Spektrum DER WISSENSCHAFT DIE WOCHE SPEZIAL

In cooperation with LINDAU NOBEL LAUREATE MEETINGS

CHRISTIAN FLEMMING / LINDAU NOBEL LAUREATE MEETINGS

Special Edition

SCIENCE SUMMIT

The 64th Lindau Nobel Laureate Meeting devoted to Physiology and Medicine

More than 600 young scientists came to Lindau to meet 37 Nobel laureates

FOTOLIA / SUPHAKIT WONGSANIT

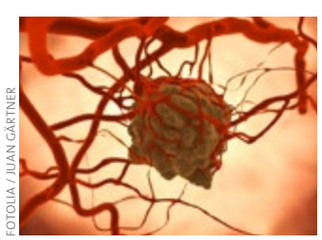
CAREER

Women to Women: Science and Family

FOTOLIA / FLASHPICS

INFLAMMATION

The Stress of Ageing



FOTOLIA / JUAN GÄRTNER

CANCER RESEARCH

J. Michael Bishop and the Discovery of the first Human Oncogene

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Dear readers,

where else can aspiring young scientists meet the best researchers of the world casually, and discuss their research, or their work – or pressing global problems? Or simply discuss soccer? Probably the best occasion is the annual Lindau Nobel Laureate Meeting in the lovely Bavarian town of Lindau on Lake Constance.

Each year, a number of journalists and bloggers are invited to these meetings. They cover the Lindau event from a subject-specific, as well as from a personal perspective. This special edition of Spektrum.de's »Woche« presents the best stories in English – suiting the international level of this unique event.

Now, enjoy our stories!

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LINDAU NOBEL LAUREATE MEETINGS

The Lindau Nobel Laureate Meetings

Since 1951, Nobel Laureates and young scientists from all around the globe come together at Lindau to discuss science and society. The Lindau Nobel Laureate Meetings foster the cross-cultural and inter-generational exchange of knowledge and help to create new networks for the future.

All articles in this edition have all been published in the Lindau Blog. Are you interested in more posts on global science issues, the latest scientific developments, intriguing personal stories and the interplay between science and society? Thinking about taking part in the discussion or contributing yourself? Visit the Lindau Blog and become a guest blogger.

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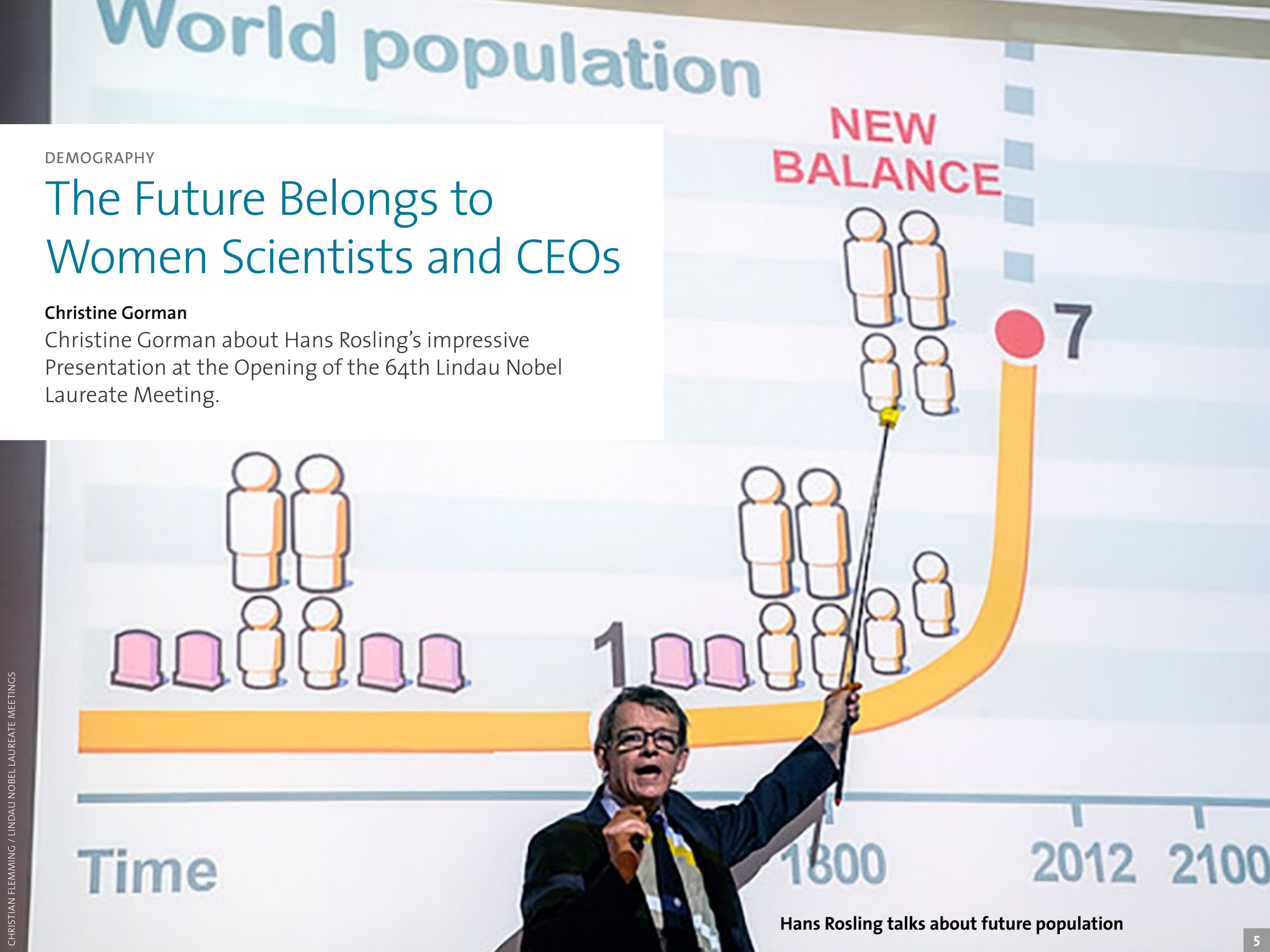
DEMOGRAPHY

The Future Belongs to Women Scientists and CEOs

Christine Gorman

Christine Gorman about Hans Rosling's impressive Presentation at the Opening of the 64th Lindau Nobel Laureate Meeting.



CHRISTIAN FLEMMING / LINDAU NOBEL LAUREATE MEETINGS

Hans Rosling talks about future population

For the first time in its 64-year history, a prestigious, invitation-only meeting of young scientists and Nobel Laureates is made up of more women than men. Between 3,000 and 4,000 graduate and post-graduate students in science applied to attend the Lindau Nobel Laureate Meeting, held every year in a picturesque Bavarian town near the southern tip of Lake Constance in Germany. »This year, for the first time, more young women than men have qualified« for the coveted 600 spots, Countess Bettina Bernadotte told participants at the opening ceremony in Lindau, Germany.

But that was probably not the most surprising thing most people learned this afternoon. More surprising was that even this highly educated group did not do so well on a pop quiz about some basic facts about global health. Before you make any snide remarks, realize that their answers were in line with those given by citizens of the U.S.,U.K. and Sweden as well as some of Rosling's fellow professors. In fact, the only group that scored better were a bunch of chimpanzees at a Swedish zoo, who, because they answered randomly, were not influenced by preconceived ideas of what the world is like.

Hans Rosling, the always entertaining and informative professor of international health at the Karolinska Institute in Sweden, posed four questions of the audience. Thanks to the interactive clickers available to all participants, we quickly discovered that less than 10% of the dignitaries, scientists and budding scientists knew that 80 percent of all children around the world are vaccinated against measles (most guessed either 20 percent or 50 percent) or that the number of children that will be born in the coming decades is actually not expected to grow significantly beyond the number that are currently born. (It's the number of adults that is going to shoot up, boosting world population to 9 billion by 2050, up from 7 billion now.) A greater number of participants came up with the correct answer for the other two questions, but the gap between perception and reality was greatest for measles vaccination and projected number of children.

The point, as Rosling explained, was not to embarrass a bunch of scientists, but to help them to realize some of the very strong cognitive biases that still hold sway whenever we talk about the next 50 to 100 years of life on earth. »If you score worse than random, then the problem is not lack of knowledge«, Rosling told the audience. It is about why the perception of the world divided between »developed« and »developing« countries refuses to budge from so many perceptive people's fundamental understanding of the world.

Who do you think scores better than the chimpanzees when Rosling's performs this pop quiz? The CEOs of international companies. <

You can read more about Rosling's quizzes in this BBC News article.

Laureates at the 64th Lindau Nobel Laureate Meeting

Top row from left: Johann Deisenhofer, Peter Agre, Ada Yonath, Arieh Warshel, Martin Chalfie, Thomas Steitz, Tim Hunt, Hartmut Michel, Brian P. Schmidt, Barry J. Marshall, Randy W. Schekman, Hamilton O. Smith

Bottom row from left: Roger Y. Tsien, Aaron Ciechanover, Ferid Murad, Elizabeth Blackburn, Oliver Smithies, Countess Bettina Bernadotte af Wisborg, Martin J. Evans, Erwin Neher, Edmond H. Fischer, Bert Sakmann, Kurt Wüthrich, Harald zur Hausen

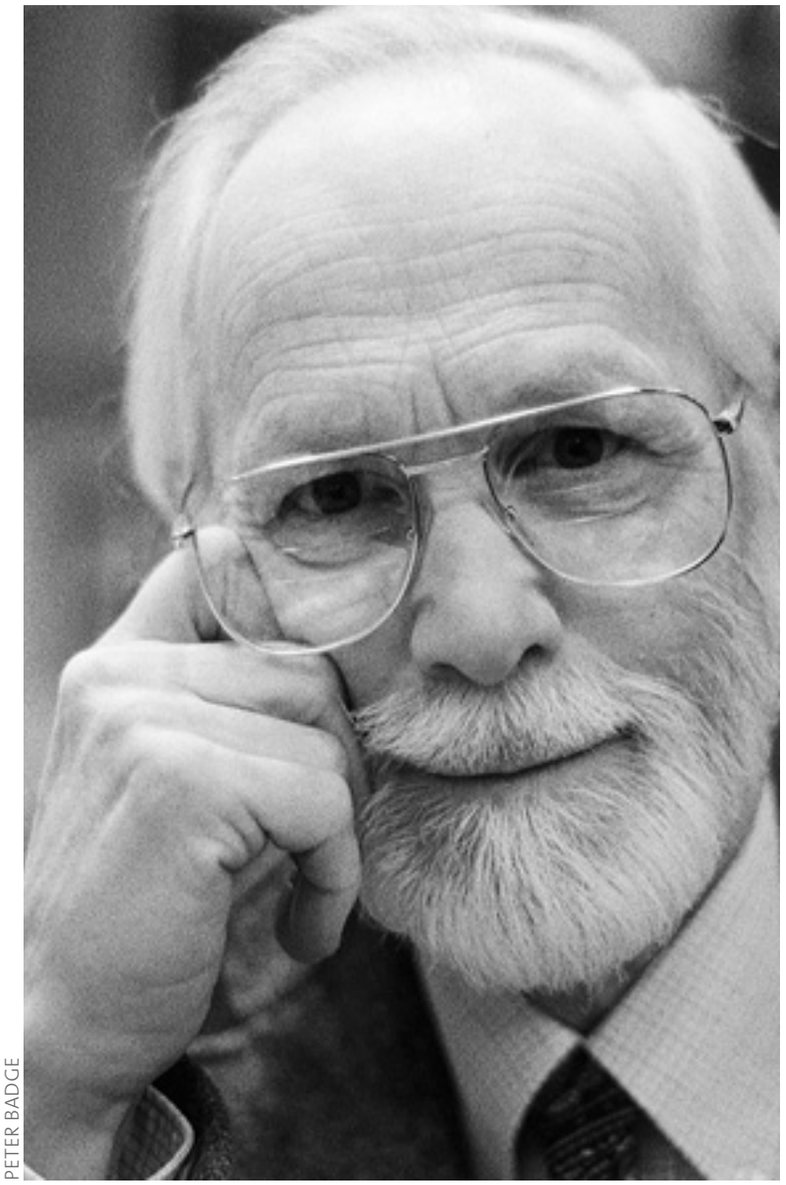
CANCER RESEARCH

J. Michael Bishop and the Discovery of the first Human Oncogene

Stephanie Hanel

At the Lindau Nobel Laureate Meeting for the first time: John Michael Bishop, who revealed how retroviral cancer genes develop on a molecular level.

ISTOCKPHOTO / JUAN GAERTNER



PETER BADGE

John Michael Bishop attended this year's Lindau Nobel Laureate Meeting. Watch J. Michael Bishop´s lecture in the Lindau Mediatheque.

In the late 1970s, J. Michael Bishop and Harold Elliot Varmus met and created one of these rare work groups where the results are so much more than the sum of its parts. Both researchers' work has changed our view on cancer fundamentally. They were able to transfer the experimental works of scientists like Deborah Spector and Dominique Stehelin in the realm of animal virology to human medicine, or more precisely: to the field of cancer research.

What seemed like a revolutionary change of perspective on cancer back then is part of today's general knowledge. Cancer genes are not necessarily foreign intruders, but important cell genes that can wreak havoc under certain circumstances – from friend to foe, so to speak.

Bishop's main areas of interest are retroviridae and oncogenes. Retroviridae are able to introduce genes into the DNA of host cells. If this happens, normal cell growth, division or differentiation can result in the creation of cancer genes, or oncogenes. The latter can become part of the host's own DNA. In the early 1980s, Bishop and Varmus discovered the very first human oncogene: c-Src. During his extensive research, Bishop not only studied oncogenes, but also their predecessors, the so called proto-oncogenes. In Bishop's own words: »Src is a wayward version of a normal cellular gene (which we would now call a proto-oncogene), pirated into retroviral genome by recombination (in a sequence of events known as transduction), and converted to a cancer gene by mutation.«

Varmus has studied tumorgenesis and breast cancer tumors, has concentrated on viral replication, especially on the HI- and the hepatitis b virus, and became director of the National Cancer Institute in 2010.

Besides being an excellent scientist, Bishop has another talent, too: for instance, he's a very good scientific writer. Maybe resulting from his self-professed love of reading? He says himself that he loves books – only science fiction and crime are not his favourites – and he enjoys writing. Another of his passions is music, a legacy from his past: Born in 1936 as the son of a Lutheran minister in Pennsylvania, he spent his childhood with piano, organ and vocal lessons, far away from metropolitan life or scientific research. In fact, nothing hinted at a career in life science. In the course of

his career, he experienced many surprising changes and variations – changes of topics, locations and colleagues. In retrospect, he likes to thank the many people he met along the way: Some had offered helpful and unconventional advice on how to advance his research and career – with a truly exceptional outcome, as we know.

J. Michael Bishop, winner of the 1989 Nobel Prize in Physiology or Medicine together with Harold Elliot Varmus, attended the Lindau Nobel Laureate Meeting for the first time this year. He gave a lecture on »Forging a Genetic Paradigm for Cancer«, read an abstract of his lecture here. He also participated in a panel discussion on the topic »Large Data and Hypothesis – Driven Science in the Era of Post-Genomic Biology«. <

Fireworks over Lake Constance

CANCER RESEARCH

Research for the Dogs – Young Scientist profiles

Kathleen Raven

Dogs play a crucial role in human cancer research.

ISTOCKPHOTO / ADAM WALICZEK

KATHLEEN RAVEN

Young Scientist Floryne O. Buishand, The Netherlands

More young scientists and physicians should know this, says Floryne O. Buishand, a Young Scientist at the 64th Lindau Nobel Laureate Meeting. With her DVM, Buishand is a small animal surgery resident at the faculty of veterinary medicine at Utrecht University in The Netherlands and also on a PhD track. At the Meeting, she wishes to make »comparative oncology« a buzzword among her peers (She quickly adds that she listens to researchers during coffee breaks and has already gained significant cross-disciplinary insight on various subjects).

But back to the dogs.

For research on stem cells and endocrine pancreatic cancer, »we are using dogs as an animal model for humans,« Buishand explained. »Dogs have spontaneous tumors, which are better than what mice develop. Mice are often immune-deficient,« she said, referring to dogs who develop tumors naturally versus mice injected with cancer in the lab. Buishand's clinical work focuses on surgical oncology. She works with pet dogs suffering from pancreatic tumors. Comparative oncology gained a foothold – or should we say »paw«-hold – in the US a few years ago; Europe still needs to catch up, Buishand said.

»The dogs' owners allow their pets to participate in the research because they want to help – they are enthusiastic about it«, she said. A clinical trial testing an agent in dogs can run between one and three years, whereas human clinical trials stretch between 10-15 years, Buishand pointed out. Comparative oncology research could help. If results from canine trials were integrated into human trials, »then we could speed up the whole process,« she said.

Buishand is technically already an »award-winning« scientist. In 2009, she won a prestigious research award from Cornell University in New York. An observer would not know this from her humble attitude. »From the moment you arrive here, you are just breathing in the inspiration«, she said, referring to the Congress. »The conference is so far exceeding my expectations.«

Meanwhile, another Young Scientist, Remco Molenaar, MSc, of the University of Amsterdam, The Netherlands, said the Lindau meeting has re-energized his efforts to

KATHLEEN RAVEN

Young Scientist Remco Molenaar, The Netherlands

look at scientific problems in new – and even unpopular – ways. Like many of the Nobel Laureates in Physiology or Medicine, Molenaar has faced intense criticism of his unique research ideas. Earlier this year, Molenaar co-authored an article entitled »The driver and passenger effects of isocitrate dehydrogenase 1 and 2 mutations in oncogenesis and survival prolongation,« in the journal *Biochimica et Biophysica Acta*.

»This was a perspective paper,« Molenaar explained. He explained that mutations in isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) occur in the development of different types of cancer, including, for example, acute myeloid leukemia and chondrosarcoma. In brain tumor patients, at least, patients with the mutation live on average three years after diagnosis. Patients without the mutation live only about one year, Molenaar said. »We have the hypothesis that the mutation causes cellular defense mechanisms to kick on, thereby causing the tumor cells to be more stressed, and more susceptible to treatments like chemotherapy, he said. »The mutation could lower the death threshold needed to kill the cells,« Molenaar said.

There's much more work to be done, and Molenaar hopes to have results from cellular experiments in by summer's end.

When Barry Marshall (Nobel Prize, Physiology/Medicine 2005) gave his talk on *Helicobacter pylori* earlier in the week, Molenaar said the following message resounded most with him: Do not immediately believe anyone who wants to prove you wrong. When Molenaar heads back to his lab after Lindau, he hopes to infect his fellow peers with excitement about research. <

Women to Women: Science and Family

Kathleen Raven

The key to the early child-rearing years is to be well-organized with a laser-like focus.

A group of Young Scientists

KATHLEEN RAVEN

Kirsty Renfree Short is not surprised. She shrugged her shoulders at the fact that female young researchers outnumber their male counterparts at the 64th Lindau Nobel Laureate Meeting, marking a first-time event in the storied Congress' history. »Women outnumber men in grad school, so, why not?« the University of Queensland, Australia, postdoctoral student and Lindau Young Scientist said. Short, along with five other female Young Scientists, stood round a tiny table before the start of the Science Breakfast on 30 June sponsored by the state of Australia. »What I want to know is why are there so many female researchers at the graduate-school level, but not high up in leadership?« asked Tracy Norman, a doctoral candidate at the Georgia Institute of Technology, USA. Your correspondent followed up the statement with a question about family. Did the women plan to have children? Three raised their hand in the affirmative. The other three? Undecided.

Adam Spencer, a self-described celebrity mathematician, moderated the talk with Suzanne Cory, immediate past president, Australian Academy of Science; Emma Johnston, director, Sydney Harbour Research Program, Sydney Institute of Marine Science; Brian Schmidt (Nobel Laureate, Physics 2011), The Australian National University; and Elizabeth Blackburn (Nobel Laureate, Physiology or Medicine 2009) University of California, San Francisco.

In her opening remarks, Suzanne Cory recalled the scarcity of female speakers at the earliest scientific conferences she attended. »I expected everything to be totally transformed by now, and it's not«, she said. The panelists nodded their heads in agreement. The three women chose science as their career path at a time when even the thought of such pursuits seemed preposterous to most. A common theme soon emerged from their stories. From the start, each female scientist adopted one attitude: I'll show them. Blackburn recalled a school teacher's reaction to her career goals. »Why would a nice girl like you want to go into science?« she said, repeating the teacher's words. Blackburn pursed her lips shut at the time, she said, but doubled down with even more determination. Johnston described the deep skepticism she faced after declaring her passion for science. »You should study law instead«, her critics said. With these stories on their minds, the panelists then turned to possible solutions to fixing this leaky pipeline.

Over at Slate.com, AAAS Mass Media Fellow Jane Hu also covered »the leaky pipeline problem« in a story titled Old Boys' Lab, which covers discouraging statistics. According to the story, 52 percent of US biology Ph.D.s are women, but that number decreases to 39 percent of postdocs before shriveling to only 18 percent of tenured professors.

Avoid the drop-off in interest

Girls and boys seem equally engaged in biological and other sciences until about year 6 of schooling, Brian Schmidt observed. Blackburn and Cory, having both attended the same all-girls high school in Australia, agreed with the observation. This drop-off could be partly explained by social pressures – conscious and unconscious – young women face in the junior and high school years. »Women may get intimidated about how to go on with their interests«, Blackburn said. The solution could be to ensure that science clubs and activities for women especially remain well-funded and supported through years 6-12, Schmidt said. At

every stage in academics, women need confidence, Cory agreed. To the mostly female audience, Cory said: »You are at a crucial age now. Don't drop off.«

The impact factor of family

One of the hazards of modern science and academia is the intense focus on tracking, Schmidt said. Citations, papers, symposiums or patents can all be considered part of the formula. But this formula overlooks the fact that a single great paper can have up to three times the impact of an average paper, Schmidt said. »We need to single out really great papers and provide those researchers with resources«, he said. After all, those who worry about the impact factor are »bottom feeders«, Blackburn said, to laughter from the audience. She went on to emphasize that women need to look at raising children, if they choose to do so, as a temporary impact on and overall scientific career that may span 40 or more years. »It's only 18 or so years of your life«, Blackburn said, as chuckles erupted again. But a family and a successful career are not exclusive of the other, all women agreed. »Putting off children until much later is not biologically the smartest thing«, Blackburn said. Raising children requires first and foremost a partner who is willing to make sacrifices as well, the panelists said. When Adam Spencer asked if female scientists should consider taking an extended break of two or three years, the answer was a resounding »No.« »Science is really a fast-moving world«, Cory said. »If you get out, even for three years, it becomes very difficult to get back in. And you lose self-confidence, connections with your peers and knowledge.« The women agreed that the key to the early child-rearing years is to be well-organized with a laser-like focus. Blackburn gave up dinners out and socializing. »My life was research and family«, she said.

Take a chance on women

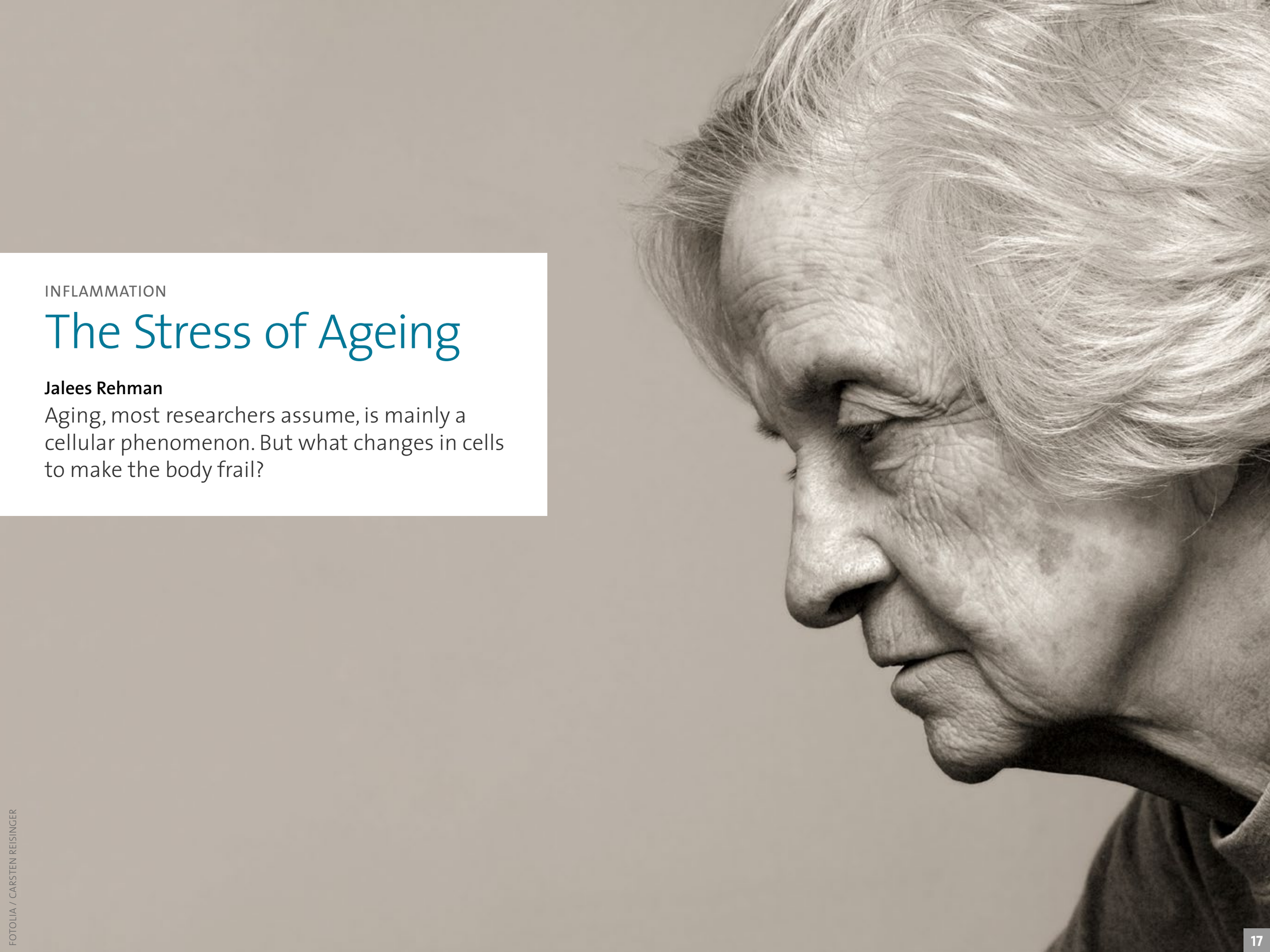
Toward the end of the talk, Cory gave the analogy of the young boy who dives into the deep end of the pool without thinking and just learns to swim. The young girl, by contrast, stays in the shallow end until she is certain that she will stay afloat, then moves deeper. To the women scientists, Cory said: »You've got to jump into the deep end.« Schmidt disagreed a little. »I would say that there are cases when the person who jumps into the deep end needs to be rescued«, he said, to audience laughter. He encouraged mentoring of both genders and better awareness of the situation. Structural changes need to occur in academia and the industry, he said. One of these could be extending the tenure clock for female researchers who choose to start a family early in their career, Schmidt said. Another option is to create childcare programs akin to what Princeton University offers, Blackburn said. When parents at that institution suddenly have a sick child who cannot attend daycare, the university provides a fully vetted babysitter immediately. Above all, the panelists agreed, women must step forward at every turn in their careers and say, »I am the person for this job. Choose me.« <

INFLAMMATION

The Stress of Ageing

Jalees Rehman

Aging, most researchers assume, is mainly a cellular phenomenon. But what changes in cells to make the body frail?



FOTOLIA / CARSTEN REISINGER

How do I knock off thirty years from my age? Faust, the protagonist in Johann Wolfgang von Goethe's famous play, poses this question to Mephistopheles in the chapter *Hexenküche* (Witches' kitchen). Mephistopheles provides some pretty good advice – considering that he is the devil and this fictitious exchange takes place in the dark Middle Ages:

Begib dich gleich hinaus aufs Feld,
Fang an zu hacken und zu graben
Erhalte dich und deinen Sinn
In einem ganz beschränkten Kreise,
Ernähre dich mit ungemischter Speise,
Leb mit dem Vieh als Vieh, und acht es
nicht für Raub,
Den Acker, den du erntest,
selbst zu düngen;

Here is the paraphrased essence of the devil's advice: Seek out a life of moderation, stop being lazy, exercise regularly by ploughing the field and avoid unhealthy foods! How does the great scholar and scientist Faust respond to these common-sense suggestions?

Thanks, but no thanks. Faust does not like manual labor and is quite happy with his current lifestyle, so he instead opts for plan B – a magic youth potion.

Nearly two centuries after Goethe's Faust was first performed, our quest for reversing the aging process continues. The magic potion which reverses aging continues to be as elusive as ever, but aging research has made substantial progress during the past few decades. One biological definition of aging is the gradual decline in function observed over time. Humans experience this age-related decline at a whole body or organ level such as memory loss or weakening of muscle strength, but aging also takes place in individual cells. Cellular aging or cellular senescence describes a form of »exhaustion« to the point where cells can no longer divide and a disruption of normal cellular activity. A substantial amount of scientific data suggests that the aging of individual cells plays a central role in the general decline of function in our muscle function, blood flow or metabolism which occurs when we grow older. But understanding cellular aging will not only unlock some of the mysteries of »healthy« aging, it may also help us understand and

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Nobel Laureate Elizabeth Blackburn in Lindau 2014

TIZIANO VECELLIO: THREE AGES OF MAN, CA 1512 / PUBLIC DOMAIN

Painting by Tiziano Vecellio: Three Ages of Man

prevent certain age-associated diseases such as heart disease or cancer.

One of the central mechanisms responsible for the aging of cells is the shortening of telomeres. Telomeres are repetitive DNA sequences at the ends of chromosomes which act as protective caps. Every time a cell divides, its chromosomes undergo a doubling process so that the two daughter cells receive equal amounts of DNA. During the DNA replication and the separation of the newly formed chromosomes, small chunks of DNA are trimmed off at the end of the chromosomes. By having protective telomere caps, the shortening process only affects the telomeres and not the essential gene-encoding parts of the chromosome.

When cells in a tissue are damaged then their neighboring cells or reservoirs of regenerative stem cells and progenitor cells have to step in, divide to replace the damaged cells. Having long telomeres would al-

low these regenerative neighbors to keep on dividing and restoring the tissue, whereas short-telomere cells would have to give up early on because their protective telomere caps would dwindle. Regenerative cells such as stem cells are frequently called upon to divide and this is why it is a good thing that these regenerative cells tend to contain high levels of an enzyme called telomerase which helps prevent the shortening of the telomeres. Telomerase thus acts as an anti-aging enzyme. The roles of telomeres and telomerase in cellular aging were first uncovered in the 1980s and 1990s by the pioneers Elizabeth Blackburn, Carol Greider and Jack Szostak, who all shared the 2009 Nobel Prize in Physiology or Medicine for »the discovery of how chromosomes are protected by telomeres and the enzyme telomerase«.

At the 64th Lindau Nobel Laureate meeting, Elizabeth Blackburn reviewed the history of how she and her colleagues identified the role of telomeres and telomerase in the cellular aging process, but also presented newer data of how measuring the length of telomeres in a blood sample can predict one's propensity for longevity and health. It makes intuitive and theoretical sense that having long telomeres would be a good thing but it is nice to have real-world data collected from thousands of humans confirming that this is indeed the case. A prospective study collected blood samples and measured the mean telomere length of white blood cells in 787 participants and followed them for 10 years to see who would develop cancer. Telomere length was inversely correlated with likelihood of developing cancer and dying from cancer. The individuals in the shortest telomere group were three times more likely to develop cancer than the longest telomere group within the ten year observation period! A similar correlation between long telomeres and less disease also exists for cardiovascular disease. Dr. Blackburn was quick to point out that these correlations do not necessarily mean that there is a direct cause and effect relationship. In fact, increasing telomerase levels ought to lengthen telomeres but in the case of cancer, too much telomerase can be just as bad as too little telomerase. Too much telomerase can help confer immortality onto cancer cells and actually increase the likelihood of cancer, whereas too little telomerase can also increase cancer by depleting the healthy regenerative potential of the body. To reduce the risk of cancer we need an ideal level of telomerase, with not a whole lot of room for error. This clarifies that »telomerase shots« are not the magical anti-aging potion that Faust and so many other humans have sought throughout history.

Why is that telomere lengths are such good predictors of longevity, but too much telomerase can be bad for you? The answer is probably that telomere lengths measured in the white blood cells reflect a broad range of factors, such as our genetic make-up but also the history of a cell. Some of us may be lucky because we are genetically endowed with a slightly higher telomerase activity or longer telomeres, but the environment also plays a major role in regulating telomeres. If our cells are exposed to a lot of stress and injury – even at a young age – then they are forced to divide more often and shorten their telomeres. The telomere length measurements which predict health and longevity are snapshots taken at a certain point in time and cannot distinguish between inherited traits which confer the gift of longer telomeres to some and the lack of environmental stressors

which may have allowed cells to maintain long telomeres.

What are the stressors which can affect cellular aging and shortening of telomeres? Blackburn listed a few of them such as stress hormones, oxidative stress and inflammatory stress. All of these stressors cause stress on a molecular level, which means they can damage proteins and other essential components of a cell. Oxidative stress, the excess production of reactive oxygen species oxidizes proteins, disrupting their structure and function to the extent that oxidized proteins become either useless or even harmful. Inflammatory stress refers to excessive inflammation which transcends the normal inflammatory response of cells from which they can recover. Prolonged inflammation, for example, can cause cells to activate a cell-death program. Recent studies in mice have shown that activation of inflammation pathways in the brain can suppress cognitive function, muscle strength and overall longevity. Blackburn also pointed out that stressors are often interconnected. Prolonged elevation of stress hormones or prolonged inflammation can increase oxidative stress. The higher the level of these stressors, the more prematurely cells will age. This means that the body of a person in their 30s or 40s exposed to high levels of inflammation or oxidative stress may already numerous cells showing signs of aging.

How do these stressors lead to premature aging? Shortening of telomeres could be one answer. If cells are chronically inflamed due to autoimmune diseases or inflammation-associated diseases such as obesity and atherosclerosis then they have to be continuously replaced by cell division which shortens telomeres. However, telomere shortening is not the only route to cell aging. Aging research groups have uncovered multiple additional pathways which can accelerate the premature aging of cells without necessarily requiring the shortening of telomeres. Inflammation or oxidative stress can activate certain aging pathways such as the aging regulator p16INK4a. Our own work has shown that an inflammatory cytokine can convert highly regenerative blood vessel progenitor cells into aged cells which no longer replicate by activating p16INK4a, and that this occurs without affecting telomere length. Judith Campisi from the Buck Institute of Aging as well as several other researchers have uncovered an important vicious cycle: Once cells begin aging, they themselves release inflammatory proteins which in turn can activate aging in neighboring cells, thus setting a self-reinforcing cascade of aging in motion.

Where does this interaction of telomere-dependent and telomere-independent aging pathways as well as the influence of known (and many unknown) stressors leave us? The molecular understanding of cellular aging is progressing steadily, but the complexity of cellular aging and the even more complex question of how organs such as the brain and heart age requires a lot more work. There will be no single molecular switch which can reverse or halt aging and triple our lifespan, but most aging researchers do not see this as their goal. Understanding specific aging pathways, as well as the genes and stressors which activate them, will allow us to prevent and treat age-related diseases as well as one day be able to provide personalized advice to individuals on how to maximize their »healthspan«. For now, we can stick to some of the broad lifestyle interventions which were recommended by Mephistopheles: exercise and a healthy diet. <

IMMUNE SYSTEM

Why Don’t Grasshoppers Catch Colds?

Christine Gorman

Insects seem to be extraordinarily resistant to infections. This mystery hasn’t been solved so far.

File this under things you never thought to ask: Why are grasshoppers and other insects resistant to so many different infections?

Jules Hoffmann asked himself that question nearly fifty years ago and in the process of trying to figure out the answer, he eventually won a share of the 2011 Nobel Prize in Physiology or Medicine. His research also helped to determine what makes the base layer of the immune system – commonly called innate immunity – work so well.

(The other part of the immune system, in vertebrates at least, is known as adaptive immunity; that's the part that is responsible for creating antibodies.)

Speaking to a packed audience at the 64th Lindau Nobel Meeting in Lindau, Germany, Hoffmann, chose to take the long view–the very long view–with the young scientists and fellow Nobelists in the conference hall.

The same genetic building blocks that give rise to the immune system found in the insects he has studied over the years are also found in sea urchins and sea anemones, Hoffmann said—species whose common ancestors date so far back in time that they are among the first animals ever to have lived on the planet.

Indeed, Hoffmann concluded from the evidence found in his and other labs that innate immunity must have evolved with the rise of multi-cellular organisms 1 billion years ago.

It started with grasshoppers

A quick peek at Hoffmann's biography shows that he started studying grasshoppers when he joined the laboratory of Pierre Joly at the French National Research Agency (CNRS) in the 1960s. Joly performed lots of transplants between grasshoppers in the course of his studies and marveled that they never succumbed to bacterial infections as a result.

Naturally, the experiments were performed under sterile conditions, but even so, you would have expected at least some grasshoppers to develop surgical infections as a result.

Hoffmann dedicated his PhD to studying this unexplained mystery in greater detail and found that he could destroy the grasshoppers' ability to stave off infection by irradiating some tissue around their hearts. Now assuming you have read this far in the story, you may be asking yourself, why would anybody care so much about grasshoppers? Perhaps you have never heard about the grasshopper swarms that ate everything in their path in the American Midwest in the 1930s or that sometimes rain havoc on the farmlands of Chad, Mali, Nigeria and other parts of western Africa?

Figuring out what makes grasshoppers so resistant to infection could well have a practical benefit for agriculture, Hoffmann took care to point out in his Lindau lecture. But, I certainly got the sense, listening to him, that he was also riveted by the intellectual challenge.

In 1978, Hoffmann became head of his own laboratory and by the 1990s, he had changed the focus of his lab's research from studying grasshoppers to studying fruit flies *(Drosophila melanogaster)*. The move, he said, came in large measure because the genes of fruit flies are easier to study. (One species of grasshopper, for example, has a genome that is 100 times larger in size than that of *Drosophila melanogaster* and six times greater than that of humans.) Fruit flies, like grasshoppers and other insects

are also highly resistant to infection with bacteria (both gram-positive and gram-negative bacteria) and fungi.

In 1996, Hoffmann and his colleagues published their work showing that a previously discovered protein named Toll, which plays a role in development, also plays a fundamental role in maintaining the fruit fly's nearly impregnable defenses against infection. His lab later determined that another protein, known as IMD, was at the center of a second immune system pathway found in insects.

Later work by Bruce Beutler (who shared the Nobel Prize with Hoffmann and Ralph Steinman in 2011) showed a similar protein, dubbed a Toll-like receptor plays a key role in the innate immune systems of mice and people.

(And in case you were wondering about viruses, fruit flies defend against viral infections with a process called RNA interference, which Hoffmann, mentioned, but said he really didn't have time to tell that story.)

It turns out that insects really only need the innate immune system to survive and thrive—perhaps because they live for such a short period of time. If they lived any longer, they probably would have needed to evolve something else to layer on top of it.

Which is exactly what, in fact, a shark-like ancestor of ours did about 460 million years ago (give or take a few million). Most of the time, humans and other vertebrates do just fine with their innate immunity. But sometimes our innate immunity gets overwhelmed by the onslaught of infection or of toxins. And that's when adaptive immunity comes into play. Well, it's not actually so cut-and-dried as that makes it sound – but that's definitely a story for another time. <

DATA-DRIVEN SCIENCE

Big Data – not a big deal, just another tool

Mohit Kumar Jolly

»Big Data«, however fancy it might appear, is just another tool that can be useful to find some associations.

CHRISTIAN FLEMMING / LINDAU NOBEL LAUREATE MEETINGS

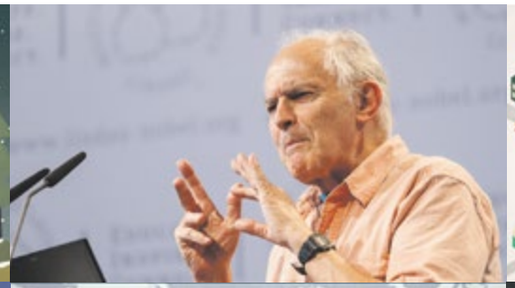
Panel Discussion: Large Data and Hypothesis-Driven Science in the Era of Post-Genomic Biology
Bruce A. Beutler, J. Michael Bishop, Moderator Stefan H.E. Kaufmann, Brian Schmidt and Jules A. Hofmann (from left)

Big Data, a buzz word these days in biological research, promises to collect and analyze the large datasets (genomics, proteomics, metabolomics etc.) to predict some novel associations between genes and diseases. »But these are just associations, and unless we go back in the laboratory and establish causal connection, it's hardly of any use. You can really get fooled badly by the big data«, said J. Michael Bishop. »There was no big data earlier, we still used to do good science«, opined Jules A. Hoffmann. »Big data is just another tool – not the only one certainly. Use it when you need it. You need not learn it yourself«, mentioned Brian P. Schmidt. Together with Bruce A. Beutler the Nobel Laureates debated about the role of big data at a panel discussion in Lindau. They discussed their expectations as well as apprehensions about the 'big data' approach. Schmidt mentioned that big data is one tool that can propose some hypothesis that can be used to drive research. Bishop added to it, saying that big data analysis and (reductionist) experiments in the laboratory often form a vicious cycle: »Let's say you identify an oncogene using big data, then you go and verify that in the lab. If you're lucky, you design a drug, and do clinical trials. Then, as expected, you'll get drug resistance. Then you again go back sequence the genome of the patient, and this cycle continues.«Bishop shared two specific examples where the predicted associations were completely misleading: »In the google flu-tracking study, they almost made us believe that they would be able to predict the spread of flu in different areas. We had high hopes, but it all failed; later they realized that the metric they used for analysis was too squishy.« More importantly, a recent big data study predicted an association between cholesterol levels and a pulmonary disease. The patients were treated with cholesterol inhibiting drugs, and the clinical trials failed miserably. Schmidt, Nobel Laureate in Physics, unlike the three other Laureates on the panel (all of them in Physiology), mentioned that he had been using the big-data approach rigorously for a long time. »But in physics, we use really stringent statistical tests before concluding anything – I do not see that kind of stringency in big data biological studies. Also, biological systems have its own unique framework.« Bishop agreed with the same, saying that analyses with big data in tumor biology often gives a list of potential oncogenes, but that is not sufficient to identify the driver oncogene (the gene that is absolutely essential for causing tumors). Beutler mentioned: »The big data approach is opposite to mine. I am a reductionist. I start my study with a phenotype, and try to identify what causes it.« On being asked about his views about big data, he said »I do not think we should argue among tools. Tools should be chosen according to the problem one's trying to address, not because everyone else uses it.« Thus, two messages came out very clearly about the big data approach in biology -

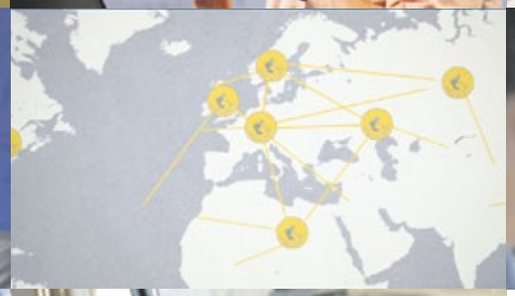
(i) It can only give associations, not causal connections or mechanisms.

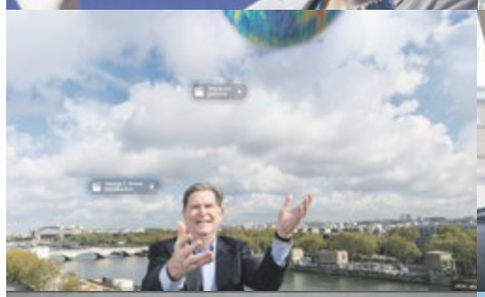
(ii) It can at maximum be an extra tool to complement the canonical reductionist approach, not replace it.

Therefore, what can be considered as a bridge between 'big data analysis' and canonical 'small scale analysis' is 'meso scale analysis' based on physical sciences where we study the set of interactions between a finite number of molecular players involved to understand how those interactions explain the emergent phenotypes. This approach has already been in use in simplier organisms (eg. bacterium) for some time to elucidate their operating principles, and is entering cancer research too. <







There are enormous problems in the world.
Maybe science is our only hope.
It is very important to have young students!

– Edmond H. Fischer, Nobel Laureate, Physiology/Medicine 1996

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Virtual Visit at the Institut Pasteur in Paris

Stephanie Hanel

Meet »Scientist Activist« Françoise Barré-Sinoussi.

NobelLabs 360° – in the lab of Françoise Barré-Sinoussi

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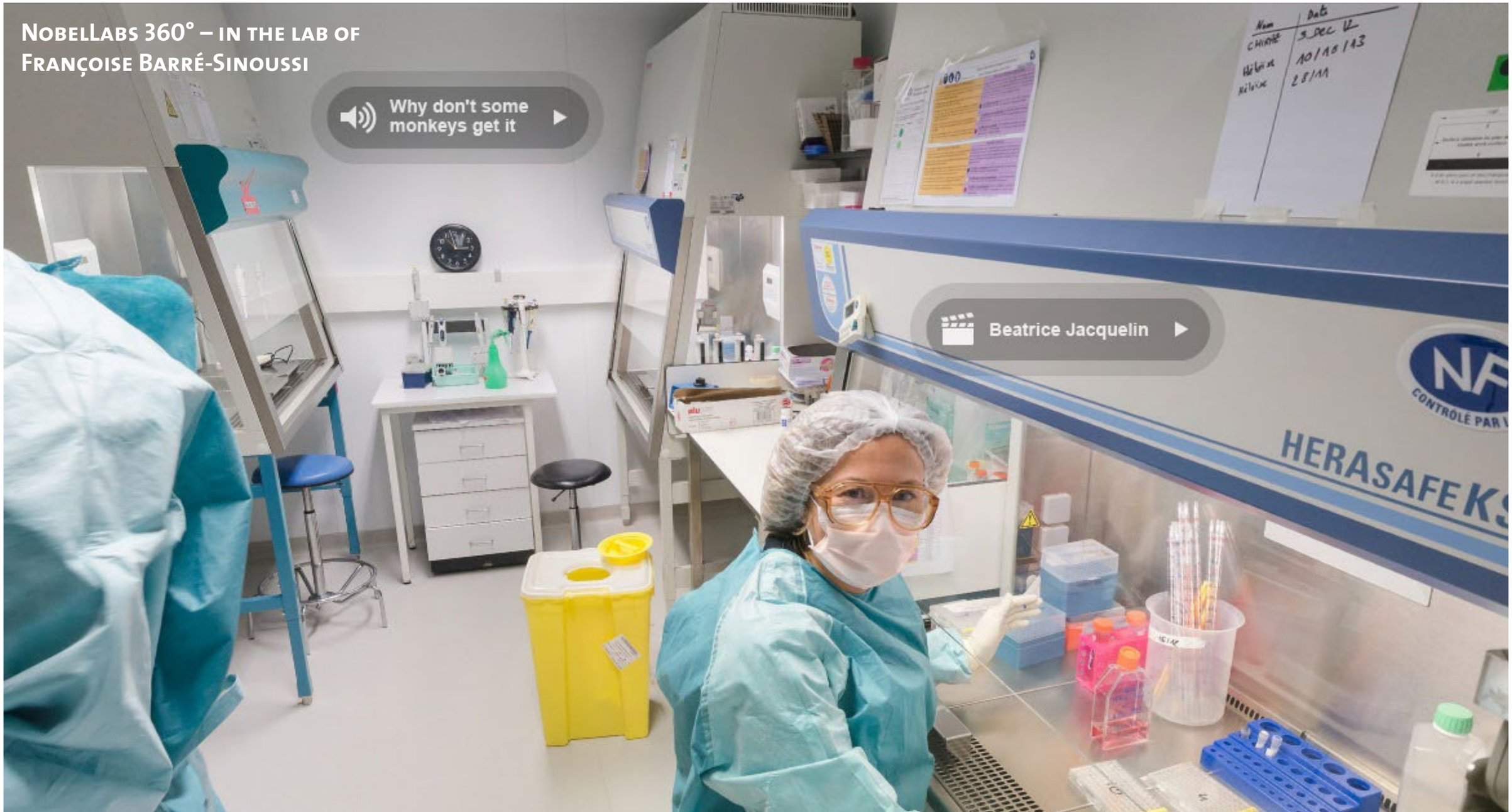
With the help of the NobelLabs 360°, we are able to visit the labs of Nobel Laureates and can almost look over their shoulders as they, together with their teams, perform their daily tasks. The multimedia presentations not only show 360° panoramas, but include several short videos and other interactive elements. Looking nosily around the lab is highly welcome!

The newest Nobel Lab is the research unit of Françoise Barré-Sinoussi, recipient of the 2008 Nobel Prize in Physiology or Medicine. The French virologist heads the department »Regulation of Retroviral Infections« at the prestigious Institut Pasteur in Paris. She was honoured by the Nobel Committee for the discovery of the HI-virus causing Aids.

Normally, it would be a great honour to be taken on a lab tour at Institut Pasteur. But with the Nobel Labs, everyone can join in. The tour starts on the rooftop terrace,



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from where the Safe Lab, the cytometry lab and the Western Blotting labs can be visited. My advice: take your time to look around, then start one of the interview videos. In one of these, Beatrice Jaquelin, an engineer in the Safe Lab, tells us about her work under strict security measures and amidst the noise of all the necessary machines. The researcher Hicham El Costa explains how the Western Blot lab studies HIV-transmissions from mother to child. Interspersed are messages from their committed boss: she supplies background information on key questions of their research, for instance: how come that Green Monkeys can be carriers of HIV without getting ill? Barré-Sinoussi also says »We can do better!«, meaning that greater international efforts are necessary to study HIV and to reduce infection rates. She is not only a researcher, but she is also an AIDS activist and has been the president of IAS, the International Aids Society, since 2012. By now, she has the inofficial title of a »scientist activist«, which see seems to enjoy.

The format Nobel Labs also reveals: nowadays, relevant scientific findings are always the result of team work. In order to understand complex systems, you always need a large team contributing findings from different angles. But at the same time, you need charismatic researchers to explain to the world the relevance of this research effort. There is a current debate going on whether the concept of giving research awards to single researchers is still up-to-date. Shouldn‘t prizes and awards go to the teams, groups or institutes that conducted most of the actual work? In the format Nobel Labs, scientific achievements are presented as what they are: the combined efforts of a strong team.

At the 64th Lindau Nobel Laureate Meeting, Françoise Barré-Sinoussi gave a lecture on the topic »On the Road Toward an HIV Cure«. Visiting her lab is an excellent preparation to understand her work – and it is easier to leave her lab behind knowing that we will soon be able to watch a video from her latest lecture here. <

Nobel Labs 360° is a non-profit educational project by the Lindau Nobel Laureate Meetings, performed by German photographer Volker Steger.

CHRISTIAN FLEMMING / LINDAU NOBEL LAUREATE MEETINGS

SCIENCE COMMUNICATION

Randy Schekman: Honest Exchange of Knowledge

Beatrice Lugger

Randy Schekman believes scientists can explain their science in an understandable and honest way. An Interview.

This morning in Lindau a bunch of journalists had the pleasure to interview Randy Schekman, Nobel Laureate in Physiology and Medicine in 2013 together with James Rothman and Thomas C. Südhof for their »ground-breaking work on cell membrane vesicle trafficking«. Schekman is not only well known for his research, but especially for his engagement in the open access movement.

During this interview Schekman pointed out, that scientists themselves should communicate in a better understandable way. Also during recruitment processes some short essays written without technical details could be of help, Schekman recommends. People today get access to scientific articles, whether they are specialists themselves, researchers in another field or interested in science at all. There is not 'only' the special scientific community but a broader audience.

Q: When the general public is interested in reading the original papers and the details of science doesn't that mean, there is at least a need for abstracts, written in a language, understandable for lay people?

Schekman: Yes, sure, that of course helps. I think scientist should be made to explain themselves clearly to other people. Therefore every paper that we publish on eLife – Schekman is editor in chief of this Open Access journal – has something that we call an eLife digest that is written for a broader audience. Broader in a sense of written for someone who has a basic understanding of life sciences. So we try to remove the technical language that would be just for specialists.

Q: Who is in charge of these special digests?

Schekman: This is mainly an editorial thing. Although I think scientist can do it, unfortunately a number of scholars simply can't be bothered. It is difficult to get them to write it in a way that could generally be understood so we have to pay people to help copy at that. We have actual a physicist in our staff, who writes these.

Q: So there is a communication specialist and scientists communicate the same way they do in a scientific paper?

KAT AUSTEN

Randy Schekman in Lindau

Schekman: I think it is a scientist's responsibility to learn how to communicate effectively with a broader public. This also has a positive effect on science itself. When I give a talk I know that most of the people in the audience are not specialists in my topic. So unless I want to talk to the two people in the front row, who are my competitors, I have to make myself clear. Teaching undergraduate students for many years has helped me. They expected these lectures to be made clear and understandable.

Q: Are communication skills something that should even be part of recruitment processes?

Schekman: That could well be a criterion. Unfortunately it is not. But it could be. When hundreds of people apply for a job, you can't read hundreds of papers. For a better recruitment process I suggest to ask each scholar to prepare a narrative, an impact statement, about their most important work. Scientists are used to this when we describe ourselves for a fellowship or a job and other applications. But I would like to make it more formal, I would like to have scholars craft an impact statement of maybe 250 words. Then the committee can create a short list of candidates and then look into the papers and letters of recommendation and refine judgments. It should be written in a way a broader group of other scholars can read and say 'Oh, wow, he discovered that'. 'I didn't know that, but that sounds really important'.

Q: Present yourself in the best way?

Schekman: Well, we are relying to the honesty of the individual to fairly represent themselvs. Not only in this context students have to be educated about the importance of the ethics of sciences. We need the honest exchange of knowledge. So students have to be educated in the proper values via scholarship and the penalties for breaking those rules, which are really severe. <

Thank you, Randy Schekman.

YASIN ENAMEE

AIDS RESEARCH

The HIV-Pandemic and Scientific Persistence – Barré-Sinoussi

Yasin Emanee

»Never give up and never stop believing that you will and can make a difference.«

Anti-Retroviral Treatment center of Gauhati Medical College in Guwahati, India

Francoise Barré-Sinoussi, Nobel Laureate in Physiology or Medicine 2008, says at the Lindau Meeting she had never imagined this pandemic when she initially started working on the virus in the early 1980s. The Nobel scientist shares this experience with patient counselors and physicians all around the globe. I have visited D. Gogoi, a patient counselor at the Anti-Retroviral Treatment center of Gauhati Medical College in Guwahati, Assam, India before my trip to Europe and the Lindau Meeting. his centre works under the National Aids Control Programme (NACO) of India. Gogoi sits in a desk surrounded by colorful posters on how AIDS (Acquired Immune Deficiency Syndrome) spreads and how it can be stopped.

She tells me, reminiscing her 20 years of service in that position, »We are doing our best; our control programs and treatment protocols are good, but the epidemic has not grown weaker. Sometimes when I feel that maybe the patient load is finally going to decrease, there is always this one patient who has been recently diagnosed with the malady, perhaps young and energetic, for whom the news of this will become the greatest turning point in his life. Many a times, I have personally escorted the victim to the psychiatry ward for a consultation before we start treatment.«

HIV thus is a multifaceted problem complicated by cultural and emotional dimensions, and warranting a similarly unique strategy for its elimination. Whereas on one end we are on the edge of understanding the scientific complications underlying the mystery of the Berlin Patient, we have the vast range of behavioral interventions that we need to devise on political and social principles that would help us get ahead of the virus. Barre-Sinoussi was apt to point out the same on multiple occasions (and in her plenary session) along with the need for scientific activism to inspire the next generations, something she considers continuing even after her imminent retirement. Asked, what is the one suggestion that she wants to give to young scientists starting out their research careers, Barré-Sinoussi answered pointedly: »*Persistence*. Never give up and never stop believing that you will and can make a difference. There is no finish line. Even when we come up with a cure for HIV, that will still mean we can use HIV as a tool for studying other diseases.« Thus science must be above everything. Diseases do not know borders, and so we cannot afford to fight them as individual groups. The Lindau Nobel Laureate Meeting 2014 is already proving a great inspiration for science on that theme. With people from across the globe discussing novel strategies to diagnose and know diseases, planning collaborations, discussing how others' research can be helpful to their own and much more, I look forth to the remaining days of the meeting with inspiring and beautiful forays into the sea of science. <

YASIN ENAMEE

Indisches Aufkärungsposter

More about the laureates' reflections of the disease problem and its solution strategies here and here.

VIRUS RESEARCH

Could A Cow Virus Cause Colon Cancer?

Christine Gorman

There is a well-known connection between red meat and colon cancer. Nobel laureate Harald zur Hausen thinks the culprit might be a virus.

DREAMSTIME / DAN CRETU

The remote possibility that I might develop mad cow disease as a result has never stopped me from diving into a nice juicy hamburger (preferably with a generous helping of ketchup and relish). But that was before I heard Harald zur Hausen hypothesize that a cow virus might be responsible for most cases of colon cancer.

CHRISTIAN FLEMMING / LINDAU NOBEL LAUREATE MEETINGS

Harald zur Hausen during his talk in Lindau 2014

And why should anyone pay attention to what Harald Zur Hausen thinks? Well, he won a Nobel Prize in 2008 for proving that most cases of cervical cancer are caused by a few strains of Human Papilloma Virus (HPV). Nor is HPV the only viral cause of cancer. Chronic infection with certain hepatitis viruses, for example, is a major cause of liver cancer.

Zur Hausen provided some intriguing factoids to support his idea at the 64th Lindau Nobel Laureate Meeting in Lindau, Germany. But he certainly does not have a smoking gun (nor did he claim to).

Still, he could not resist tweaking the »cancer is genetic misregulation« crowd, including perhaps J. Michael Bishop, who gave a talk the day before, entitled »Forging a Genetic Paradigm for Cancer.«

»The common idea is that human cancers occur because of an imbalance between proto-oncogenes and tumor suppressor genes,« zur Hausen told the audience of 600 young scientists who had won a competition among 3000 to 4000 appli-

cants for the honor of attending the meeting. »That viral infections can cause cancer is a great disturbance to this beautiful picture.«

Of course, zur Hausen concedes that genes play a role—even in cervical and liver cancer. But those tumors will not take hold for the most part without the viral infection having occurred in the first place.

A viral cause for colon cancer?

Zur Hausen's intriguing line of evidence consists mostly of provocative questions that take on the received wisdom—questions that he is more than willing to follow with further investigation of the sort that will eventually prove his hypothesis right or wrong.

For example, the received wisdom is that the connection between red meat and an increased risk of colon cancer has something to do with the number of heterocyclic amines that form during the cooking of red meat.

And yet, zur Hausen reported, »fried, grilled or smoked fish or chicken actually have the same or higher concentration of heterocyclic amines as red meat.« In other words, why would heterocyclic amines be a problem for one kind of cooked meat, but not another?

Then zur Hausen relayed the curious fact that the country of Mongolia has very low colon cancer rates, but it also has highest meat consumption per capita of any country in the world. Perhaps the fact that Mongols eat mostly yak, mutton goat, canned meat and horsemeat has something to do with the apparent mystery.

Colon cancer incidence is relatively low in India (where vegetarianism is quite prominent), some Arabic countries (where goat is more common) and Bolivia as well, zur Hausen said. The Bolivian situation is a bit complicated by the fact that so many of the beef cattle there appear to be mixes from different species.

The evidence suggests to zur Hausen that the risk factor for colon cancer in red meat has to do with the *Bos taurus* species of beef—the most common around the planet. Perhaps, he posits, there an undiscovered virus that is causally involved in human colorectal cancer with respect to raw or undercooked red meat (beef especially).

So far, his lab has found 18 different genetic sequences that might be evidence of a viral culprit. »But I don't want to talk too much about the identity of these virus or virus isolates because it's under active investigation,« he said.

At this point, the bovine virus-colon cancer link is clearly more speculation than science, but zur Hausen wasn't done yet.

As his talk was winding up, the Nobel laureate added yet another wrinkle to his mix of provocative hypotheses. Breast cancer, he noted, is one of the few cancers in which immune suppression results in a DECREASE in its incidence.

There are plenty of potential reasons why that might be the case—but one possibility is that breast cancer, too, might have a viral component. And sure enough when zur Hausen compared breast cancer and colon rates in Bolivia, Mongolia and India, he found they tracked each other—not absolutely identically—but in a very similar way.

His best guess is that if there is viral agent responsible for breast cancer, that it may be related to but not the same as the one for colon cancer

Oh dear, another reason (besides increased risk for heart disease and food poisoning) to avoid hamburgers, especially if they're medium rare. <

INFECTIOUS DISEASES

From Mice and Fruit Flies Towards Novel Infection Treatment

Susanne Dambeck

Susanne Dambeck on the Research of immunologists Bruce Beutler and Jules Hoffman who are both at Lindau for the first time.

FOTOLIA / AAALI

HOLGER MOTZKAU

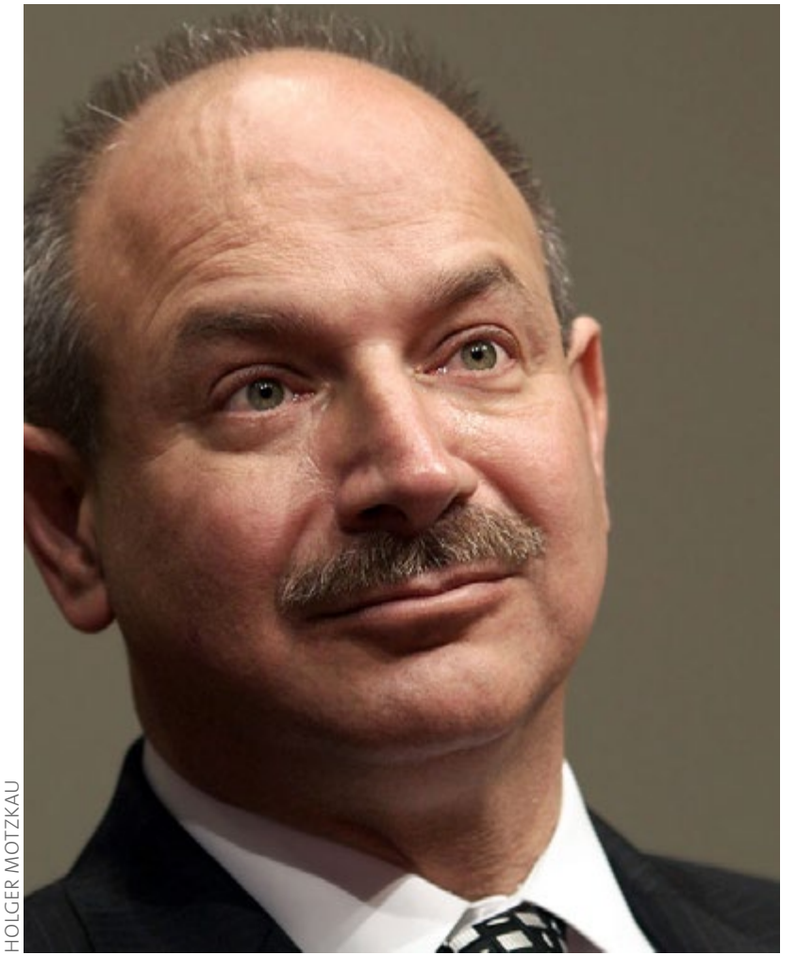
Jules A. Hoffmann won the 2011 Nobel Prize in Physiology and Medicine, together with Bruce Beutler

Ever since the discovery of the role of pathogens more than a hundred years ago, researchers asked: but how does the body identify pathogens in order to combat them? Bruce Beutler and Jules Hoffman both made important discoveries on the workings of the immune system. This year, both will attend the Lindau Nobel Laureate Meeting for the first time.

On October 3rd in 2011 at 2:30 a.m., Bruce Beutler was lying wide awake in his apartment in San Diego. He was still on Hong Kong time, where he had received the Shaw Prize in Life Sciences. He also knew that the Laureates for the 2011 Nobel Prize in Physiology and Medicine would be announced that day – in Stockholm, nine time zones ahead of him. Bleary-eyed, he looked at his cell phone: there was one new email, with just two words in the subject line: Nobel Prize. Too excited to read more than the introductory congratulations, he ran downstairs and called a colleague: »Bets, I think I won the Nobel Prize!« Confirmation was difficult, there being too much traffic on the Nobelprize.org website. Once the good news was confirmed, Beutler called his his sons, his mother, and his closest friends and colleagues, rousing most of them from sleep.

Beutler won the Nobel Prize for his breakthrough on the innate immune system, more precisely: on toll-like receptors. He discovered that one toll-like receptor, TLR4, was responsible for the identification of bacteria on a molecular level. Mice without functioning TLR4 were unable to beat bacterial infections. Beutler is a doctor by training, but always was a scientist at heart. Already as a teenager he had worked in his father's lab: Ernest Beutler was a renowned pioneer in modern hematology. His parents had fled with him from Germany in 1935. Young Bruce was just as gifted as his father: He finished high school at age 16 and graduated from college at 18. He went to medical school at the University of Chicago, just like his father – but the pull of the lab was stronger.

Jules Hoffmann was awarded the Nobel Prize together with Beutler: he had described the role of the toll-gene for the innate immune system of fruit flies. The third recipient, Ralph M. Steinman, who had coined the term »dendritic cells« in the 1970s, died three days before the prize was announced of pancreatic cancer. Since



HOLGER MOTZKAU

Bruce Beutler won the 2011 Nobel Prize in Physiology and Medicine, together with Jules Hoffmann

the Nobel Committee hadn't been aware of his death, he is still considered a Nobel Laureate; normally, the prize is not awarded posthumously. Hoffmann is a Luxembourg-born French biologist who has spent his career working with the model organism drosophila melanogaster, or fruit fly. He had studied and worked in Strasbourg, and now is the research director of the National Center of Scientific Research (CNRS) there.

Today, toll-genes and toll-like receptors are known to exist in mammals, insects and even plants. In fruit flies, they play a crucial role in embryonic development, as well as in the immune system. Ten human TLRs are known, mice have three additional TLRs. With their presence in the dendritic cells, they are also considered to form an important link between the innate and the adaptive immune system. Many drug development efforts have targeted these receptors and have for instance developed treatment strategies against autoimmune diseases like rheumatoid arthritis. Labs around the world are working on novel strategies to modulate the immune responses to bacterial or viral infections. <

CHRISTIAN FLEMMING / LINDAU NOBEL LAUREATE MEETINGS

BACTERIAL INFECTIONS

On Man and Microbes – Barry Marshall

Hanno Charisius

The bacterium *Helicobacter pylori* causes stomach ulcers. But it may have a helpful side, too.

Barry Marshall in Lindau 2014

In the summer of 1984, the Australian scientist Neil Noakes took some bacteria from a petri dish, mixed them with lukewarm beef extract – the normal nutrient solution for bacteria in the lab – and filled a little more than one cup into a beaker. Then he handed this mix to his colleague, the gastroenterologist Barry Marshall, who downed it without complaining.

Three days later, Marshall felt nauseated and his mother told him he had bad breath. Next he started vomiting. But he still waited a few days before taking the antibiotics that were supposed to kill the bacteria in his stomach. A gastroscopy not only clarified his diagnosis, but ultimately resulted in his winning the Nobel Prize in Physiology and Medicine about twenty years later.

With his famous self-experiment, Marshall was able to demonstrate that *Helicobacter pylori* bacteria can cause acute gastritis which in turn may cause ulcers. He had asked neither an ethics commission nor his wife for permission to conduct this experiment. His colleagues thought him completely insane to take a risk like that. Back in the 1980s, the prevailing theory was that gastric ulcers were mostly a psychosomatic affliction caused by too much stress. Accordingly, patients were treated with tranquillizers, anti-depressants, psychotherapy or antacids. Instead the young doctor Marshall treated them all with antibiotics, and his results were impressive. From his clinical practice, he developed the theory that the spiral-shaped Helicobacter bacterium causes gastritis, painful stomach ulcers and even stomach cancer. Because he had had no suitable test animals at hand, he used his own body for the described experiment.

From this moment on, the only good Helicobacter was a dead one. Loads of antibiotics were used to combat this germ. Some experts even wanted to eradicate Helicobacter as a precautionary measure. And Marshall received the Nobel Prize in 2005, together with his former co-worker Robin Warren. In the meantime, even Marshall has become more sympathetic when he talks about the germ that made him famous – almost as if it where an old friend. During his lecture at the 64th Lindau Nobel Laureate Meeting, he points out that this single-cell organism might even help to fight some diseases.

Indeed, *H. pylori* is one of humanity's old friends and companions: the germ has been with us for at least 50,000 years, and probably longer. Roughly fifty percent of all humans carry it around in their stomachs. Interestingly, the percentage of infected people has been decreasing since the 1950s, with richer countries having much lower rates than the rest of the world. In the US, less than 25 percent of adults and only about 5 percent of all school children are infected. Marshall says that better hygiene and clean drinking water are responsible for the bacteria's eviction.

Doctors claim that Helicobacter is responsible for three out of four stomach ulcers, two thirds of all gastric tumors and practically all duodenal tumors; the duodenum is the part of the small intestine that comes directly after the stomach. So its extermination should be a good thing – shouldn't it?

But at the same time as the germ was retreating, other health problems occurred. Since the 1950s, the number of patients with allergies, asthma or autoimmune diseases has sky-rocketed. Children without Helicobacter in their stomachs are more likely to suffer from skin allergies or hay fe-

ver. The bacteria also seem to provide a certain protection against coeliac conditions, also known as wheat gluten intolerance. The bacteria might even manipulate our appetite: the New York based doctor Martin Blaser assumes a connection between its eradication and the growing obesity problem worldwide.

Blaser was in fact one of the first scientist who noticed that the germ is not only causing harm. He first thought about its positive aspects when he saw data on patients with stomach ulcers, who seldom suffered from heart burn or esophageal cancer. On the other hand, people without Helicobacter in their system don't develop many ulcers, but are much more likely to have heart burn and reflux problems, sometimes even resulting in cancer.

Nowadays, even Barry Marshall sees the germ' two faces – the dangerous and the helpful. Many studies suggest that *H. pylori* is an important training partner for our immune system: it seems to be able to contain the immune response. If the bacteria are missing, our immune system over-reacts when confronted with pollen, wheat gluten or peanuts. Marshall thinks that this connection was a vital mechanism during human history: when groups of *Homo sapiens* left Africa in prehistoric times, these bacteria prevented them from developing severe allergies against all new plants they encountered on their long journey. If they had stayed in Africa and only eaten plants and animals from their immediate vicinity, no slow down switch for the immune system would have been necessary. »One theory says that only with the help of these bacteria, we humans were able to adapt to a varied diet«, Marshall explains.

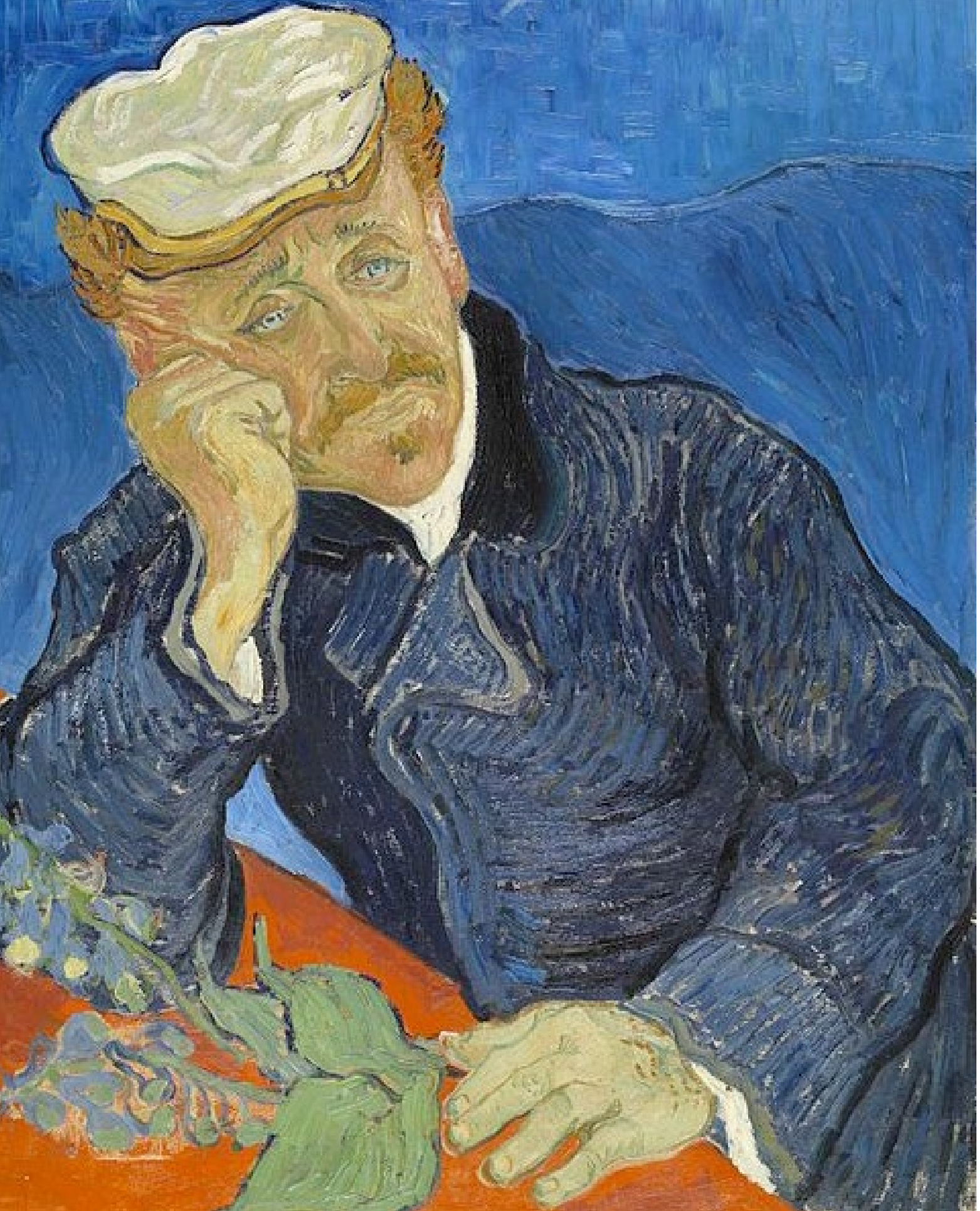
So now, instead of fighting his favorite germs, Marshall focuses on studying the effects of reinfections of humans. But not with a gulp from some meat extract, as he did in the past. There are many different *H. pylori* variants that vary greatly in aggressiveness. Only the more harmless should be used for experiments like that, says Marshall, who already secured patents in that area of interest.

Whether reinfection really offers a certain protection against allergies is currently tested on mice in several research groups. But even humans are swallowing these germs again in the name of science, Marshall is currently planning clinical studies. But he expects adults to profit only little from his results. Contact with these microbes seems to be crucial in the first few years of life during the development of the immune system.

But the thought to give bacteria to newborns that might later cause cancer makes most people feel uneasy. Another idea will probably be more easily accepted: We can only provide the components of the bacteria that are needed to keep the immune system in check, Marshall said. This shouldn't cause inflammation but could still help to curb our immune system. Molecules on the bacterium's surface would be possible candidates for this job.

Although Marshall talks more in a friendly way about his former opponent now, in one situation he remains uncompromising: »If the bacterium causes trouble, it has to go.« As long as it makes no problems, it may stay. But there are very effective antibiotics to get rid of it.

Besides *Helicobacter pylori*, more than 1,000 other types of bacteria live on and in the human body, resulting in a total number of about 100 trillion bacteria. So there should be no lack in substitute training partners for our immune system. <



VINCENT VAN GOGH: DR. PAUL GACHET, 1890 / PUBLIC DOMAIN

MEDICAL RESEARCH

Physician-Scientists: An Endangered Species?

Jalees Rehman

Can excellent scientists be excellent physicians at the same time?

»Portrait of Dr. Paul Gachet« – Painting by Vincent van Gogh

»I would like to ask you about a trip to Thailand.« This is not the kind of question I expected from a patient in my cardiology clinic at the Veterans Administration hospital in Indianapolis. Especially since this patient lived in rural Indiana and did not strike me as the adventurous type.

»A trip to Thailand?«, I mumbled, »Well, ummm ... I am sure ... ummm ... I guess the trip will be ok. Just take your heart medications regularly, avoid getting dehydrated and I hope you have a great vacation there. I am just a cardiologist and if you want to know more about the country you ought to talk to a travel agent.«

I realized that I didn't even know whether travel agents still existed in the interwebclickopedia world, so I hastily added »Or just use a travel website. With photos. Lots of photos. And videos. Lots of videos.«

Now it was the patient's turn to look confused.

»Doctor, I didn't want to ask you about the country. I wanted to know whether you thought it was a good idea for me to travel there to receive stem cell injections for my heart.« I was thrilled because for the first time in my work as a cardiologist, a patient had asked me a question which directly pertained to my research. My laboratory's focus was studying the release of growth factors from stem cells and whether they could help improve cardiovascular function. But my excitement was short-lived and gradually gave way to horror when the patient explained the details of the plan. A private clinic in Thailand was marketing bone marrow cell injections to treat heart patients with advanced heart disease. The patient would have to use nearly all his life savings to travel to Thailand and stay at this clinic, have his bone marrow extracted and processed, and then re-injected back into his heart in order to cure his heart disease.

Much to the chagrin of the other patients in the waiting room, I spent the next half hour summarizing the current literature on cardiovascular cell therapies for the patient. I explained that most bone marrow cells were not stem cells and that there was no solid evidence that he would benefit from the injections. He was about to undergo a high-risk procedure with questionable benefits and lose a substantial amount of money. I pleaded with him to avoid such a procedure, and was finally able to convince him. I remember this anecdote so well is because in my career as a physician-scientist, the two worlds of science and clinical medicine rarely overlap and this was one of the few exceptions. Most of my time is spent in my stem cell biology laboratory, studying basic mechanisms of stem cell metabolism and molecular signaling pathways. Roughly twenty percent of my time is devoted to patient care, treating patients with known cardiovascular disease in clinics, inpatient wards and coronary care units.

As scientists, we want to move beyond the current boundaries of knowledge, explore creative ideas and test hypotheses. As physicians, we rely on empathy to communicate with the patient and his or her family, we apply established guidelines of what treatments to use and our patient's comfort takes precedence over satisfying our intellectual curiosity. The mystique of the physician-scientist suggests that those of us who actively work in both worlds are able to synergize our experiences from scientific work and clinical practice. Being a scientist indeed has some impact on my clinical work, because it makes me evaluate clinical data on a patient and published pa-

pers more critically. My clinical work helps me to identify areas of research which in the long-run may be most relevant to patient care. But these rather broad forms of crosstalk have little bearing on my day-to-day work, which characterized by mode-switching, vacillating back and forth between my two roles.

Dr. J. Michael Bishop, who received the Nobel Prize in 1989 with Dr. Harold Varmus for their work on retroviral cancer genes (oncogenes), spoke at panel dicussion at the 64th Lindau Nobel Laureate Meeting about the career paths of physician-scientists in the United States. Narrating his own background, he said that after he completed medical school, he began his clinical postgraduate training but then exclusively focused on his research. Dr. Bishop elaborated how physician-scientists in the United States are often given ample opportunities and support to train in both medicine and science, but many eventually drop out from the dual career path and decide to actively pursue only one or the other. The demands of both professions and the financial pressures of having to bring in clinical revenue as well as research grants are among the major reasons for


Dr. J. Michael Bishop

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why it is so difficult to remain active as a scientist and a clinician.

To learn more about physician-scientist careers in Germany, I also spoke to Dr. Christiane Opitz who heads a cancer metabolism group at the German Cancer Research Center, DKFZ, in Heidelberg and is an active clinician. She was a Lindau attendee as a young scientist in 2011 and this year has returned as a discussant.

JR: You embody the physician-scientist role, by actively managing neuro-oncology patients at the university hospital in Heidelberg as well as heading your own tumor metabolism research group at the German Cancer Research Center (Deutsches Krebsforschungszentrum or DKFZ in Heidelberg). Is there a lot of crosstalk between these two roles? Does treating patients have a significant influ-

ence on your work as a scientist? Does your work as cancer cell biologist affect how you evaluate and treat patients?

CO: In my experience, my being a physician influences me on a personal level and my character but not so much my work as a scientist. Of course I am more aware of patients' needs when I design scientific experiments but there is not a lot of crosstalk between me as a physician and me as a scientist. I treat patients with malignant brain tumors which is a fatal disease, despite chemotherapy and radiation therapy. We unfortunately have very little to offer these patients. So as a physician, I see my role as being there for the patients, taking time to talk to them, provide comfort, counseling their families because we do not have any definitive therapies. This is very different from my research where my aim is to study basic mechanisms of tumor metabolism. There are many days when I am forced to tell a patient that his or her tumor has relapsed and that we have no more treatments to offer. Of course these experiences do motivate me to study brain tumor metabolism with the hope that one day my work might help develop a new treatment. But I also know that even if we were lucky enough to uncover a new mechanism, it is very difficult to predict if and when it would contribute to a new treatment. This is why my scientific work is primarily driven by scientific curiosity and guided by the experimental results, whereas the long-term hope for new therapies is part of the bigger picture.

JR: Is it possible that medical thinking doesn't only help science but can also be problematic for science?

CO: I think in general there is increasing focus on translational science from bench-to-bedside, the aim to develop new treatments. This application-oriented approach may bear the risk of not adequately valuing basic science. We definitely need translational science, because we want patients to benefit from our work in the basic sciences. On the other hand, it is very important to engage in basic science research because that is where – often by serendipity – the real breakthroughs occur. When we conduct basic science experiments, we do not think about applications. Instead, we primarily explore biological mechanisms.

Physicians and scientists have always conducted »translational research«, but it has now become a very popular buzzword. For that reason, I am a bit concerned when too much focus and funding is shifted towards application-oriented science at the expense of basic science, because then we might lose the basis for future scientific breakthroughs. We need a healthy balance of both.

JR: Does the medical training of a physician draw them towards application-oriented translational science and perhaps limit their ability to address the more fundamental mechanistic questions?

CO: In general, I would say it is true that people who were trained purely as scientists are more interested in addressing basic mechanisms and people who were trained as physicians are more interested in understanding applications such as therapies, therapeutic targets and resistance to therapies. They are exceptions, of course, and it is ultimately dependent on the individual. I have met physicians who are very interested in basic sciences. I also know researchers who were trained in the

basic sciences but have now become interested in therapeutic applications.

JR: When physicians decide to engage in basic science, do you think they have to perhaps partially »unlearn« their natural tendency of framing their scientific experiments in terms of therapeutic applications because of their exposure to clinical problems?

CO: We obviously need application-oriented science, too. It is important to encourage physicians who want to pursue translational research in the quest of new therapies, but we should not regard that as superior to basic science. As a physician who is primarily working in the basic sciences, I make a conscious effort to focus on mechanisms instead of pre-defined therapeutic goals.

Looking to the future

Dr. Opitz's description of how challenging it is to navigate between her clinical work in neuro-oncology and her research mirrors my own experience. I have often heard that the physician-scientist is becoming an »endangered species«, implying that perhaps we used to roam the earth in large numbers and have now become rather rare. I am not sure this is an accurate portrayal. It is true that current financial pressures at research funding agencies and academic institutions are placing increased demands on physician-scientists and make it harder to actively pursue both lines of work. However, independent of these more recent financial pressures, it has always been extremely challenging to concomitantly work in two professions and be good at what you do. Dr. Bishop decided to forsake a clinical career and only focus on his molecular research because he was passionate about the research. His tremendous success as a scientist shows that this was probably a good decision.

As physician-scientists, we are plagued by gnawing self-doubts about the quality of our work. Can we be excellent scientists and excellent physicians at the same time? Even if, for example, the number of days we see patients are reduced to a minimum, can we stay up-to-date in two professions in which a huge amount of new knowledge is produced and published on a daily basis? And even though the reduction in clinical time allows us to develop great research programs, does it compromise our clinical skills to a point where we may not make the best decisions for our patients?

We are often forced to sacrifice our weekends, the hours we sleep and the time we spend with our families or loved ones so that we can cope with the demands of the two professions. This is probably also valid for other dual professions. Physician-scientists are a rare breed, but so are physician-novelists, banker-poets or philosopher-scientists who try to remain actively engaged in both of their professions.

There will always be a rare population of physician-scientists who are willing to take on the challenge. They need all the available help from academic institutions and research organizations to ensure that they have the research funds, infrastructure and optimized work schedules which allow them to pursue this extremely demanding dual career path. It should not come as a surprise that, despite the best support structure, a substantial proportion of physician-scientists will at some point feel overwhelmed by the demands and personal sacrifices and opt for one or the other career. Even though they may choose drop out, the small pool of physician-scientists

will likely be replenished by a fresh batch of younger colleagues, attracted by the prospect of concomitantly working in and bridging these two worlds.

Instead of lamenting the purported demise of physician-scientists, we should also think about alternate ways to improve the dialogue and synergy between cutting-edge science and clinical medicine. A physician can practice science-based medicine without having to actively work as a scientist in a science laboratory. A scientist can be inspired or informed by clinical needs of patients without having to become a practicing physician. Creating routine formalized exchange opportunities such fellowships or sabbaticals which allow scientists and clinicians to spend defined periods of time in each other's work environments may be much more feasible approach to help bridge the gap and engender mutual understanding or respect. <

After a long Lindau day:
Evening at the conference venue

ROLF SCHULTES / LINDAU NOBEL LAUREATE MEETINGS

SYNTHETIC BIOLOGY

Synthetic Genes, Synthetic Cells – Synthetic Life

Hanno Charisius

Nature needed about one billion years to create the simplest single-cell organisms that swam around in the primordial soup. Now, scientists are eager to create synthetic life – but better and faster.

Hamilton O. Smith 2014 at Lindau

Hamilton Smith (Nobel Prize in Chemistry 1978 with Werner Arber and Daniel Nathans) started his lecture at the 64th Nobel Laureate Meeting in Lindau with a quote from Richard Feynman (Nobel Prize in Physics 1965):

»What I cannot create, I do not understand.«

Feynman had probably meant physical models, whereas Smith referred to living organisms. In his laboratory at the J. Craig Venter Institute, he tries to create synthetic cells: »I hope that if we create that, we will understand.«

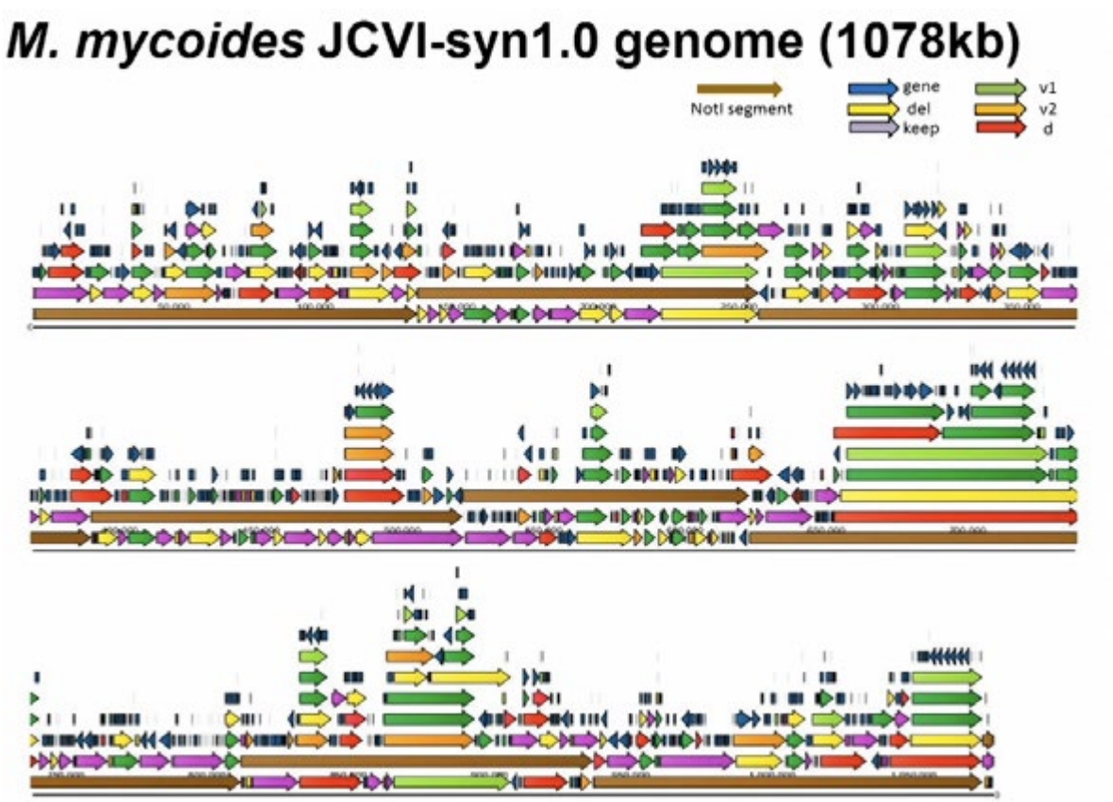
Nowadays, the entire human genome has been decoded. But how a live human being develops from DNA molecules, a human being that can breath, eat, walk, study, love, receive Nobel Prizes and award them – nobody really understands yet. Even for single-cell organisms, this isn't crystal clear. Even the simplest bacteria exhibit genes without apparent function, that are not essential for life. During evolution, a lot of 'genetic waste' has accumulated that might have been useful at some point, but was rendered useless by mutations. Some genetic fragments were in fact smuggled into the genome by viruses, others were created by accidental duplications of genetic segments. Numerous molecular mechanisms lead to many genetic variations – rendering evolution possible in the first place. But over time, many of these genes and segments have become useless.

Currently Smith tries to tidy up the genome of Mycoplasma mycoides, a microbe normally living in the digestive tract of ruminants. Originally Smith and his team wanted to use the genome of Mycoplasma genitalium, the bacterium with the smallest known genome – it needs only 475 genes to live. Smith estimates that about 100 of these are non-essential. But since *M. mycoides* has a much higher cell division rate, although its genome is twice as large, experiments with *M. mycoides* proved to be more effective. During this 'minimal cell project', the researchers switch off one gene after another and study the effects on the microbes. (And the slower the microbes grow, the longer the researchers have to wait for their results.) Smith's final goal is »a genome that is very understandable – we are searching for the genetic kernels of life«. In sorting out the genes, Smith uses three gene categories. The genes he analyses are either

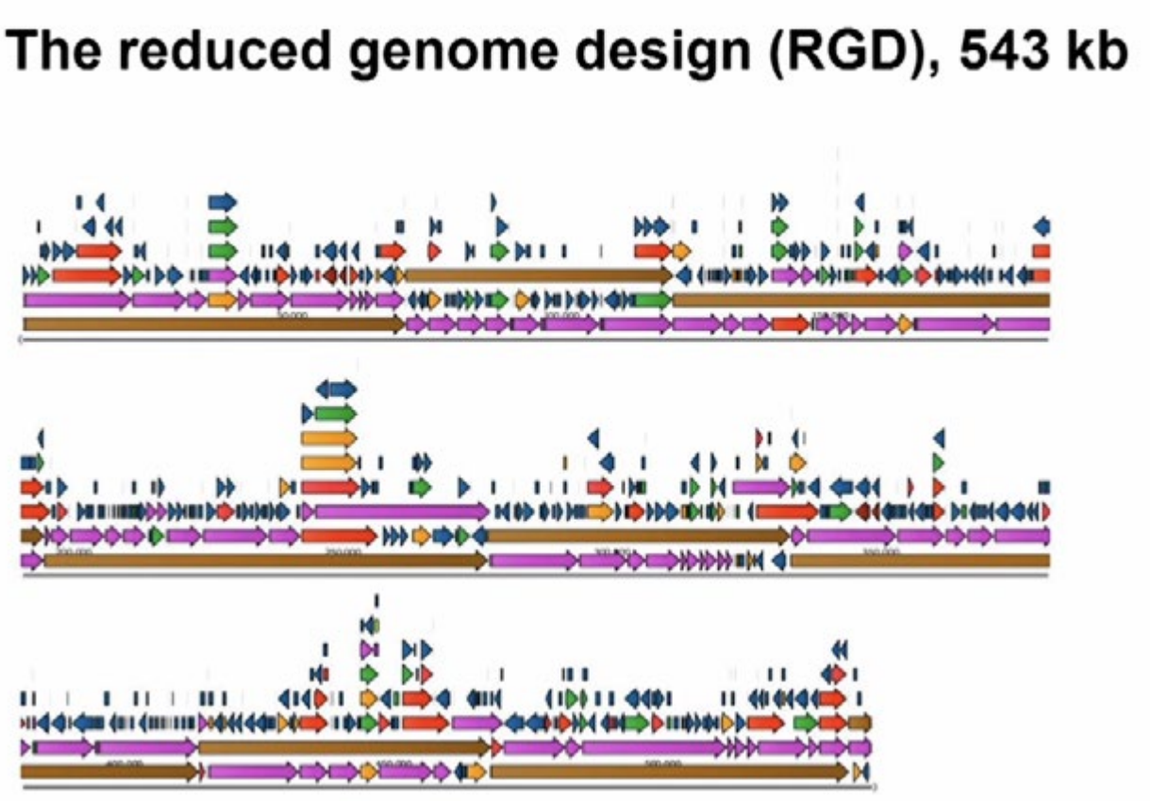
- *essential for life*
- *not essential, but knocking them out leads to slower cell growth*
- *non-essential*

Smith also assumes that all genes from the last group can be switched off without negative impacts on the microbes. Concerning the middle category, the researchers have to carefully weigh all options. When all is done, the result should be a bacterium that can still multiply rapidly, at least in laboratory conditions that offer plenty of nourishment, constant temperatures, but no competitors. The researchers' goal is a fifty percent genome reduction in a happily thriving microbe that divides at least once in 100 minutes.

During his Lindau lecture, Smith called the genetic waste »spaghetti code«, a programmer term used to describe some messy program code that was written, for instance, by too many programmers and



The genome before ...



... and after the modifications

SCREENSHOT OF H. SMITH'S LECTURE AT LINDAU 2014

has become completely chaotic, although it still functions. The tidying up of a code like this is called »refactoring« if the program's function remains the same. And that is exactly what Smith and his team are doing with the genetic code of a bacterium: Its genome is reduced to the absolute minimum requirements of life, to the »core machinery of life«, as Smith puts it.

Smith likes using computer terms to describe his work. He compares the genome of any organism with its software, the rest is hardware (the cytoplasm, proteins and enzymes), controlled by said software. As soon as a cell receives a new genetic program, it starts to put this program to use. In order to test their own synthetic programs, Smith and his team replaced the bacterium's DNA with synthetic DNA containing their basic program. To date, the old 'hardware' has not adopted the new program 'update'. In computer speak, troubleshooting and maintenance are called »debugging«: Smith and his team will be busy with debugging for some time. But recent successful projects suggests that the researchers might succeed: four years ago, Smith's team caused a sensation by bringing bacteria to life with a completely synthetic genome designed on their computers. Nowadays automated synthesising machines that can create any DNA form the four original bases, or with Smith's words: »simply a piece of software written in a four-letter code.« But the researchers did not invent a new bacterium, they copied the *M. mycoides* genome with a few variations to later identify their creation in the living cell. They transplanted this syn-

thetic genome into bacteria that are closely related to *M. mycoides* – the new genome took over and controlled the cells, as planned. Because this experiment confirmed the software metaphor so nicely, it became an important stepping-stone towards creating synthetic life. This novel discipline is called synthetic biology, its goal is the creation of organisms with new biological functions that don't already exist in nature. Until recently, biotechnologists could only make small changes in genomes, like switching off certain genes or inserting new genes, to give plants, bacteria or animals new functions. Often the resulting bacteria produce some protein that is needed for drug development or production. But things get more difficult when another substance besides proteins is the target. The 2006 transplantation of an entire metabolic pathway caused quite a stir. The resulting yeast cells were able to produce artemisinic acid, that can be converted into an anti-malaria drug. Thus the transplantation of an entire genome was the next logical step, although the novel synthetic organism doesn't produce anything useful yet.

All of these developments were only made possible by past discoveries worth several Nobel Prizes. A few examples: Arthur Kornberg won the 1959 Nobel Prize, together with Severo Ochoa, for discovering »the mechanisms in the biological synthesis of DNA«, especially the role of polymerase in DNA duplication. James Watson and Francis Crick won the 1962 prize for their famous description of the DNA double helix. And Smith, Arber and Nathans received the 1978 prize for discovering type II restriction enzymes, enzymes that are able to cut the DNA at specific nucleotide sequences very precisely. Two years later, Paul Berg, Walter Gilbert and Frederick Sanger won the prestigious prize: Gilbert and Sanger had developed a new DNA sequencing method. Today's hundreds of genome studies published every month were made possible only by these sequencing methods, as well as by the subsequent price slump in genome analysis in recent years. Berg was one of the first researchers to combine genes from different organisms, and is considered one of the founding fathers of genetic engineering. He was also one of its first critics: He co-initiated the Asilomar in 1975, where scientists shaped voluntary guidelines concerning the safety of recombination DNA technology, resulting in a research moratorium about certain gene regions and combinations effective for several years. Finally in 1986, Kary Mullis was honoured for his discovery of a technique to amplify DNA sequences in the lab, making the resulting improved PCR (polymerase chain reaction) the central method in molecular biology.

Without these findings, Smith and his team would not be able to pursue their goal to create synthetic life. They not only want to understand – they also want to apply their knowledge. The novel microorganisms they are trying to create are supposed to produce everything from drugs and biofuel to chemicals. The researcher's imagination has no limits, only the present-day knowledge. »We can chemically design any DNA sequence«, Smith explains, »but we cannot yet design a gene at the computer with a specific enzymatic activity. We can best modify existing protein designs.« Nature's programs can be copied and modified, but no synthetic formula for life has yet been found or invented. But computer programmers learn by copying existing programs until they truly understand how the stuff works. Then they can start to get creative. <

FANDOM

Autographs vs. #NobelSelfie

Vincenzo Hiemer

Meeting Participants Renata Gomes and Adam Spencer had a Nobel Laureate Fan Competition. Find out who won!

ADAM SPENCER

Adam Spencer snapping a selfie with Ada Yonath

For people attending a Lindau Nobel Laureate Meeting for the first time it is often a surprise how approachable and fun-loving the Laureates actually are. But once the surprise has set, the big hunt for autographs and pictures begins.

Young Scientist Renata Gomes had the idea to transform her meeting bag into a wearable autograph card and started to collect signatures from this year's Nobel Laureates. When we heard about this we posted a photo of her and Martin Chalfie on Facebook to encourage her on the quest of collecting as many laureate autographs as possible.

Australians are widely known for being easygoing – Sidney University's science ambassador and self-proclaimed geek Adam Spencer however felt the fire of competition inside of him when he heard about Renata's autograph hunt. He had already started a #lnlm14 Twitter craze with a series of Selfies with Nobel Laureates and now wanted to know who the better 'hunter' was.

The Lindau Blog Team decided to host this fierce battle of Nobel fandom for the whole community to enjoy. So let the battle begin! In the end Renata managed to get over 20 autographs on her bag making it the most scientific and fashionable autograph card of the year.

CHRISTIAN FLEMMING/LINDAU NOBEL LAUREATE MEETINGS

Renata Gomes showing her hunting trophy.

Adam Spencer on the other hand succesfully got over 30 selfies with Nobel Laureates. To see them all go to his Twitter: https://twitter.com/adambspencer. Therefore we hereby declare Adam Spencer the winner of the competition! Congratulations, Adam! Renata fought bravely but in the end Adam showed his killer instinct and scored the victory. <

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