will be by prevention. For example, we can prevent numerous diseases by vaccination against their causes. Examples include polio, measles, hepatitis B and cervical cancer. We need to know the causes of cancer in order to prevent the disease. The fact that we have not eradicated lung cancer caused by smoking and that we have allowed the tobacco industry to continue to control the agenda is a public disgrace — but the United States has blazed the path and in California we are doing better on this front than most other places.

Has a career spent working on cancer made you more or less fearful of the disease?

Some things haven't changed. My wife has colon cancer and the lead drug for that disease is the same one I was prescribing when I was a young physician 50 years ago, which is pretty sobering. So yes, it is a fearsome disease; even with therapy you may never have a truly comfortable day in your life again. By combining our eventual understanding about every lesion in the cancer genome with the emerging prospects of immunotherapy, though, I think the future is pretty bright.

Is the current relationship between academia and the pharmaceutical industry the best model for drug development?

It is a bit like what Winston Churchill said about democracy: it's a terrible system except for all of the others. We are in a market economy and we're going to stay that way because the development of drugs is very expensive. Some companies have shut down their research arms completely, relying on academia for new discoveries. The danger is that the money invested by pharmaceutical companies in academic research is very targeted, which could dilute the academic enterprise by crowding out fundamental research.

What do you see as the next frontiers in rational drug design?

Ultimately, it lies in understanding the signalling pathways so well that we can feed a computer all the DNA sequence data and have it tell us what are the likely targets for therapy, and what potential for drug resistance lurks in the tumour. The frontier is bioinformatics that uses genomic data to design a regimen that is free of pitfalls.

Twenty-five years after winning the Nobel prize, what inspired you to attend Lindau for the first time this year?

I have always had a major calendar conflict at this time of year, but having met students who have been here and also having my colleague Elizabeth Blackburn recommend the experience, I decided I would give it a try. It is more substantive than I had anticipated and my experience with the young researchers has been excellent.

How did winning the Nobel prize change your life?

The most important thing is that being awarded the Nobel prize has not changed the way I feel about myself. It also has not changed the way my colleagues think of me, and has not affected my bank account very much either! I do not see it as a burden, as some people have described it, because I do not take it too seriously. However, it was definitely an asset while I was chancellor at UCSF because, rightly or wrongly, it said something to the general community about the quality of the institution. Of course, it has also made it possible to come to a place like Lindau, which is a plus (except for the jetlag). ■

Kipp Weiskopf is an MD/PhD student at Stanford University in California and works on the interaction between the immune system and cancer. He has developed drugs that target CD47 and stimulate immune cells, particularly macrophages, to recognize cancer cells as foreign and attack them.

MATTHEW CHALMERS

Q&A Torsten Wiesel
Progress in sight

Torsten Wiesel is president emeritus of Rockefeller University in New York City. He shared half of the 1981 Nobel Prize in Physiology or Medicine with David Hubel for their discoveries concerning information processing in the visual system. He tells Stefano Sandrone about his greatest scientific achievement and his vision of the future.

What kind of student were you?
I was rather mischievous and not particularly focused on my studies. I was more interested in sport. When I turned 17, I became more serious about academia and began to evaluate myself more. It was then that I decided I would become a doctor. I read a lot and I met lots of different people. I was raised in the largest psychiatric hospital in Sweden, where my father was director and chief psychiatrist. This undoubtedly greatly influenced the development of my values and other aspects of my life.

Why did you choose medicine?
I went into medicine partly because of my upbringing in the hospital. Also, my eldest brother became schizophrenic in his early twenties and I wanted to better understand his condition. As a doctor I became quickly frustrated with the lack of adequate treatment of mental illnesses, and returned to my professor in neuroscience who allowed me to work in his laboratory for a year. During that year, he received an enquiry from Stephen Kuffler at Johns Hopkins University in Baltimore, Maryland, who was looking for a postdoc. And so it was by pure luck that I ended up working in one of the best labs in the world. This marked the beginning of my scientific career, although it also meant that I never completed my PhD.

What was your relationship like with David Hubel, the other half of your scientific team?
When I met David at Johns Hopkins I realized he was a very smart guy and we immediately recognized our shared interests. Though we were very different, we complemented one another. I called him my 'scientific brother' as we were not close friends outside science — our families did not interact and we did not go to the movies or that kind of thing. We usually carried out two experiments per week on Tuesdays and Thursdays, often working through the night, then the next day we would analyse the data and plan the next experiment. It was brilliant how this worked for 20 years.

Were you aware of the importance of your research into the visual system?
We never talked about it. People told me it was important and my response was: the longer the research takes, the better it is. There was a lot of work to be done and although I was aware that people got the Nobel prize for such research and then went on the lecture circuit, I wanted to continue in the lab. I believe that if you decide to do something then you put your whole heart and energy into it. Had my science not worked out, I would have gone back to Sweden to be a doctor. Certainly, in terms of discovery, I got the most satisfaction from our studies of how the visual cortex is able to encode the orientation properties of an object.

How different is the external 'real' world from what we see?
The external world can be very different to our perception of it, depending on what our senses tell us. Some insects can see in different ways and their world is very different from ours. Because the basic wiring is the same in all humans, we can agree on certain things like colours and textures. But it is also clear that some people are better at certain things than others, such as mathematics, painting or writing. This is related to high-level functioning of the brain. However, we do not even understand the basic circuitry behind auditory perception, such as how we hear music or voices.

Will we ever fully understand the brain?
Someone asked me this question after my speech at the Nobel dinner, and I replied: "Never, I hope." Although understanding the brain will be beneficial to helping solve problems associated with ageing, for example, I worry what might happen if governments get access to all the tricks. There are lessons to be learned from the atomic age here. There are things about which we always have to be vigorous and defensive.

What will be the next paradigm shift in neuroscience?
There are so many problems ranging from cells to circuitries that it is difficult to predict. In my area of competence, neurophysiology, we still need to understand the mechanisms of hearing and the circuitry of higher functions that allow us to recognize objects. I would like to know how the auditory system, with relatively few fibres, analyses information coming into the brain. We have such wonderful abilities to recognize voices as well as faces, yet we have no idea about how the brain and the auditory cortex make this possible. In general, we do not yet know how the brain is wired. In the 1960s and 1970s there was a big effort in artificial intelligence and a lot of resources invested, but it was pretty much a fiasco. The time was not right for that then, but the simultaneous launch of the BRAIN [Brain Research

through Advancing Innovative Neurotechnologies] Initiative, announced by President Obama in 2013, and the Human Brain Project in Europe, also announced in 2013, might be more timely.

How does Sweden, home to the Nobel prize, treat its laureates?
The prize is most revered in Asian countries. If you have a Nobel prize and you visit China or Japan you are received as if you were a king. In Sweden less so, because the mentality is that we should all be treated as equals. A friend of mine once requested a table by the window when making a reservation at a restaurant to celebrate my birthday and mentioned that I was a laureate, only to be told that it made no difference. And you don't get better seats in the theatre, either. Here in Lindau it is different, of course. But I would like to see more people giving talks here, even if they are not recipients of the prize, because it shouldn't be an institution for ageing scientists. You want students to be exposed to the best there is.

What tips would you give to a young scientist today?
Science should be fun: you should enjoy what you do. In this era of 'big science', there are still areas in neuroscience where an individual or small laboratory can make an important contribution, such as the study of the sensory and motor systems and the cortical circuitry underpinning the higher function of recognition of objects and places. My advice for an undecided brilliant young person looking for an area of research is to enter the field with the sincere intention of helping to solve the intriguing questions of how the brain works.

What is the most important lesson you have learnt?
To respect other people's point of view, even if you disagree. Lots of discoveries in science have been met with claims that they must be wrong, but it is a mistake to say that on the grounds that something doesn't agree with dogma. I have a deep sense of respect for everybody. From a janitor to a president, I deal with each person in the same way. ■

Stefano Sandrone is a PhD student at King's College London. He studies neuroplasticity and connectional neuroanatomy, and has a special interest in the history of neuroscience.

JONATHAN SPRAGUE/REDUX/EYEVINE

Q&A Brian Kobilka

Stuck on structure

Brian Kobilka shared the 2012 Nobel Prize in Chemistry with Robert Lefkowitz for their studies of G protein-coupled receptors. He is professor of molecular and cellular physiology at the Stanford University School of Medicine in California. Haya Jamal Azouz asks Kobilka what it takes to spend 30 years answering a single research question.

What are G protein-coupled receptors (GPCRs) and why are they interesting?
GPCRs are proteins found on the surface of all cells in the body that recognize and bind hormones and neurotransmitters. Their principal purpose is to transmit a signal to active proteins on the inside of the cell, thereby changing the cell's behaviour. There are more than 800 GPCRs in the human genome. They mediate the majority of the body's response to hormones and neurotransmitters, and are responsible for the senses of sight, smell and taste. GPCRs are involved in so many aspects of normal physiology, including homeostasis. It is interesting to understand how protein structures mediate signalling behaviours; understanding the structures may be helpful in developing more selective and effective drugs for these receptors, which represent approximately 30% of current drug targets. My initial interest in β-adrenergic receptors came from my clinical experience using β-agonists to treat asthma and β-blockers to treat heart disease.

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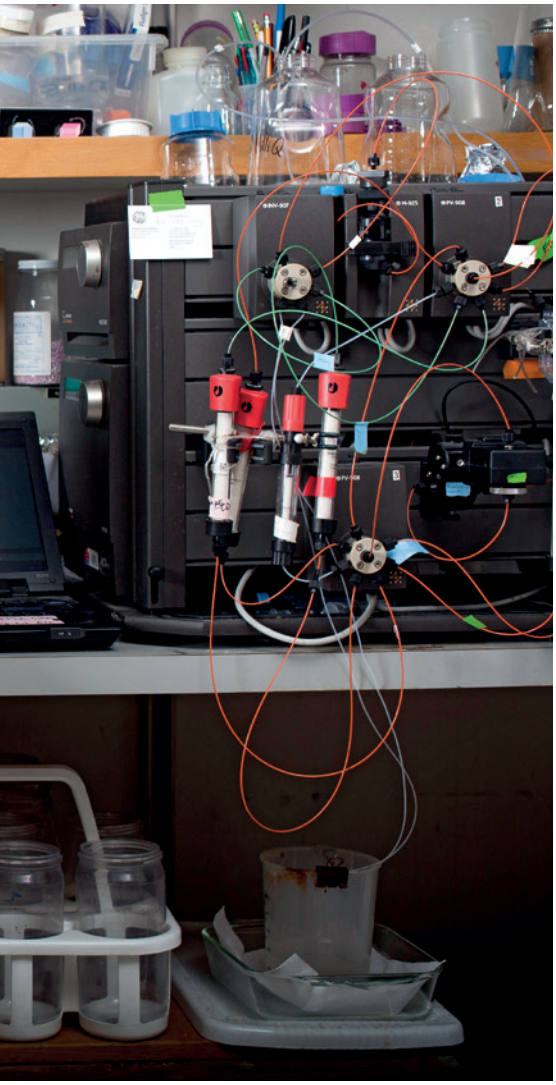

Why is the structure of GPCRs so hard to crack?
To determine the structure of proteins such as GPCRs it is necessary to crystalize the protein. The diffraction patterns of X-rays that pass through the crystals can then be used to determine the crystals' 3D structure. The first GPCR structure to be solved — rhodopsin, which is a protein in the rods of the retina that can respond to a single photon of light — was an incredible challenge. Even though rhodopsin is abundant and is one of the most biochemically stable GPCRs, it has relatively little polar surface area, which makes it difficult to form crystals. Solving the structure of the β-receptor, a different GPCR that is activated by the hormone adrenaline, was even more challenging. Unlike rhodopsin, there is no tissue in which the β-receptor is expressed at high levels so we had to use cultured cells to produce the receptor. The β-receptor is flexible and biochemically unstable and it is difficult to obtain enough protein to allow crystallography trials.

Did you expect the project to be so tough?
No! When we set out in the early 1990s, we didn't know the first thing about crystallography or about the biochemical behaviour of these proteins, for example whether they were dynamic or unstable. Using a technique called fluorescence spectroscopy we were able to get structural information that provided insight into why it was so difficult to crystallize the β-receptors. We learned that the β-receptor did not operate as a simple two-state on–off system, but that its shape was complex and flexible. For proteins to crystallize they must all be in the same conformation — that is, they must all have the same shape — but our fluorescence studies suggested that the β-receptor did not exist in a single conformation even when bound to an antagonist or agonist. A population of receptors in solution have different shapes — subtle differences, but sufficiently large to prevent crystal formation.

"My wife understands what I do and does not ask why I spend so much time in the lab."

What breakthrough allowed you to determine the structure of the β_2 adrenergic receptor?
We finally obtained our first crystals in 2004, but they were too small to be analysed using conventional X-ray sources. I showed pictures of the crystals to Gebhard Schertler, who at the time was helping to develop a microfocus X-ray beamline at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. We saw the first diffraction patterns at the ESRF in July 2005, confirming that we had a protein crystal. The quality was too poor to determine the 3D structure but the result gave us hope that we could improve the quality of the crystals. My wife joined me for the first experiment at the ESRF that July, and she was the first to see a diffraction pattern, confirming that we had a protein crystal.

Until then I had felt that the project might fail, so I didn't think it was suitable for a student or postdoctoral researcher to work on. Afterwards I recruited two very talented postdocs to join the effort and they succeeded in determining structures of the β_2 adrenergic receptor in 2007 with the help of Stanford colleagues and collaborators from other universities.

How has your wife contributed to your success?
She has been extremely supportive and although she is not a trained biochemist she is very good at finding ways to make the research process more efficient. We met in our first biology class in college and we have worked together ever since, so she understands what I do and does not ask why I spend so much time in the lab.

Were you driven by fear of another group discovering the GPCR structure first?
I had always hoped that someone would get the result, but of course we wanted to be first. We knew there were other groups working on similar projects and there were often rumours that one group or another had crystals. Even as recently as spring 2007, while we were working to obtain the final data for our two structures, there was a detailed rumour that a group in France had the β_2 structure and that a paper had been submitted. That turned out to be false, but it was fortunate for us because it prompted a friend at a Danish pharmaceutical company to donate US$100,000 to our project at a time when things were tight financially.

Did you ever imagine that you might win a Nobel, and what effect it would have?
The first time I really became aware of the prize was in the 1990s when I visited Stockholm while on vacation with my family. We visited the city hall where the ceremony is held and our tour guide described the ceremony. I thought about how exciting it would be, but it never occurred to me that I might win it until 2012, when I found out I'd been chosen. That first year was very disruptive, in part because I accepted too many invitations to speak at conferences and visit universities, often overseas. The volume of e-mail also increased dramatically and as a result I wasn't spending enough time focusing on my research.

Will you continue working in this field?
Yes. There are plenty of challenges ahead in the GPCR field. A crystal structure only gives us a snapshot of the protein in a single state, but these proteins are in constant motion between different states. The role that dynamic behaviour plays in receptor function is of great interest to membrane-protein structural biologists, biochemists, pharmacologists and pharmaceutical-company scientists. There is a lot more work required before we understand how receptors signal to G proteins and other cell-signalling and regulatory proteins such as kinases and arrestins. We also know very little about how receptors work in their native environment: the plasma membrane of living cells. Developing methods to study receptor structure and dynamics in living cells may be even more challenging than crystallographic studies. It will help us to understand the versatile signalling behaviour of GPCRs at a molecular level. By versatile, I mean that one receptor may signal through different intracellular signalling proteins. A better understanding of this behaviour may help us to develop more effective drugs. ■

Haya Jamal Azouz is a medical student at Alfaisal University in Riyadh, Saudi Arabia, where she investigates novel approaches to cancer therapy.

CHARLOTTE STODDART/NPG

Lorna Stewart (far left) quizzes young researchers John Lee, Claudine Gauthier and Alina Solomon (far right) about what they think happens as our bodies age.

GERONTOLOGY

Will you still need me, will you still feed me?

As the Lindau Nobel Laureate Meetings turn 64, laureates and young researchers discuss growing old — and whether exercise and stress reduction can slow the ageing process.

BY LORNA STEWART

"What is the life expectancy of the world population today?" asks Hans Rosling, a global-health researcher at the Karolinska Institute in Stockholm, during the opening ceremony of this year's Lindau Nobel Laureate Meeting. The 700-strong audience of young researchers and Nobel laureates reach for their keypads. "Is it 50, 60 or 70 years old?" he continues. The audience casts its vote. The correct answer, 70, gets the fewest hits.

"Even chimps do better than that," jokes Rosling, hinting that the audience would have got closer to the correct value had they answered at random. But the serious point he is making is that our notions of global demographics are outdated. And scientists need to know the facts if they are to set priorities for future medical research. Global life expectancy has risen dramatically during the past century, raising profound issues concerning the role of medical practice and the demands on scientific research.

The science and ethics of ageing was a theme at the meeting, and also the focus of a series of discussions, captured by the *Nature Video* team (see www.nature.com/lindau/2014). During those conversations I kept returning to one question: should we concentrate efforts on treating conditions that affect us in old age or devote resources towards earlier stages in life, when exercise or stress reduction could have greater long-term benefits?

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At Lindau, I discussed this issue with three young researchers and two Nobel laureates, and since then I have also put the question to other researchers in the field of ageing.

Ageing is linked to a multitude of biological processes, but scientists know suprisingly little about why, and how, we age and die. "It's a large and complicated business, the biology of ageing," says Thomas Kirkwood, who is associate dean for ageing at Newcastle University, UK. "We age because it was never a priority for our genomes to invest in the kind of maintenance and repair that could keep you going very much longer — or hypothetically forever," he adds.

To date, hundreds of genes connected to ageing and longevity have been identified, but there is no master switch. Instead, most of these genes perform functions that help to

maintain cells, such as repairing damage to DNA or regulating antioxidant levels.

Individually, genes have a relatively small impact on lifespan, but together they account for 25% of our longevity, Kirkwood says. That means that one-quarter of your chance of living into old age comes from your parents, he explains, with the remainder left to chance and environmental factors. "We don't know yet exactly how the remaining 75% breaks down, but I wouldn't be surprised if it turns out that as much as half of that is influenced by things like exercise and healthy nutrition," he says.

The difficulty in ageing research is in identifying the physiological and psychological changes that are attributable to an underlying ageing process and those that are caused by age-related diseases. In the hunt for the recipe for long life, scientists have frequently turned to individuals and populations who show exceptional longevity. Earlier this year, researchers gained a fresh perspective on the biology of ageing when they analysed[1] DNA isolated from tissues obtained during the autopsy of a Dutch woman named Hendrikje van Andel-Schipper, who had lived disease-free until the ripe old age of 115.

"We should consider a balance between adding years to life and adding life to years."

Studying van Andel-Schipper's body after her death in 2005, Henne Holstege, a geneticist at the VU University Medical Center in Amsterdam, the Netherlands, and her co-workers concluded that stem cells hold the key to understanding the limits of an individual's lifespan. They found that, by the end of her life, the majority of van Andel-Schipper's white blood cells had come from just two stem cells. At birth, humans have 20,000 stem cells; it is not unusual for someone in old age to have so few remaining stem cells, but scientists had been uncertain whether it was old age or disease that causes this loss. Van Andel-Schipper had been particularly healthy, so they proposed that it was the ageing process that had caused the reduction in her stem-cell count. Mouse studies[2] have found that stem cells decrease in number steadily throughout the mouse's lifespan — researchers suspect that this is also the case in humans. The chromosomes in van Andel-Schipper's two remaining blood stem cells had much shorter telomeres — caps at the ends that protect the chromosomes from deterioration— than those found in other cells. They suggested that her stem cells had reached the end of their ability to keep replenishing.

Each time a cell replicates, its telomeres shorten. When telomeres are too short, the cell will either stop replicating and become senescent or it will die. If a cell with shortened telomeres continues to replicate it can become abnormal. Exactly why some people's telomeres shorten more slowly than other people's is not fully understood, but clues are emerging.

Elizabeth Blackburn, who won the 2009 Nobel Prize in Physiology or Medicine for her work on telomeres, is taking steps to keep hers long. She says that the key is to avoid getting stressed. Since uncovering the link between stress and telomeres[3], Blackburn has taken up exercise and meditation, and at Lindau she encouraged me to do the same. Her view is that focusing on medical and lifestyle interventions when you're young benefits not just the individual — families will have more time to spend with their loved ones, too.

MARATHON TASK

Alongside the mechanisms of biological ageing, researchers are also interested in conditions that are related to growing older, such as Alzheimer's disease, cardiovascular diseases, diabetes and cancer. Such diseases are becoming more prevalent as people live longer, and understanding and treating them is the focus for some of the young researchers who took part in the *Nature Video* discussion.

Alina Solomon, a neurologist at the Karolinska Institute, works with people who have dementia. She sees commonalities across diseases of old age. "Several of these non-communicable diseases at older ages have common risk factors, so if we address them we can address several of these problems at the same time," she says. She thinks that the best approach for biomedical sciences is to focus on helping us live healthier, not just longer, lives. "We should consider a balance between adding years to life and adding life to years," she explains.

Solomon's view is shared by Oliver Smithies, joint winner of the 2007 Nobel Prize in Physiology or Medicine for his work on embryonic stem cells. He says that older people should not be the priority for medical science. At the age of 89 and still working in his laboratory at the University of North Carolina in Chapel Hill every day, not to mention piloting light aircraft in his spare time, Smithies is well placed to comment. "We have to be realistic about it," he says, but notes that facing facts is where the problems start. "We are sentimental and we say everybody has a right to life, which is true, but we can't afford to preserve every life. Why live to be 80 with aches and pains?"

Claudine Gauthier, a postdoc working on blood-vessel ageing at the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany, also thinks that there are good reasons to focus medical science on a younger cohort — people aged 40–50 years old. She sees middle age as an inflection point in the ageing trajectory, a period when a body might be particularly sensitive to intervention. "If you look at any health parameter, the variance of it increases dramatically once you get to middle age," she says. This means that interventions or lifestyle changes might have a bigger impact here than at any other age. "Maybe the way to be healthy when you're 30 is not the same way to be healthy when you're 50."

It comes down to prevention, she adds. "If you want to tackle ageing you've got to do it in a younger population because I don't think it's sustainable in the long term to just cure every disease." Blackburn agrees. "We can't think of them as diseases of ageing," she says. "Cancer unfolds silently, often for years, and then you say: 'I got cancer'. No, you didn't 'get' cancer, that's a process that's been going on for ages."

LIVE HEALTHIER FOR LONGER

'Health-span' is a phrase that came up a lot at the meeting. The idea is to focus on the number of years that you remain healthy and active, rather than on the number of years that you live. Many people I spoke to said that the focus for biomedical science should be on extending good health, not just on extending life. But are living longer and being healthy really at odds with one another?

It depends on how you view health, says Kirkwood. A large-scale survey[4] of people over 85 years of age in Newcastle, UK, showed that most have multiple health problems but still regard themselves as in good or excellent health when comparing themselves to their contemporaries. "People have this notion that they will be bundles of misery suffering all kinds of illness and woe," he says. "What we found was very far from the case. A large number of people were living very active, full and busy lives." Perhaps, then, part of ageing healthily is about adjusting what we expect to be able to do. The good news, says Kirkwood, is that is there is nothing in our bodies to programme our death. "Our bodies are designed for survival, they're just not built well enough to survive indefinitely."

John Lee, a PhD student at Drexel University College of Medicine in Philadelphia, Pennsylvania, understands this problem. He wants to live to 150, but thinks that it is more likely that his grandchildren will achieve this feat, rather than him. He is working on developing exoskeletons to help people who have had a spinal-cord injury, and believes that technological solutions may ultimately fix our crumbling bodies and help us to age better. "We don't expect to be running marathons at 150," he says. But, with this kind of help, we could be over 100 and still doing things "as if we were 30 again — or maybe 50". ■

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