The European Molecular Biology Laboratory Magazine

Issue 90 Winter 2017/18

EMBL etc.

Curiosity

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Nucleus Curious realms

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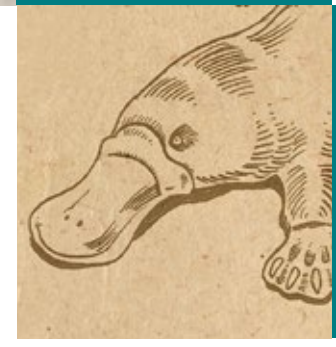

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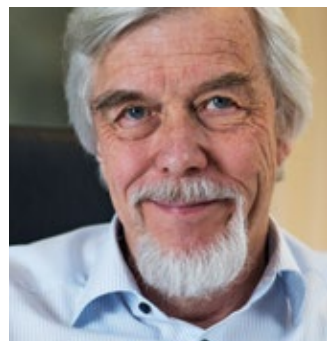

PHOTO: RODICA PETRUSEVSCHI/EMBL-EBI

Editorial

Curiosity is a profoundly human trait. We start asking questions almost as soon as we learn to speak, and continuously redefine our understanding of the world by questioning it.

Curiosity drives science and technology. It kick-starts ambitious projects and stirs our imagination. It is notorious for getting us into sticky situations, and sometimes out of them. In this edition, we explore what curiosity looks like at EMBL.

Jacques Dubochet, former EMBL group leader, talks to us about his 'aha!' moment, and how different branches of science may be connected (page 5). Dubochet was recognised in 2017 as a co-recipient of the Nobel Prize for Chemistry for his incredible work on cryo-electron microscopy at EMBL.

An EMBL staff member and two alumni reveal how curiosity led them to join ice core drilling expeditions in Greenland and Antarctica (page 16), sail the world's oceans (page 19), and study life in space at NASA (page 22). We shed light on some of the peculiar genomes in EMBL-EBI's Ensembl genome browser (page 38), and ponder how open data is changing the way we ask questions in science (page 30).

We pay a visit to Hamburg, where the Centre for Structural Systems Biology (CSSB) is helping to answer essential questions about infectious diseases (page 34). We also look behind the scenes at the EMBL fly kitchen (page 26) and reflect on what curious flies have taught us (page 28).

Oana Stroe
Features editor

Word to remember

Tardigrade

Noun, pronunciation:
\ ˈtär-də-ˌgrād \

Also known as water bears, tardigrades are microscopic animals that can survive in extreme conditions, including space (page 23).

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A curious case of serendipity

Jacques Dubochet, Nobel laureate and former EMBL group leader, reflects on curiosity, a key 'aha!' moment, and how different branches of science may be connected

A question I had as a child, which kept turning over and over in my mind, was thinking about planet Earth and asking: where exactly am I on it? As the night drew in, I saw shadows cast on the ground – shadows cast by me – and I knew that tomorrow it was going to be light again. To find out what was going on, I took a trip to my local library. You could call what drove me curiosity. But I wouldn't call it that. Trying to understand what was around me, this was just a way of life.

Much later, as a scientist, I wanted to understand how water was made. Although it is a remarkable substance, it causes a lot of trouble for people trying to zoom in on life at high resolution using an electron microscope. If a person tries to use an electron microscope to study structures in a sample – such as the membrane of a virus or a cell from a mouse's ovary – the microscope's powerful vacuum will cause liquid water in the sample to evaporate. The structures left behind are warped or may even be destroyed. Although freezing a sample would prevent the water from evaporating, frustratingly, the ice crystals that form during the freezing process wreak similar havoc. So, along with my team, I set out to vitrify water – a way of freezing liquid water so quickly that ice crystals don't form. This way, it would be possible to see tiny structures intact.

It was serendipity, luck, and – from time to time – some major failures that led me to the key 'aha!' moment that is part of the reason I was awarded the Nobel Prize.

This moment happened at EMBL in Heidelberg in 1980 when Alasdair McDowall, a technician in my lab, was attempting to vitrify small droplets of water on films to be used in an electron microscope. One day, after changing our cooling device by replacing liquid nitrogen with liquid ethane, he called me to the microscope because he saw something that he didn't understand. It was a frozen droplet of some amorphous material – since it didn't have any ice crystals, we figured it couldn't be water. We warmed it slowly to try to see how it evaporated, in order to try to find out what the droplet was made of. At 135 Kelvin – or around minus 138 degrees Celsius – the droplet transformed in a moment into polycrystals that we immediately recognised as ice crystals. So the frozen droplet we had seen before had been exactly what we had been told was impossible to create: vitrified water. I remember just at this moment I told Alasdair, 'here we have something essential'.

Then it took the work of many people over the next 35 years to advance cryo-electron microscopy techniques to the point that some individual atoms can be seen. Using cryo-electron microscopy, people have seen the structure of the hepatitis B virus, the Zika virus, and rhinovirus C, which is associated with acute asthma in children.

I am a biophysicist and never thought of myself as a chemist. Nevertheless, in the end, I shared the Nobel Prize in chemistry. This may be understood in two ways. One is that I have reached my highest level of incompetence! A better way, perhaps, is that science is unity and physics, biology, chemistry are all different intertwined ways of understanding the same reality – a reality that is much bigger than we can wrap our little heads around.

Jacques Dubochet was a group leader at EMBL in Heidelberg (1978-1986)

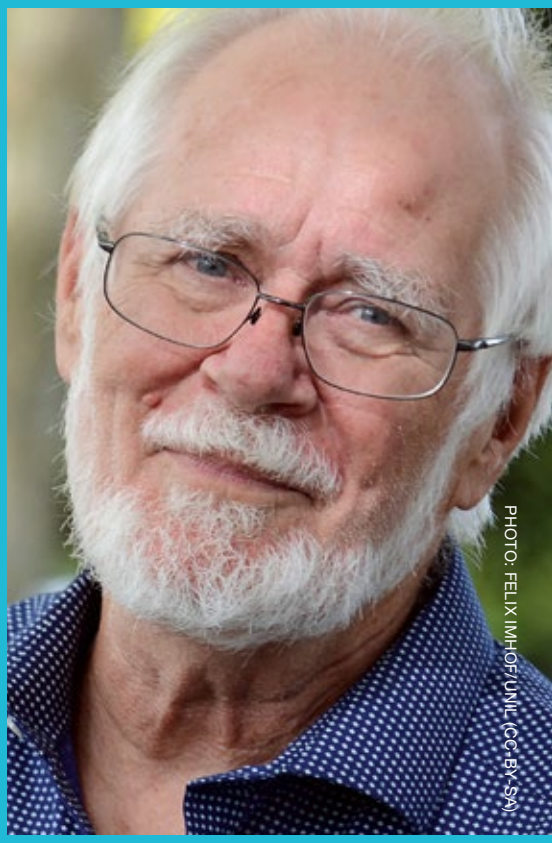


PHOTO: FELIX IMHOF/UNIL (CC-BY-SA)

Jacques Dubochet was a co-recipient of the 2017 Nobel Prize for Chemistry.

Funding agreed for imaging centre

IMAGES: WWW.RENDER-VISION.DE

The imaging technology centre is due to begin operations in 2021.

German state and federal governments agree on funding for a high-resolution microscopy centre in Heidelberg

BY ANNIKA DUDA

The letter of intent was signed on 31 August during an official ceremony at EMBL's Heidelberg campus by representatives of the German government together with industry and foundation partners. The new centre for light and electron microscopy will be a unique service facility for the life sciences and unite cutting-edge equipment, experts, and data analysis. This imaging technology centre will be open to visiting scientists from all over the world as well as industry partners. It will make new technologies at EMBL available to foster a better understanding of the molecular basis of life and disease.

Access to technology

During the ceremony, EMBL Director General Iain Mattaj and Jan Ellenberg, project leader of the imaging centre and Head of the Cell Biology and Biophysics Unit at EMBL, presented the construction plans and the concept for the new imaging technology centre to representatives from government, the Boehringer Ingelheim Foundation, and partners from industry. "We can only advance our knowledge by bringing together the latest technologies and making them available to all scientists," said Ellenberg. "EMBL has a long-standing, excellent track record and unique expertise in the imaging area. So Heidelberg is an obvious place to build a new imaging service centre."

Collaboration and training

The imaging technology centre will provide access to the latest technologies for scientists at EMBL as well as for up to 300 visiting scientists annually, well before they become commercially available. To facilitate this EMBL is cooperating with leading microscopy companies. Thermo Fisher Scientific, Leica, and ZEISS will contribute a total sum of ten million euros to the project. To train scientists to work with these high-end technologies, the Boehringer Ingelheim Foundation will donate five million euros towards the operation of the new centre.

The new centre will cover a floor area of 4,500 square metres and cost 45 million Euros. HeidelbergCement will provide building materials.

Ground-breaking is planned for summer 2018 and the imaging technology centre is due to begin operations in 2021. The centre will unite the best microscopes, experts, and analysis techniques under one roof, and host a permanent exhibition that provides visitors with information about EMBL and the world of microscopy. "With the help of these new technologies we will be able to answer questions that have been puzzling scientists for years, the answers to which will be relevant to all of us," said Mattaj.

BEHIND THE SCENES OF EMBL'S NEW IMAGING TECHNOLOGY CENTRE:
BIT.LY/imagingcentrevideo

Jacques Dubochet awarded Nobel Prize for Chemistry

EMBL alumnus Jacques Dubochet recognised for cryo-electron microscopy work carried out at EMBL

BY ADAM GRISTWOOD

PHOTOS: WILLY BLANCHARD/EMF, UNIVERSITÉ DE LAUSANNE

Alumnus Jacques Dubochet has been named as a co-recipient of the 2017 Nobel Prize for Chemistry for developing cryo-electron microscopy (cryo-EM) to determine the structure of the molecular building blocks of life in high-resolution.

Working as a group leader at EMBL in Heidelberg in the 1980s, Dubochet, together with colleagues, developed a method to freeze thin layers of biological samples without forming ice crystals – a technique known as vitrification. The team then studied these layers in an electron microscope, a development that simplified the process of visualising biomolecules. This was the birth of cryo-EM, one of the cornerstones of modern structural biology.

"Jacques developed a technique that has had a tremendous impact on our ability to determine the structure of molecules and understand their function," explains Iain Mattaj, EMBL Director General. "As one of the inventors of cryo-electron microscopy sample preparation, it is fitting that his huge contributions to research and technology innovation have been recognised by the Nobel committee."

Dubochet and his teams have also developed important methods that built on his invention, including a technique that enables the cutting of vitreous sections of high-pressure frozen tissue that allows the insides of cells to be imaged. Today, cryo-EM is a method that EMBL makes available to scientists around the world. Thanks to a new imaging technology centre, set to be constructed at EMBL in Heidelberg, even more scientists will soon have access to this and other cutting-edge imaging technologies.

Dubochet joins a list of 177 Chemistry Nobel laureates who have been recognised since 1901.

Exploring ways to reduce carbon

EMBL and HeidelbergCement have co-signed a Memorandum of Understanding that aims to encourage beneficial knowledge exchange in areas related to CO_2 emission reduction, avoidance and recovery, as well as driving innovation. EMBL and HeidelbergCement will focus their collaborative activities on the coordination of conferences and workshops, bringing international experts to EMBL's Advanced Training Centre to learn about and debate these important research areas.

MORE ONLINE:
BIT.LY/waystoreducecarbon

Training milestones

It has been 40 years since EMBL launched its first course – read online how courses and conferences have changed over the past 40 years, currently welcoming approximately 7300 attendees annually.

MORE ONLINE: BIT.LY/40yearscc

EMBL-EBI's dedicated bioinformatics training programme celebrated its tenth anniversary in September. International experts convened to share their thoughts on the big challenges for bioinformatics training and how the field might change in the next ten years.

MORE ONLINE:
BIT.LY/10yearsemblebitraining

PHOTO: PATRICK DELAPIERRE/ INSERM

EMBL Council selects new Director General

Edith Heard selected unanimously, mandate scheduled to begin 1 January 2019

BY DAN NOYES

At its 53rd meeting in June, EMBL Council selected Edith Heard as the organisation's fifth Director General. Heard's mandate is scheduled to begin 1 January 2019.

"Today is a great day for European science," said Patrick Cramer, Chair of EMBL Council, following Heard's appointment. "I am extremely pleased with the comprehensive search for the next Director General conducted by the search committee. The committee, composed of leading scientists and science managers from eleven countries, unanimously chose Edith Heard. Edith is an outstanding molecular biologist and scientific leader with a lot of international experience. Her clear scientific vision, her participatory leadership style, and her engagement at all levels of research, service, and training make her a perfect choice. Under the leadership of the current Director General, Iain Mattaj, EMBL has advanced to become a world-renowned institution. We have sent out a clear signal that we will stay on this path and develop EMBL as a model for research and services for the future."

"Edith Heard is an excellent choice to be my successor," said EMBL Director General Iain Mattaj. "Edith has enormous credibility as a leading scientist in Europe and worldwide. Her experience in developmental and cell biology and genomics make her a perfect scientific fit for EMBL. She is also an accomplished leader with a strong European vision. While at the Institut Curie, Edith has demonstrated her ability to choose and mentor excellent junior group leaders. I have every confidence in her ability to steer EMBL towards future success. I look forward to working with her during the transition."

Great honour

"I am extremely honoured to be offered this opportunity to serve European science as Director General of EMBL," said Edith Heard. "As a deeply committed citizen of Europe, I will endeavour to promote the scientific excellence and service to the scientific community that characterise EMBL. EMBL represents a flagship for European research and is a model for the molecular life sciences worldwide. My ambition is to keep it at the forefront of international research and service provision, producing the leaders of the future

and nurturing a spirit of research and training that is conducive to discovery and innovation. I intend to work very closely with EMBL's Council and Scientific Advisory Committee, as well as the Heads of Units and group and team leaders, so that together we can elaborate the best plans of action for my leadership to be a success."

Ground-breaking discoveries

Professor Heard is currently Director of the Genetics and Developmental Biology Unit at Institut Curie and holds the chair of Epigenetics and Cellular Memory at the Collège de France. Heard studied Natural Sciences at Emmanuel College, Cambridge University, before going on to complete a PhD in cancer research at the Imperial Cancer Research Fund in London. Since then she has worked at the Institut Pasteur (Paris), Cold Spring Harbor Laboratory (NY, USA) and the Institut Curie (Paris).

Heard's areas of research include epigenetics and developmental biology and she has expertise in chromosome and RNA biology. Her team focuses on the process of X-chromosome inactivation, which occurs when one of the two X chromosomes present in all the cells in a woman's body is silenced during development. Heard and her colleagues have shown that X-chromosome inactivation is highly dynamic during development and that it displays remarkable evolutionary diversity. Thanks to their work on the X chromosome, they also recently discovered a novel level of chromosome organisation: topologically associating domains (TADs), which are conserved units of chromosome folding and encompass gene regulatory landscapes.

"I will promote scientific excellence and service to the scientific community that characterise EMBL"

Heard was made a Fellow of the Royal Society in 2013 in recognition of her ground-breaking discoveries in epigenetics. She was elected as Professor at the Collège de France in 2012. She is also a member of the EMBO, a European Research Council (ERC) Advanced Investigator and has been honoured with awards including the Prix Jean Hamburger, the Grand Prix de la Fondation pour la Recherche médiale, the 2017 European Society for Human Genetics Award and, most recently, the 2017 Inserm Grand Prize.

European Photon and Neutron sciences campus.

EMBL and ESRF renew collaboration agreement

EMBL and the European Synchrotron Radiation Facility (ESRF) extend their Joint Structural Biology Group

BY ISABELLE KLING

EMBL and ESRF have re-expressed their commitment to working together by extending their bilateral collaboration agreement until 2021. The first agreement was signed in 1997, soon after the opening of ESRF. It sets out how the two institutions collaborate on developing new instruments and offering innovative services to structural biologists worldwide.

Under the agreement, EMBL and ESRF scientists and engineers have automated most instruments on the X-ray beamlines, allowing users to collect diffraction data more easily and efficiently on increasingly small crystals. One recent joint achievement is the full automation of the process of protein structure determination, from protein crystallisation to online data collection, via robotic crystal harvesting. This pipeline will be particularly useful to systematically screen how small molecules bind to proteins, an important part in the drug development process. It is therefore not only of interest to academic users but also increasingly to pharmaceutical companies.

FULL STORY ONLINE:
BIT.LY/esrfrenewedcollaboration

Fish on fire

EMBL's Paola Kuri and Maria Leptin explain the importance of their work visualising ASC speck formation in real time

BY MARGAUX PHARES

While immune sensing mechanisms vary widely between animals, ASC specks – particles that play a key role in triggering inflammation – form in humans as well as zebrafish. This has been revealed in a study published in *The Journal of Cell Biology*.

Maria Leptin: There is a huge interface between inflammation and health. Inflammation, on one hand, is good. It alerts the body to danger and sends in professional cells to deal with it. On the other hand, it's what makes you feel bad, and it can go seriously wrong! Allergies and many diseases such as Alzheimer's are linked to inflammation when it is not kept in check and becomes chronic, which has also been linked to higher ASC speck numbers. Inflammatory systems have to be poised so that they quickly turn on when there is real danger, yet do not turn on spontaneously.

Paola Kuri: Inflammation is not just limited to immune cells – it can happen in tissues and cells that are not normally linked to the innate immune system. ASC is everywhere inside zebrafish, including the gut, gills, and brain, but I was particularly interested in the skin cells of the animal, which come into contact with the outside world. This is why looking at an entire organism becomes relevant. Shedding light on how inflammation works in these tissues contributes to our understanding of how and why inflammation can go wrong.

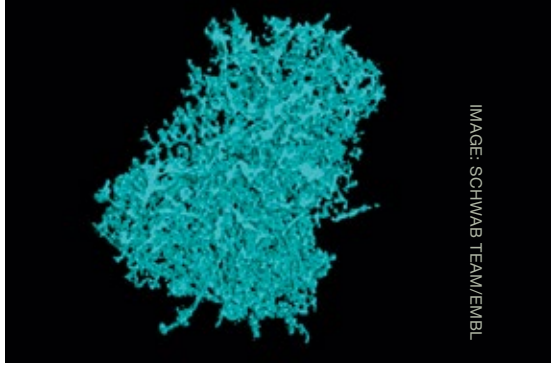


IMAGE: SCHWAB TEAM/EMBL

Combined images from light microscopy and electron microscopy reveal what a speck formed *in vivo* (in blue) looks like.

Kuri P *et al. Journal of Cell Biology*, published online July 12, 2017. DOI: 10.1083/jcb.201703103

FULL STORY ONLINE: BIT.LY/fishonfire

How wine-making yeast can feed wine-spoiling bacteria

EMBL scientists show how microbes can create niches for each other

BY SONIA FURTADO NEVES

In a study published in *Cell Systems*, scientists in Kiran Patil's lab at EMBL have detailed how the microbes involved in making wine, yoghurt, and other fermented foods can feed each other. The work also shows that a small change in the environment can shift the interaction from a one-way relationship into a mutual dependency.

The yeast *Saccharomyces cerevisiae* ferments grape juice into wine. If lactic acid bacteria – which ferment milk into yoghurt – start growing in the wine, they can spoil it. Olga Ponomarova and Natalia Gabrielli discovered conditions in the lab under which the yeast can feed the bacteria. The EMBL scientists found that if yeast is growing in an environment with excess nitrogen, it secretes amino acids that the bacteria can feed on. They found that this happens not only with lab-grown strains, but also with yeast taken from wine and kefir. In all these cases, the bacteria can't survive without the yeast.

But the yeast and the bacteria can also come together with more palatable results, such as in chocolate, sourdough bread, and the fermented milk drink kefir. The relationship is not always one-sided, though. The scientists found that in kefir, where the carbon source is lactose – a sugar which the yeast can't digest – the two microbial partners are dependent on each other: the yeast produces amino acids for the bacteria, which in turn break down the lactose that the yeast can't handle.

Ponomarova O, Gabrielli N *et al. Cell Systems*, published online 27 September 2017. DOI: 10.1016/j.cels.2017.09.002

PHOTO: DANIEL GO (CC BY 2.0)

Looping the loops: How chromosomes form

EMBL researchers and collaborators take important steps in unravelling chromosome formation

BY EDWARD DADSWELL

In almost every cell in our bodies, two metres of DNA is packed into a nucleus less than one hundredth of a millimetre across. To fit into such a small space, our DNA has to be carefully coiled and packaged with various proteins. During cell division, the DNA molecules – in paired copies – are compacted still further, giving rise to the chunky X-shaped structures that are probably the most familiar manifestation of our chromosomes. How this compaction process happens is mysterious, but one important player is a ring-shaped protein complex called condensin. Two recent studies involving EMBL group leader Christian Haering and his team have revealed important features of condensin and how it might work to compact chromosomes.

In the first study, published in *Cell*, the Haering group used X-ray crystallography to reveal a groove in the condensin complex that accommodates the DNA molecule. Despite the presence of this groove, it appeared the complex should only bind to DNA quite weakly. A closer look revealed a novel method of DNA binding in which one of the proteins that makes up the condensin complex – called kleisin – encircles the DNA, creating a kind of safety belt to hold it in place. When the Haering group modified the safety belt to prevent it from closing, they found that condensin does not associate with chromosomes any more.

Motorised process

The second study, published in *Science*, was a collaboration between Haering's group and researchers at Columbia University in New York and the Kavli Insitute of Nanoscience Delft in the Netherlands. They found that condensin acts like a molecular motor, using energy to travel significant distances along the DNA molecule. They also showed that condensin was able to take a second DNA molecule and move it in relation to the first.

This provided strong support for the loop extrusion model, which posits that DNA is compacted by interacting with many ring-shaped protein molecules, each one pulling a loop of DNA through its centre. This compacts the DNA strand in the same way that a long thread can be packed into a shorter space by pulling loops of it through a backing material to make a carpet. Haering's group and their collaborators suggest that condensin could hold on to one side of a DNA loop and feed the other side of the loop through its ring, enlarging the loop as required by the loop extrusion model.

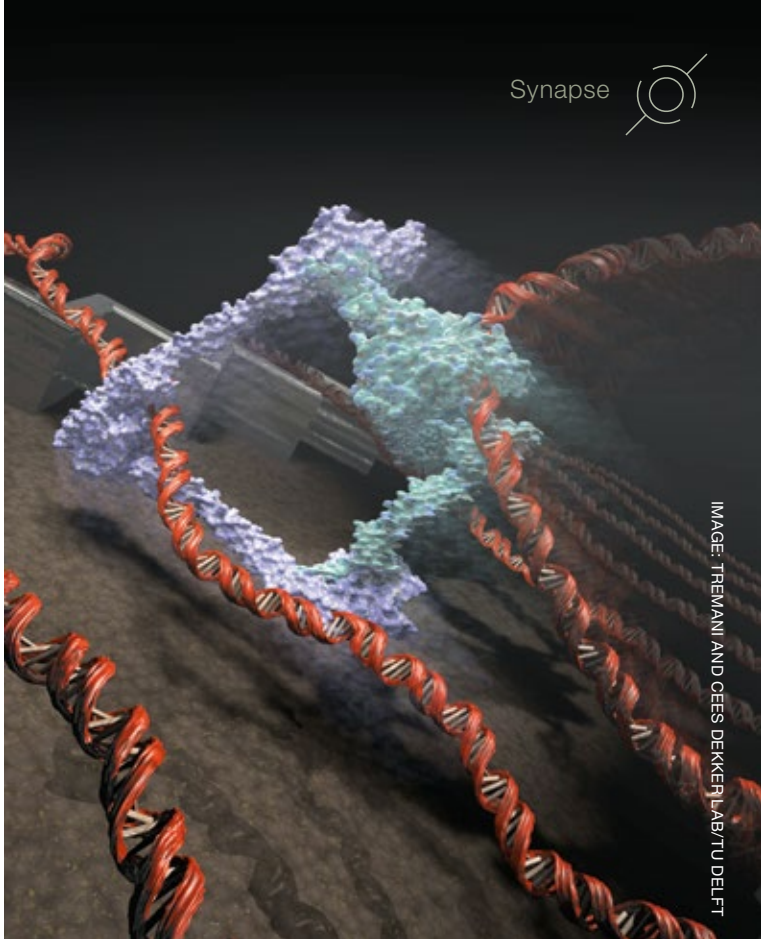


IMAGE: TREMANI AND CEES DEKKER LAB/TU DELFT

The condensin complex has a groove (right-hand side) which holds one part of a DNA strand, while another part of the strand is fed through the main condensin ring (left).

Kschonsak M *et al. Cell*, published online 5 October, 2017. DOI: 10.1016/j.cell.2017.09.008.
Terekawa T, Bisht S, Eeftens JM *et al. Science*, published online 7 September, 2017. DOI: 10.1126/science.aan6516.

FULL STORY ONLINE:
BIT.LY/howchromosomesform

Research highlights

A summary of some recent research papers from across EMBL

BY BERTA CARREÑO

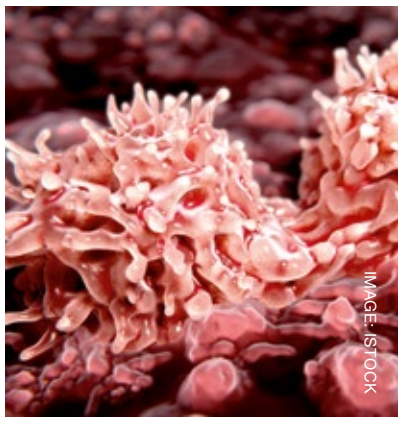


IMAGE: ISTOCK

HipSci: The human stem cell bank

Stem cell researchers have produced one of the largest collections of high-quality human induced pluripotent stem cell lines (iPSCs) from healthy individuals. This resource is a result of a close collaboration between the Stegle group and their partners in a major international collaboration. The datasets are freely available via EMBL-EBI.

Kilpinen *et al., Nature*, doi:10.1038/nature22403

Bowel cancer study reveals impact of mutations on protein networks

Scientists used a computational analysis method developed by EMBL-EBI researchers and their colleagues to explore how common mutations affect proteins in bowel cancer cells, and whether identifying these proteins can help predict the cancer's response to treatment.

Roumeliotis *et al., Cell Rep*, doi: 10.1016/j.celrep.2017.08.010

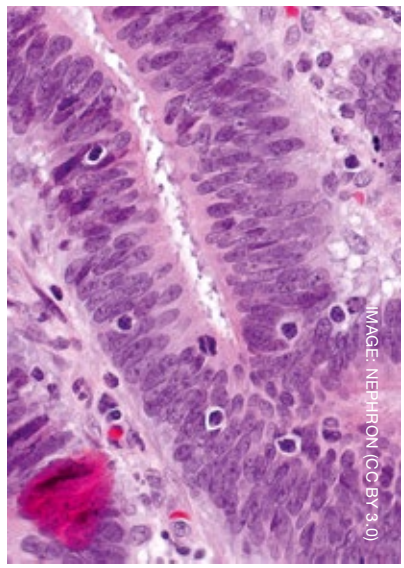


IMAGE: NEPHRON (CC BY 3.0)

IMAGE: SPENCER PHILLIPS/EMBL-EBI

Mouse genes could help decipher human disease

Researchers in the Parkinson group and their collaborators have fully characterised thousands of mouse genes for the first time. The results offer hundreds of new disease models and reveal previously unknown gene functions.

Meehan *et al., Nat Genet*, doi: 10.1038/ng.3901

Newly found regulator of important developmental protein

Scientists in the Ephrussi and Müller groups have discovered that some important proteins, including one known as Oskar, contain a specific variant of the LOTUS domain that regulates the protein Vasa, which is important for germline development in animals. The team have discovered how the proteins interact by determining structure of the Oskar LOTUS domain bound to Vasa.

Jeske *et al., Genes Dev*, doi: 10.1101/gad.297051.117

PHOTO: FLYBASE.ORG

Using distant relatives to understand the effects of sequence variation

The Furlong group have studied the occupancy of key regulatory factors in two distinct strains of Drosophila to better understand the effects of natural sequence variation. The paper analyses the relationship between DNA sequence and function during evolution.

Khoueiry *et al., eLife*,
doi: 10.7554/eLife.28440

Predicting the behaviour of the cytoskeleton

The Leptin and Nédélec groups have developed a theoretical framework to predict whether a network of protein filaments – such as that which makes up the cytoskeleton, giving a cell its shape – will contract, expand, or retain its size. This provides a foundation for studying a broad range of processes involving cytoskeletal networks.

Belmonte *et al., Mol Syst Biol*,
doi: 10.15252/msb.20177796

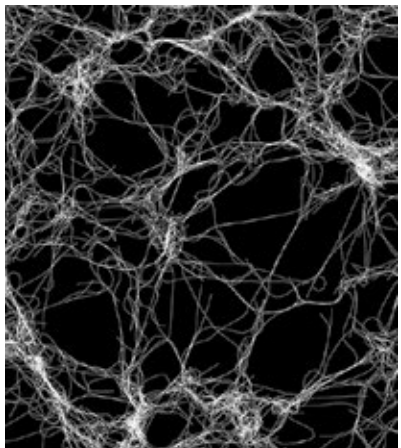


IMAGE: COURTESY OF NEDELEC GROUP

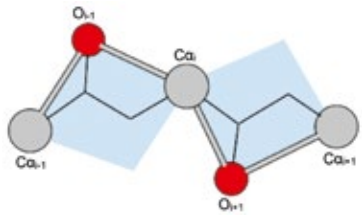
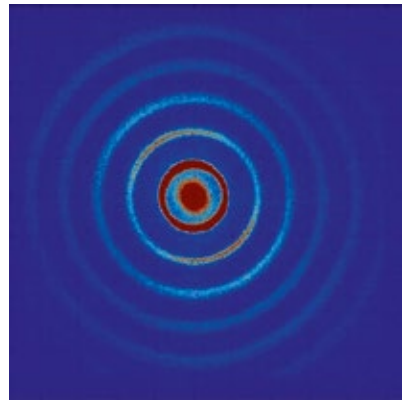


IMAGE: LAMZIN GROUP

New validation tool for protein backbone geometry

Researchers in the Lamzin group have unveiled DipCheck, a new method that uses a novel 3D parameter space to validate the geometry of the hugely diverse backbones that build up the structures of proteins. DipCheck is now available to researchers across the globe through a new web service.

Pereira & Lamzin, *IUCrJ*,
doi: 10.1107/S2052252517008466



A new version of ATSAS to elucidate macromolecular structures in solution

The Svergun group have presented numerous recent improvements and new developments to ATSAS, a program suite for small-angle scattering data analysis from macromolecular solutions. The software has over 13,000 users worldwide.

Franke *et al., J Appl Crystallogr*,
doi: 10.1107/S1600576717007786

PHOTO: SPENCER PHILLIPS/EMBL-EBI

Novel hearing loss genes identified

Researchers from the Flicek and Parkinson groups and their collaborators have found 52 previously unidentified genes that are critical for hearing. The study shows how these newly discovered genes could provide insights into the causes of hearing loss in humans.

Bowl *et al., Nat Commun*,
doi: 10.1038/s41467-017-00595-4

MORE ONLINE:
BIT.LY/researchhighlightswinter2017

Computational models of cancer available

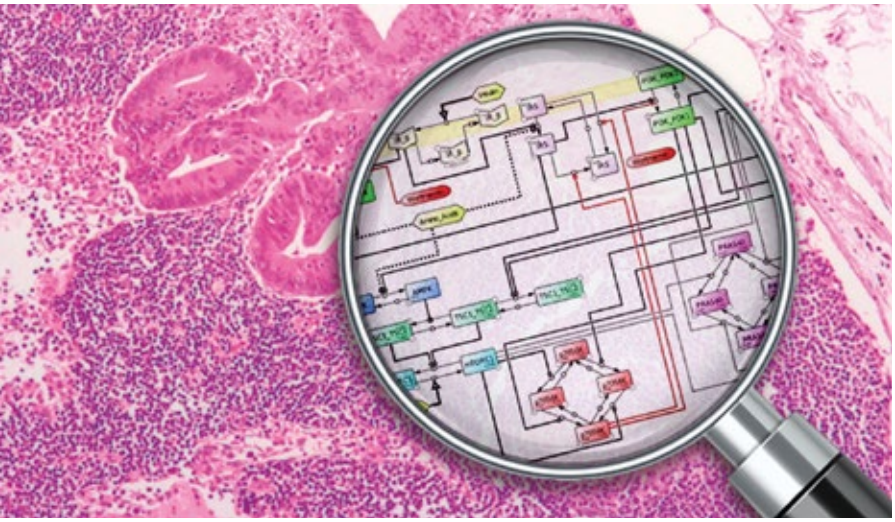


IMAGE: SPENCER PHILLIPS\EMBL-EBI

EMBL-EBI's BioModels Database hosts thousands of new patient-derived models

BY OANA STROE

Personalised computational models of how our bodies work have the potential to become a powerful tool for understanding, and eventually treating, complex illnesses like cancer. Because each person is biologically unique, computational models personalised using biological data extracted from individuals can help us understand why some people respond to medical treatments in unexpected ways.

What did they do?

One example of this approach is a recent study published in the journal *Science*, which employed computational analysis to investigate dissimilarities between different cancer cells and amongst cancer patients. The 6,753 models used in the analysis were derived from tissue samples collected from cancer patients, and span 17 major human cancer groups (which encompasses 21 different types of cancer). All these models are now freely available through EMBL-EBI's BioModels Database.

Computational modelling uses mathematics, physics, and computer science to represent and simulate the behaviour of complex systems, such as cells. Computational models are *in silico* representations of the systems being modelled.

Why does it matter?

Researchers studying cancer can use these models as a starting point towards exploring what happens in tumours at the molecular level. The models can also be used in the development of better cancer treatments with fewer side effects – efforts that could, in the future, result in personalised treatments tailored to the unique needs of individual patients.

"Each model is associated with a single patient," explains Varun Kothamachu, postdoc at the Babraham Institute and a visiting researcher at EMBL-EBI. "It contains information about the metabolism of the tumour sample, as well as metadata about the age and gender of the patient, plus the clinical outcome.

"Researchers can add information from patient-derived tissue samples to a base model in order to build these patient-specific models. In their current form, patient-derived models can be an excellent starting point for building *in silico* models to understand drug response. This would allow researchers to analyse how different drugs work on individual patients, in addition to supporting the identification of more effective drug targets for treating cancer."

Uhlen M *et al. Science.* Published online 18 August; DOI: 10.1126/science.aan2507

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Curious realms

Meet three people from the EMBL community whose curiosity has got them working on science in extraordinary places

ILLUSTRATION: AAD GOUDAPPEL

Science from ice

PHOTO: COURTESY OF SIMON SHELDON

Casey Station on the Antarctic coast is around 15,800 km from Sheldon's office at the Niels Bohr Institute. At this point he still needs to travel 550 km inland for his next field operation.

Working on scientific instruments has taken EMBL alumnus Simon Sheldon to the ends of the Earth

BY EDWARD DADSWELL

It's the weekend. You're in a tent and there's a storm blowing outside. A snowstorm. It's been going on for nearly five days. There are snowdrifts taller than you are, although the visibility's so low you can barely see them. You're on Flade Isblink – an ice cap nine degrees from the North Pole. Help, if you need it, has to come from a military base 50 km away. The wind speed is 40 mph, the temperature is -12 °C, your tents are collapsing to the left and right, and the last of your three generators has just packed up.

This is how things looked for EMBL alumnus Simon Sheldon on 21 May 2006, when he was one of a team of nine on an ice core drilling expedition to Greenland. When the weather turned harsh, their generators began breaking down as a result of various manufacturing faults and the intake of snow into the air inlets.

Despite a series of repairs, by the fifth day of the storm they had no working generators. They ended up using two Primus stoves to heat the main tent while they salvaged parts from two generators to make one working one. "We had one tent that was just full of engine parts everywhere," says Sheldon. "A few of us got covered in oil up to our elbows, and with such a limited supply of water there was no chance of washing it off." Finally they managed to restore power, and within two days the weather calmed, becoming relatively mild for Greenland. He can smile about it now, but at the time it wasn't clear how things would turn out. "It was never a life or death situation," he explains, "but it was tough. We came pretty close to abandoning the project."

Sheldon has spent more than a year and a half of his life in the polar regions – a total of 550 days spread over fourteen years. Based at the Niels Bohr Institute in Copenhagen, he currently runs a laboratory in the field of quantum technology, but until May 2017 he worked as an engineer on ice core drilling projects in Greenland and Antarctica. This role took him to Greenland twelve

times and Antarctica three times, for periods ranging from just over a week up to three months. His focus was primarily on developing drilling technology and the instrumentation for analysing ice core samples. He also built up expertise in field operations, dealing with things like the logistics of getting teams into the field, setting up camp, and using satellite and radio communications. "I enjoy planning operations, trying to recognise where problems can occur and reducing the chances of them happening," he says. "But in the field, things always take you by surprise. There's always something that breaks, something that's been working for years and then suddenly gives up. There's a lot of – shall we say – excitement from a technical point of view."

Onto the ice

Sheldon first became curious about travelling to Antarctica when he was a teenager. It was a combination of two things: one was watching films and reading stories about the Heroic Age of Antarctic Exploration, such as Shackleton's failed attempt to cross Antarctica in 1914, and the daring rescue mission that followed. Another was a fascination with the idea of going to a place that had been visited by relatively few people, and getting to live in a real survival situation in a harsh environment. "I'd always enjoyed camping," says Sheldon, "and this seemed like camping taken to the ultimate extreme."

"I couldn't believe I'd finally got there"

For a long time, it was just an idea. Not something he believed would ever be part of real life. After studying applied physics at university he began working for a company called Cambridge Instruments, developing technologies for electron microscopy and electron beam lithography. In 1993 he made the move to EMBL in Heidelberg, joining the group of Max Haider where he worked on techniques to improve electron microscopy images. He also met his future wife, EMBL alumna Susanne Lønstrup. After a few years they left to settle in Susanne's home country of Denmark. Sheldon spent six months refurbishing an old farmhouse they'd bought there, before taking up a position in the geophysics department at the Niels Bohr Institute. He joined an engineering team focused on improving ice core drilling equipment for the recovery of scientific-quality ice cores, and designing instrumentation for analysing ice core samples. He was 36 when he visited Antarctica for the first time. "When I first stood on the ice it was an incredible feeling," he says. "I couldn't believe I'd finally got there."

Warm atmosphere

In the 2013-14 austral summer, Sheldon was working in Antarctica as part of an Australian-led operation at Aurora Basin North. Returning from a break, he saw the principal investigator drop part of an ice core, shattering it. "If you consider the amount of time and effort you put in personally, and the costs involved in sending a team to Antarctica and running these drilling operations, the value of these ice cores is tens of thousands of euros per metre," Sheldon explains. "So when I saw him drop this piece of ice, it was horrifying." It turned out >>

Sheldon (far right) and colleagues celebrate Christmas with 'Santa Claus' in Antarctica.

PHOTO: COURTESY OF SIMON SHELDON

"We're busy, there's lots to do, and it's expensive to be there, so the clock's ticking"

>> that his colleague had made a fake ice core by freezing water in a bag, so it was all an elaborate joke. "I was so devastated, he couldn't keep up the pretence for more than a minute or so before he had to tell me," says Sheldon. "But immediately I could see the funny side – it was a very good prank."

Lighter moments like this provide a welcome balance to the hard work of being in the field, which often involves working twelve or more hours per day in very tough conditions. The work of people like Sheldon and his colleagues serves a serious purpose too. The ice cores they collect play a vital role in studies of ancient climate, allowing scientists to better understand the interactions between atmospheric composition and the Earth's temperature, and to refine models of current climate change. Sheldon's group has also collaborated with researchers such as Eske Willerslev, an evolutionary geneticist whose work has involved extracting ancient DNA from the bottom of ice cores, where they make contact with the underlying rock. Willerslev's research has revealed a warmer past in southern Greenland several hundred thousand years ago, with various insect species crawling and buzzing amid forests of conifer trees.[1]

Digging a trench in the snow at -45°C and 2750 m altitude.

PHOTO: COURTESY OF SIMON SHELDON

Strange sights

Greenland and Antarctica are extraordinary places to work, but for Sheldon and his colleagues there's rarely time to enjoy their surroundings. "We're busy, there's lots to do, and it's expensive to be there, so the clock's ticking and we don't usually have time to pay attention to anything other than the job we're there for," he says. "But when we've finished a project we might have to wait several days or even weeks before a plane can come to pick us up. Then we do have a chance to look around."

He describes otherworldly sights, such as sastrugi – grooves in the snow formed by wind erosion – and snow particles that the wind rolls along the surface, forming crystalline lumps that create striking light effects when the sun shines on them. At coastal stations in Antarctica he's seen Weddell seals, emperor penguins and their chicks, and the special type of black moss that appears on the rocks during the summer. Then there is the grandeur of icebergs floating past – so large that they're often visible several kilometres out to sea. "It might not happen often, but it's good to have those opportunities every now and then," he says. "To stand back and really appreciate where you are."

[1] Willerslev E *et al.* (2007) Ancient biomolecules from deep ice cores reveal a forested southern Greenland. *Science* 317:111-114. DOI: 10.1126/science.1141758

Science at sea

A talent for organisation has taken EMBL's Steffi Kandels-Lewis across the globe

BY EDWARD DADSWELL

It's the weekend. You're sailing in sunlit waters. You moor your boat and take a dinghy to the shore, where you have a beer with your friends. You're on one of the Marquesas Islands, part of French Polynesia in the South Pacific. You're here to meet Bernard – a local tattoo artist – who has already tattooed some of your friends, and today will give you a tattoo as well. Your first. You sit on the terrace of Bernard's home, the jungle all around you, as he inks the design into your foot. Two figures riding a wave.

In French Polynesia, local tattoo artist Bernard prepares the design for Steffi's tattoo.

This is how EMBL's Steffi Kandels-Lewis spent a Saturday morning in August 2011, when she was a crew member on the schooner *Tara* as part of the Tara Oceans expedition. She'd arrived a week earlier, joining *Tara* in the harbour on Nuku Hiva, the largest of the Marquesas Islands. "When I got there I was told, 'Oh, everybody's off getting a tattoo, and when are you getting yours, Steffi?'" she explains. "I said, 'I'm not getting a tattoo, no way!'" Her friends kept working away, however, saying they'd buy her a tattoo for her birthday, which was just a few days later. "In the end what convinced me was the feeling that I wanted something to remember this journey by," she says. "Spending a month on this boat in the South Pacific was a huge challenge for me – I thought, 'I'll probably never do something this crazy again in my life!' And I didn't want to get a tattoo just in a studio somewhere, so this was a unique place and gave me a story to tell. It's a very special thing."

Filling in the details

Launched in September 2009, the Tara Oceans expedition was a four-year project that collected around 35,000 seawater samples from various depths and locations around the world. Analysis of these samples, including imaging of the organisms present and sequencing their genomes, has provided an unprecedented insight into ocean biodiversity – particularly at the microscopic level – allowing scientists to better understand the role of plankton in regulating the Earth's climate, and to observe the effect of climate change on marine ecosystems such as coral reefs. Kandels-Lewis was the operations manager for the project, a role that involved coordinating the collection of samples from the boat and their subsequent distribution to research labs in Europe and the United States. Every six weeks she travelled to meet the boat in whatever part of the world it was located, collecting the most recent samples and bringing new equipment and consumables.

Trying to manage this process, often in very remote parts of the world, was no easy task. Some of the samples needed to be kept at low temperature, so Kandels-Lewis often had to arrange for several hundred kilos of dry ice to be shipped there with her, since many of the places where the boat stopped had no local supplies. Then there were the challenges of dealing with customs paperwork, which typically had to be completed three weeks in advance. "The people in customs want to know how many millilitres of seawater you're sending, how >>

Steffi on board *Tara*.

PHOTO: S. BOLLET/TARA EXPEDITIONS

Tara set sail around the world for four years during the Tara Oceans expedition.

"For me the real curiosity is the relationships between people, and how they work together"

>> many millilitres of ethanol, how many millilitres of formaldehyde, so you need to know all of that," explains Kandels-Lewis. "And if you tell customs you're sending 32 boxes and you end up with only 30, you have to create two fake boxes because otherwise they won't let you send any of it!"

Dreams and reality

Trained as a molecular biologist, Kandels-Lewis came to EMBL in 2001 to manage the lab of Eric Karsenti, then head of the Cell Biology and Biophysics Unit. "Eric loves sailing," she explains. "He'd read Charles Darwin's book about the voyage of the *Beagle* and he was telling me for eight years that he wanted to do something similar." Finally, in 2008, Karsenti announced that he'd found a boat: *Tara*. Kandels-Lewis saw it for the first time that year, in the French port of Villefranche-sur-Mer, where she met some of the team Karsenti was assembling. She recalls the doubts she had about getting involved. "Eric told me, 'You just need to do what you do for the department.' Well, the department was not so difficult to run! I knew how to set up a lab, but I'm not a marine biologist and I felt like I had no idea about this project. Then, after a while, I realised that no one had any idea!" she says, laughing. "So I thought, 'Well, I'll just keep doing this until someone tells me to stop.' And no one ever did – I think they were just happy that there was someone there to start organising things. It's a miracle that we got our act together but everybody was very motivated and we made it work."

Alongside her work on the logistics of collecting and distributing samples, Kandels-Lewis ended up organising many other aspects of the project, including meetings, contracts, finances, team rotations, and flight bookings. "I would get phone calls in the middle of the night," she says. "So-and-so is not at the airport or not on the boat. I arranged the flights, I knew where everybody had to be and when." Though she insists that she's not a qualified project manager, it's clear that Kandels-Lewis is a formidably organised person. "I don't just have a Plan B, but often a Plan C, D, E, F, and G," she says. "I don't want to end up in a situation where I'm confronted with a problem and I don't have a solution, so I always have at least three – just in case."

As she discusses the challenges of coordinating the project, it becomes clear what a good pairing she and Karsenti make. "Eric had been talking to me about this for eight years. I just thought, 'Oh yeah, let him talk!'" she says with a smile. "But, to be honest, you have to be a dreamer.

You need to have someone crazy like Eric, because if you're organised and structured like me you just think, 'We can't do this – there's no money, we don't have the right people, we don't have a boat, we don't have this, we don't have that.' Eric was always over-optimistic – he'd just say, 'OK, let's go!' You need people like that to move forward. Everybody trusted him and believed in him and somehow it all worked."

Psychological depths

For Kandels-Lewis, the most fascinating thing about Tara Oceans was not finding out what was hidden in the deep sea, but rather what was going on beneath the surface of the project's human relationships. "Of course I'm interested in the discoveries we've made, and I've learned a lot – I know that if you jump into the water you're entering this soup of viruses and bacteria and other creatures," she says. "But for me the real curiosity is the relationships between people, and how they work together. I've learned a lot about psychology – it's not something I have any training in, but I've gained a lot of life experience, let's say."

When she visited the boat, people would often see her as someone to whom they could vent their frustrations. "They weren't really connected to people on land – they received orders and often didn't understand the context because the communication was all by email," she explains. "Every time I went there, people wanted to know what's going on, or there were problems because not everybody liked each other on the boat. It was a community with its own dynamics, confined in a very small space."

Unexpected turns

This was a significant concern for Kandels-Lewis when she herself spent time as a crew member: once for four weeks in the South Pacific, sailing from Nuku Hiva to Papeete, and another time for three weeks sailing from Savannah, Georgia, to New York City. "I was worried about being with so many people in this small space," she says, "but actually I really liked the sense of community on board. I made some good friends I never would have met otherwise. But it's very difficult to explain – it's something you have to experience." When they sailed the boat to Manhattan it was New York Fashion Week, and everyone on board was invited because the expedition was sponsored by the French fashion designer agnès b. "It's like you've been completely isolated, and then suddenly everybody's looking at you, everybody's talking to you," explains Kandels-Lewis. "We'd all grown together as a community on the boat and then all of a sudden we were mingling with these fashion types and photographers, feeling totally exposed. It was very strange."

Despite these occasional problems in adapting to life on and off the boat, Kandels-Lewis makes it clear how much the experience of working on Tara Oceans means to her. "It's left me with so many incredible memories. I never would have imagined getting involved in something like this because I'm not an adventurous person – this is really not me at all. I'm not someone who takes a backpack and hikes through the Andes or something. I need to be pushed, and I'm very happy that I got certain pushes because this project has given me enough experiences for three lifetimes and I'm so grateful for that."

PHOTO: C. GUIGUAND/TARA EXPEDITIONS

Samples collected during the Tara Oceans expedition have already led to important genetic and environmental discoveries.

Science in space

PHOTO: NASA

Above New Zealand, two astronauts work on constructing the International Space Station in 2006.

EMBL alumna Sigrid Reinsch trained as a cell biologist – now she helps run experiments in space

BY EDWARD DADSWELL

It's the weekend. You're indoors, working on a job application. Outside, there are voices and cars, the broad blue of the San Francisco Bay, and – a few hundred kilometres up – the silence of low Earth orbit. At that altitude, there's not much: some tenuous air, the occasional piece of space debris, and a lone space station – Mir. Inside, an astronaut drifts over to inspect some wheat seedlings growing in a small steel chamber under artificial light. These plants will help determine whether humans on long-term exploration missions might one day feed themselves by growing crops in space.

For now, you have more worldly concerns. You need to feed yourself and your young family – not by growing crops in space, but by finding a job on Earth. The position you're applying for is at NASA, where big things are in progress. Some 3,000 km to the east of you in Huntsville, Alabama, work is being completed on the Unity module – the first US-built component of what will become the International Space Station (ISS). When Unity is launched and joined to the Russian Zarya module later in the year, the ISS – and its programme of scientific research – will start to become a reality. A job at NASA ought to be an exciting prospect, but somehow you're not convinced it's the right thing.

Problems on Earth

That was the situation for EMBL alumna Sigrid Reinsch in the spring of 1998, when she was coming to the end of a postdoc position at EMBL in Heidelberg. After six years living in Germany, she was looking for a job back in her home country. "I applied for tons of university positions in

the US and none of the applications worked out," she says. "I ended up going on a US tour and trying to figure out what other types of jobs I could do. In desperation, I was hanging out in a friend's office in San Francisco and she told me about this job at NASA."

"EMBL was like the Disneyland of biology – any experiment you could think of, you could do"

At that time NASA was looking to expand its space biology programme, a major component of which is research relating to long-duration spaceflight. This includes experiments to determine the effects of radiation exposure or weightlessness on humans and other organisms. Most of NASA's space-borne biological experiments were being carried out on Mir and on Space Shuttle missions, gradually transferring to the ISS following the arrival of the first crew in 2000, the deorbit of Mir in 2001, and the end of the Space Shuttle programme in 2011. When Reinsch was applying for a job in 1998, NASA was aiming to recruit more scientists with training in cell and developmental biology.

The position she applied for was for someone with experience of research on the cytoskeleton – the network of protein filaments and tubules that gives cells their structure, and which is involved in processes like organising the cell's contents, cell migration, and cell division. The cytoskeleton had been the subject of Reinsch's PhD and her subsequent postdoctoral work in Eric Karsenti's group at EMBL, so she decided to apply. She was keen on the biological research aspect of the job, but had no particular interest in spaceflight experiments. "I felt very strongly that we have enough problems on Earth that we should focus on," she recalls, "rather than doing experiments in space."

Reorientation

Almost twenty years after accepting a job offer from NASA, things are a little different. "My opinion has changed," says Reinsch with a smile. Initially her work at NASA involved research on the clawed frog *Xenopus*, an important model organism in biological studies. This included research on the development and functioning of the vestibular system – that part of the inner ear that assists with balance and spatial orientation, and which is often disturbed in conditions of weightlessness. Later she worked on projects focusing on the development of biofuels, which NASA is considering as a possible energy source for long-term human space exploration. Since 2014, she's been involved in the GeneLab project, which aims to maximise the scientific return from experiments carried out on the ISS. "The purpose of GeneLab is to get the biggest bang for the buck out of any spaceflight experiment," Reinsch explains. "We don't change the funded, peer-reviewed proposal for an experiment but we investigate whether we could carry out additional analyses or add components to augment the experiment in some way."

An important component of GeneLab is an open access database to house various types of biological data, not only from spaceflight experiments but also from ground-based experiments with important implications for space research, such as experiments that simulate weightlessness or study the effects of radiation. "The database is very easy to use," says Reinsch, "and it's designed to encourage collaboration between research groups."

EMBL alumna Sigrid Reinsch

Taking on tardigrades

While much of Reinsch's early career involved research on frogs, she's recently branched out into working with various invertebrate species, including tardigrades. These are microscopic creatures typically less than a millimetre long that live in almost every environment on Earth, including deserts, the deep sea, and the poles. They're famous for being able to enter a state of suspended animation by vastly reducing the water content of their bodies. This allows them to survive extreme conditions including temperatures just a degree above absolute zero and higher than the boiling point of water, pressures many thousands of >>

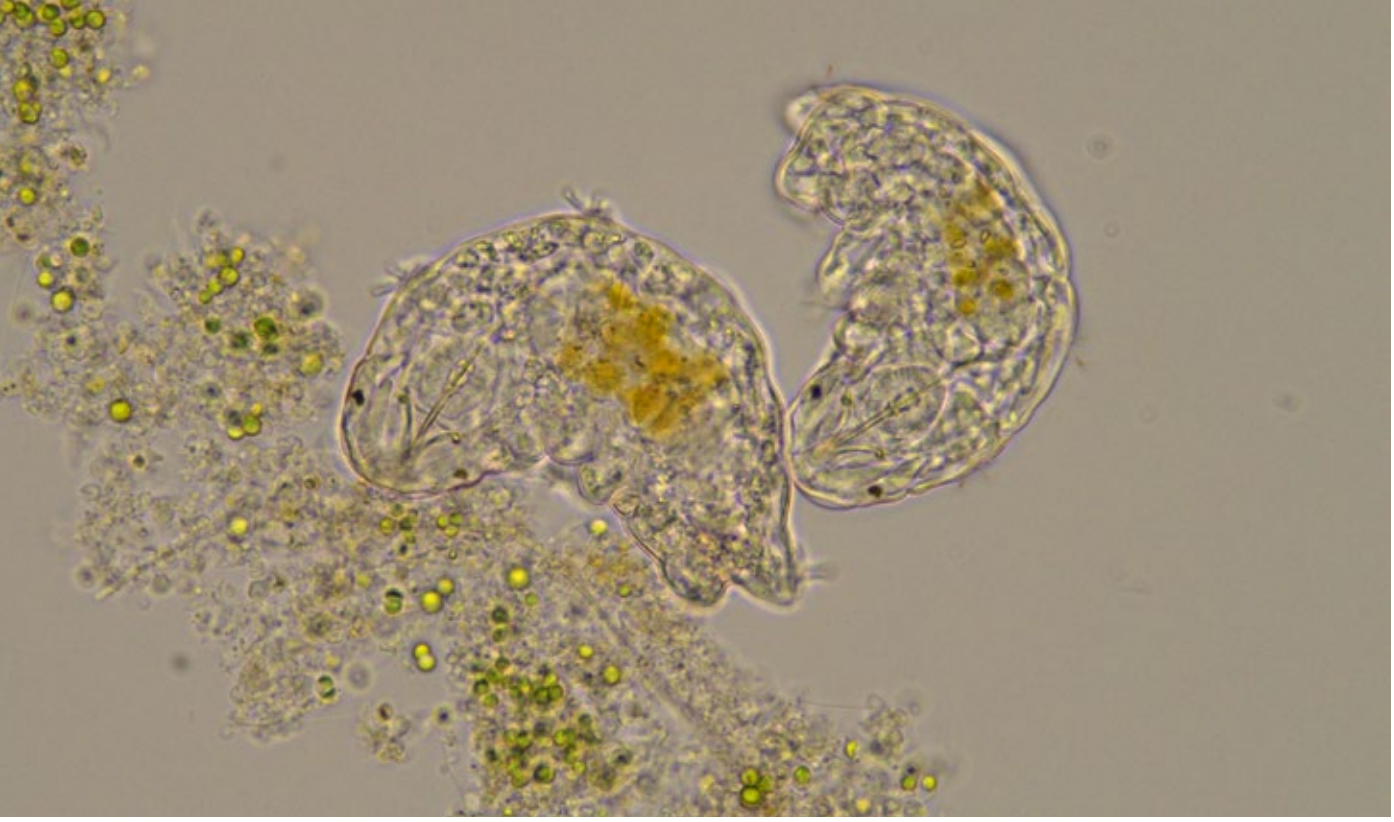

PHOTO: SIGRID REINSCH

Tardigrades are the only known animal to have survived the vacuum of space. In this ground-based microscope image, a recent meal of green algae is visible through the tardigrades' transparent bodies.

>> times higher than atmospheric pressure, and radiation levels that would be fatal to most animals. They're also the only animal to have survived the vacuum of space, as demonstrated in an experiment carried out by the European Space Agency (ESA) in 2007.[1]

This extreme resilience, and the biological mechanisms behind it – such as an ability to protect DNA from radiation damage, or repair it afterwards – make tardigrades an interesting animal for scientists seeking a way to help humans and other organisms tolerate long-duration spaceflight. An understanding of the limits of endurance of terrestrial organisms can also assist astrobiologists in identifying places to search for life in other parts of the solar system.

Reinsch's work with tardigrades came about when she was asked to explore alternative uses for a piece of ESA-designed hardware known as the European Modular Cultivation System (EMCS). Reinsch and her colleagues demonstrated that the EMCS – originally designed for plant growth experiments – could successfully support a range of other organisms including bacteria, brewer's yeast, *Dictyostelium* – a type of slime mould, nematode worms, and tardigrades. "That's how I got into working with tardigrades," she explains, "by taking this cool piece of hardware and saying, 'OK, besides plants, what else can we use it for?'"

"My curiosity is hard to corral"

Reinsch is currently technical monitor for another experiment involving tardigrades, led by Tom Boothby at the University of North Carolina. Boothby's experiment will monitor both immediate and long-term changes in gene activity over several generations of tardigrades living on the ISS. The hope is that understanding the genetic changes that allow tardigrades to cope with the stresses of spaceflight will help in developing methods for humans to more safely spend prolonged periods in space.

A different kind of science

Research in space presents many challenges. The chemicals that might be used in a typical lab experiment are not all approved for experiments on the ISS, and many levels of containment are required to ensure that chemicals can't escape. And something as simple as liquid transfer becomes a major problem. "In microgravity, a droplet won't drop into a container, so you need a syringe-like apparatus to transfer liquids," explains Reinsch. "Spaceflight experiments also have to be very minimalistic. The astronauts on the ISS don't have a lot of time to devote to experiments, so in large part the experiments have to be able to run themselves. You also have a limited number of samples and you don't get a chance to run the same experiment multiple times. You really have to plan effectively and anticipate any problems that might occur."

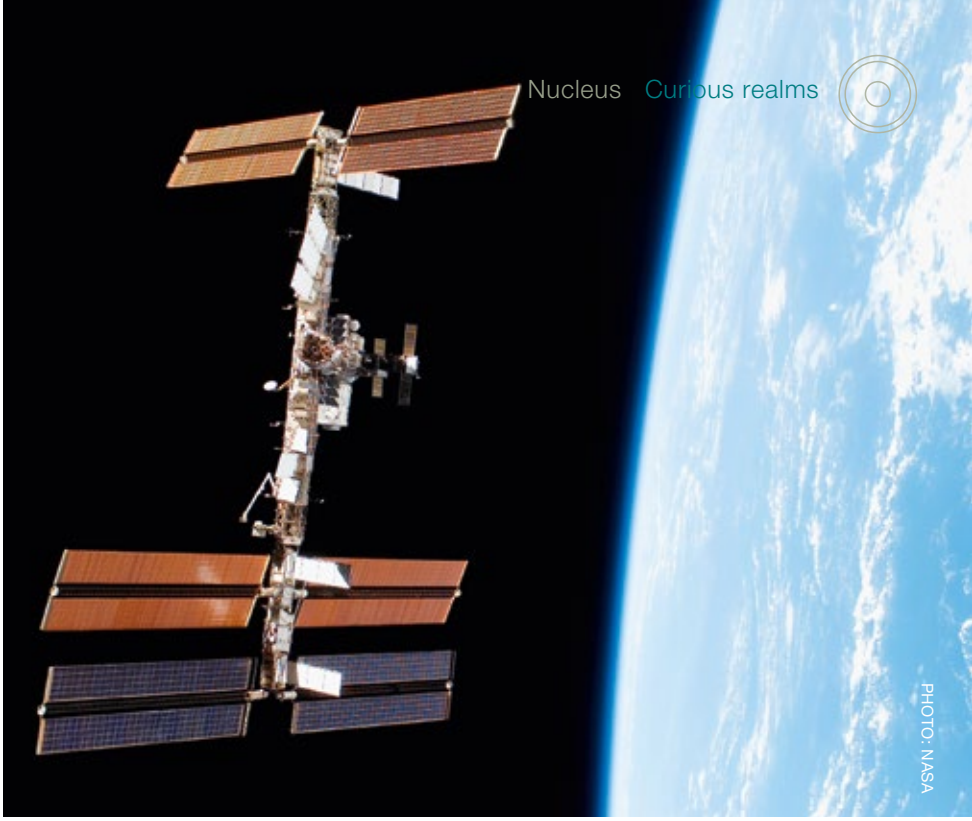
PHOTO: NASA

Floating approximately 400 km above the Earth, the International Space Station provides a platform for scientific research in space.

For Reinsch, this approach to science has definitely required some adjustment. "I had a great time working at EMBL. To me, it was like the Disneyland of biology – any experiment you could think of, you could do," she says. "With spaceflight research there are all these extra constraints you have to deal with. I've had to learn how to do science in a very different way."

When asked if she'd like to be one of the astronauts up there doing experiments, Reinsch remains practical. "In my mind, yes; in my body, no. I have problems just going on a boat, so I think I'd find it difficult dealing with the disorientation of being in space. Also, the fluids in your body migrate upwards because they're not pulled down by gravity, so you have a lot more fluid in your head than you're used to. I'm already prone to headaches so I think that would be a really bad idea for me," she explains. "But if I could go and not have any of those physical problems, of course I'd love to. It would be very cool."

Despite her initial scepticism about spaceflight research, Reinsch is now enjoying the role she plays in getting the best science from the ISS, and is keen to see what discoveries will emerge. "There are so many things I want to know, let me tell you," she says. "My curiosity is hard to corral, and NASA is a great place for someone with a curious mind. Studying life is really wonderful and always continues to astound me. Getting to do that is the best thing that could ever happen to me."

[1] Jönsson K I *et al.* (2008) Tardigrades survive exposure to space in low Earth orbit. *Curr Biol* 18:R729-R731. DOI: 10.1016/j.cub.2008.06.048


PHOTO: NASA

ESA astronaut Samantha Cristoforetti retrieves samples from the Cell Biology Experiment Facility on the ISS.


PHOTO: NASA

NASA astronaut Michael López-Alegría replaces the experiment container for the European Modular Cultivation System on the ISS.

PHOTOS: MARIETTA SCHUPP/EMBL

Behind the scenes in the Fly Room

Lab manager Anna Cyrklaff takes a tray of fly specimens to be transferred into new vials.

Curious about what goes on in EMBL's Fly Room? Prepare to be a fly on the wall

BY EDWARD DADSWELL

One of the most intriguingly named rooms at EMBL in Heidelberg is the Fly Room. Inside, all of one wall and most of another are filled with shelf upon shelf of vials, each containing *Drosophila melanogaster* – the common fruit fly. Alongside the shelves are a series of workstations equipped with microscopes and paintbrushes. Seated at one of these workstations, EMBL staff scientist Imre Gaspar takes a vial of flies and a handheld instrument that looks like a smaller version of the nozzle you use to fill your car with petrol. Instead of dispensing fuel, however, this nozzle emits carbon dioxide. Gaspar slides it past the cotton wool stopper on the vial and uses it to anaesthetise the flies inside, so he can study them.

"This used to be done with anaesthetics like ether," says Gaspar. "I've used ether on flies in the past but after a while it can make you feel dizzy, so carbon dioxide is a better choice. It temporarily anaesthetises the flies, so they lay motionless under the microscope. You can then use a paintbrush to sort the flies according to whether they have the characteristics you want."

Working with flies

If researchers want to understand what a particular gene does, they often need to study a fly strain that's

missing a copy of that gene, or has a mutation in it. Usually this won't cause any visible change to the fly, so changes to the fly's genome are made with an associated marker gene that does have a visible effect. There are various commonly used marker genes, including ones that produce white eyes (fruit flies normally have red eyes), notches in the ends of the wings, or wings that curl upwards, away from the body. The sorting process with a microscope and paintbrush can therefore be carried out by looking for these changes in the flies. The selected flies can then be studied, or crossed with other flies to create a new strain.

These fly strains are used by many research groups at EMBL, most often to understand aspects of fly embryo development, which is coordinated by a precise sequence of interactions between parts of the fly's genome and its associated proteins. While flies might seem far removed from humans, the process of embryonic development is similar across the animal kingdom, and many other fundamental cellular processes are similar too. Research on flies can therefore provide important insights into the way human embryos develop, and the way our cells behave.

Because of this close link to development, the Fly Room is located in and run by the Developmental Biology unit at EMBL, but the flies that are bred here are used by fly researchers across EMBL.

Fundamentals of flykeeping

One important aspect of looking after flies is giving them the right food. In another part of the building, EMBL has a Fly Kitchen with dedicated staff responsible for fly food preparation. "Apart from some antibacterial compounds, most of the ingredients for the fly food are things you can buy in an ordinary grocery store," explains Gaspar. "Things like yeast, malt extract, and apple juice. These are then mixed with agar and poured into vials, so the food turns into a gel as it cools. The vial is then ready to house and feed a new set of flies."

"You can use a paintbrush to sort the flies"

Other important considerations are temperature and humidity. Ensuring that these are carefully controlled is one of the responsibilities of lab manager Anna Cyrklaff, who has run EMBL's fly facility for almost twenty years. Aside from the main Fly Room, EMBL has several fly stock rooms that need to be kept at different temperatures – some at 18 °C, others at room temperature (around 21 °C), and others at 25 °C. "Stocks that are less important can be kept at 18 °C," explains Cyrklaff. "They still survive but the time taken to produce each new generation of flies is longer and the stocks require less attention. On the other hand, fruit flies are most comfortable in the 25-degree room, which is close to their preferred temperature in the wild. There the generation time is around 10 days, so if you need to work as fast as possible, that's where your stocks should go."

The stock rooms need to have a humidity of around 50-60%. If it falls below that, flies lay fewer eggs and generally don't live as long. "In the summertime the humidity often gets too high, so we might have to add more agar to the fly food to absorb water," explains Cyrklaff. "And in the winter it can get too low. Usually we deal with this by adjusting the climate control system in the stock rooms, but in extreme cases you can add water to the trays where the vials are stored, to bring the humidity back up."

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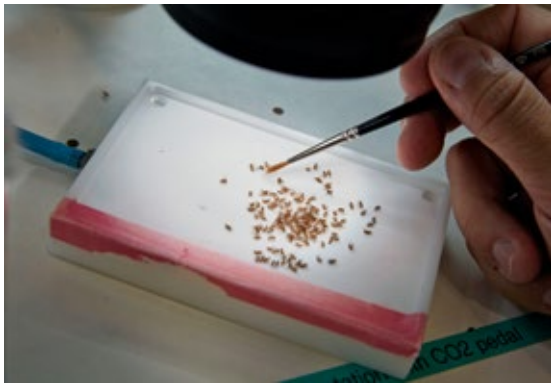
Staff scientist Imre Gaspar examines fly specimens.



After the flies have been anaesthetised with carbon dioxide, a paintbrush is used to sort them under the microscope.

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Flipping flies

Another requirement for looking after flies is regularly 'flipping' them into new vials. This ensures that they have fresh food and that their waste products don't build up inside the vial. Experienced practitioners like Cyrklaff and Gaspar are able to do this without allowing any flies to escape. They tap the vial on a table to make the flies fall down to the bottom, then quickly take out the stopper, tip the flies into a new vial, and put a stopper in it. This process needs to be repeated regularly – more often at higher temperatures where the flies are breeding more rapidly. At 18 °C it needs to be done every six weeks; at room temperature, every 20 days; and at 25 °C, around every 10 days.

Alongside the stocks of fruit flies that are kept in vials, Cyrklaff also regularly creates fruit fly population cages – larger containers holding many thousands of flies. These are used when EMBL researchers – whether in Heidelberg or at other sites – require large numbers of fly embryos to study.

Has working so closely with flies made Cyrklaff and Gaspar look any differently at flies outside the lab? "Because of their various mutations, our laboratory stocks tend to be much less resilient than flies in the wild. Sometimes it's very hard work to maintain them, so you do feel a kind of pride when you see that a stock has produced many larvae and they're looking healthy," explains Gaspar. "But that only applies in the lab. If I saw the same thing in my kitchen, I'd be disgusted!"

Cyrklaff agrees. "We definitely don't enjoy breeding flies at home!"

What bizarre flies have taught us

Rules for development, lab-made genes and the effects of radiation: what researchers have learned from fruit fly research

BY SONIA FURTADO NEVES

Flies with oddly-coloured eyes, flies with multiple pairs of wings, flies with legs on their head. Since the early 20th century, scientists have been creating curious-looking flies. These flies were bred not because of some fascination with the bizarre, but for what they could tell us about how traits are passed from parents to offspring, how embryos develop into adults, and how our environment affects us. From chromosomes to courtship dances, here are some examples of what humans have learned – and are still learning – from fruit flies.

The genetics of behaviour

Male fruit flies court females. They dance, tap the female with their front legs, play her a song. And it all seems to be driven by a gene called fruitless, which is processed differently in males and females. Humans don't seem to have a fruitless gene. But just like the general rules that govern development hold true for flies and humans, scientists investigating the fruit fly gene could uncover general principles that apply to our own neurons and behaviours too.

PHOTO: KIM (CC-BY-NC-ND 2.0)

White-eyed flies helped scientists understand that genes are housed in chromosomes.

What genes are

In the early 20th century, Thomas Hunt Morgan noticed that among the common, red-eyed fruit flies in his lab was a male with white eyes. By breeding white-eyed males with red-eyed females and looking at the eye colour of their descendants, Morgan and colleagues deduced that the gene that caused flies to have white eyes must sit on one of the sex chromosomes. This was before anyone knew what chromosomes were made of – a time when genes were a concept that hadn't been pinned down to a physical entity. The discovery of white-eyed flies sparked the notion that every gene is carried on a specific chromosome.

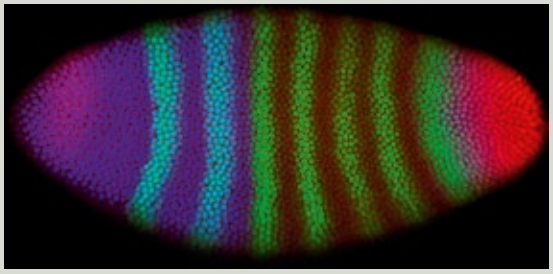

IMAGE: FLYEX (CC-BY-NC-ND 2.5)

A stripy pattern in a fruit fly embryo revealed the role of enhancers in switching genes on.

IMAGE: KAROLINSKA INSTITUTE

The gene that controls how many wings a fruit fly has also determines how many fingers you have.

How genes are controlled

One of the genes that drive fruit fly development is called even-skipped (shown above in green). When EMBL alumni Christiane Nüsslein-Volhard and Eric Wieschaus looked at flies with mutations in even-skipped, they saw a striking pattern: normal segment, faulty segment, normal segment, faulty segment. Years later, this gene was one of the first that scientists were able to stain with fluorescent markers, to track it under the microscope rather than just looking at its effects. This new view brought another tantalising pattern into focus: even-skipped lit up in seven stripes across the embryo. After decades of research, scientists have found that each stripe has a dedicated genetic switch, called an enhancer, which switches this gene on. This showed that enhancers can create patterns and order in development, by activating genes at the right time and place. But if they act at the wrong time or place, they can also spur disorder, like the uncontrolled growth of a tumour.

Making genes in the lab

Advances in the field of synthetic biology mean that scientists can now think beyond simple effects of mutations. Justin Crocker's lab at EMBL, for instance, created this wingless fly, below, by giving it an artificial, lab-made gene. Their aim is to study more nuanced situations, where a trait is controlled by balancing and fine-tuning many different genes. If the approach works, as scientists learn more and techniques continue to advance, there may come a day when an artificial gene could be used not to generate a strange-looking fly but to treat a sick person.

Given all these useful insights curious flies have given us over the years, it's not surprising that this year's Nobel Prize for Physiology or Medicine was the sixth time the accolade honoured research on fruit flies.

PHOTO: JUSTIN CROCKER/EMBL

Justin Crocker's lab at EMBL created this wingless fly by giving it an artificial, lab-made gene.

Effects of radiation

In an effort to understand what genes were, scientists turned to X-rays. They exposed flies to radiation, and looked for evidence that individual genes had been altered. What they found was evidence of the damaging power of radiation, not just to those exposed but also to their offspring. Hermann J. Müller, one of the pioneers of this approach, created 100 different mutant fly types in less than a year. Those mutants are part of the reason why today there are safety measures in place around radiation sources, from CT scanners to nuclear power plants. They also raised the prospect of intentionally manipulating genes to control a baby's traits.

Normally, fruit flies have only one pair of wings. But if a fly has a mutation in a gene called ultrabithorax, it will have two pairs of wings. This gene is one of several that ensure a fly's body parts have the right appendages, and are arranged in the right order, from head to tail. Humans also have these genes, and they seem to act in a similar way in our body, controlling things like the development of the brainstem and the inner ear, or how many fingers and toes you have.

PHOTO: ISTOCK

ILLUSTRATION: SPENCER PHILLIPS

A smart cabinet of curiosities

How open data is changing our pursuit of discovery

BY OANA STROE

In the 16th Century, a cabinet of curiosities (in German: *Wunderkammer*) was a popular way to show off one's private collection of extraordinary objects. Animal specimens, skeletons, minerals, unusual handmade objects and intriguing antiquities from the New World could all be revealed with a flourish, and rouse in visitors a keen sense of curiosity in this new Age of Wonder.

Over time, cabinets of curiosities morphed into modern museums. Both feed two profoundly human tendencies: curiosity, and the desire to collect and preserve knowledge. Today, these same tendencies are driving a sea change in science: disruptive technology, a tsunami of data and the democratisation of data access.

Now, curious visitors to EMBL-EBI data resources can gaze into a new kind of menagerie: the wonders of the molecular world, carefully tended in public databases that anyone can access.

"A collection of physical objects makes you feel something straight away..."

A collector's view

So how has the database changed the way we collect and make sense of data? "The first obvious difference between a cabinet of curiosities and a database is the content," explains Jee-Hyub Kim, Data Miner and EMBL-EBI alumnus. "On the one hand, a collection of physical objects makes you feel something straight away. Just imagine what it must have felt like for someone who may have never even seen the ocean, to see and touch a starfish or coral – these objects must have looked so alien!

"It's difficult to create this sort of rapport with something as intangible as data. That's why you need a good interface and visualisation tools – to allow the user to explore and interact with a dataset or a digital object."

Visualisation is a very powerful thing: being able to "see" connections inspires people to keep exploring. The people who build EMBL-EBI data resources understand this, and strive to build interfaces and visualisations that keep researchers engaged.

One example is the Protein Data Bank in Europe (PDBe), a resource for collecting, organising and disseminating data on macromolecular structures, such as proteins. Apart from being a central repository for scientists studying proteins, PDBe allows users to see and interact with digital, 3D models of proteins.

A recent update to PDBe takes these gigantic files, which often exceed 10GB for a single digitised protein, and reduces their size by up to 500 times. This means that if you want to see how a molecule interacts with a protein, you can bring up a visualisation on any Internet-connected device. That includes phones and tablets, which allows many more people throughout the world to explore PDBe and use it as a learning tool. >>

"The sublime combination of high-tech visualisation, collaborative software programming and open data is truly democratising biology"

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A multidimensional cabinet

"Traditional cabinets of curiosities organised items by type, so in a sense they were like an ontology of shapes, because they classified artefacts according to what they looked like," says Chuck Cook, Scientific Services Manager at EMBL-EBI. "You could draw a parallel with the modern database, which organises biological data resources in a similar way – into categories. In the database, information and categories are interlinked, so in a way the database is like a 'smart' or multidimensional cabinet of curiosities."

Even as technology advances at breakneck pace, science is more accessible than ever. The sublime combination of high-tech visualisation, collaborative software programming and open data is truly democratising biology.

"With a traditional cabinet of curiosities, the collector was the ultimate authority," adds Andy Yates, Team Leader of Ensembl Genomics Technology Infrastructure at EMBL-EBI. "EMBL-EBI keeps its 'collections', or services, open to researchers everywhere. In doing so, we're making the contents – and ourselves – open to reanalysis and review. It's a necessary move if we want our resources to be truly useful.

"We work within the scientific community, and that means we are open to critique – at a speed that would have been unthinkable even 15 years ago. Previously, we would have probably published the latest version of the Ensembl genome browser on a CD, sent it off in the post and that was it. There was no instant feedback, no self-regulation, nothing. It's only in the past few years that this kind of openness has become workable, due to improved communication channels, and now it is actually expected by our users."

Opening up the cabinet

"Data accessibility is crucial for anybody doing science, which is a massive change," continues Yates. "Cabinets of curiosity were private collections with limited accessibility. Some owners opened their doors to the public, but it was still only a small number of artefacts – the most peculiar ones – that were on display. Most things were indexed and locked away."

EMBL-EBI hosts many tens of petabytes of data, and a big part of its work relates to making datasets easy to find. Without indexing, there is no way of knowing what is in a database, or how it got there. Indexing is as central to public data resources today as it was to early collections.

Data curation and annotation activities are intense at EMBL-EBI. Once you have generated a sequence and identified a gene, you have to search that gene against a huge amount of pre-existing data. The curation process includes labelling and describing datasets consistently so that any researcher can discover and make use of the data for their own experiment. This helps research communities build knowledge and make connections between different studies and disciplines. Without descriptions – also called metadata – samples and sequences are cast adrift in a sea of data. "Without metadata, exploring a database is like wandering through the basement of the Louvre blindfolded, hoping you'll find the Mona Lisa," says Yates.

Asking questions

So how is data availability changing the way we answer scientific questions? According to Chuck Cook, "people are going to become more dependent on big data, and scientists who can't use big data will be left behind professionally. As we become more specialised, running isolated experiments is becoming more difficult. To delve deeper into research, we will need to collaborate with people from lots of different backgrounds. And to do that we need a common language – that's something we are actively working on."

"Biologists have to turn into programmers, to a certain extent," agrees Yates. "That's how the scientific questions are changing. The researcher will come up with a hypothesis and then prove or disprove it through data mining of large data resources. That requires some degree of programmatic knowledge. The questions may be similar, but they can be much more complex. We will still repeat, and repeat, and repeat our questions and analysis, gently refining the answers we get."

"The time it takes to go from scientific discovery to application is becoming much shorter," adds Rob Finn,

Team Leader for Sequence Families and EMBL-EBI's Metagenomics resource. "This is partly because the data is connected, so you get the whole biological context rather than just looking at one thing in isolation. That means you're better informed to design your next experiment."

"The time it takes to go from scientific discovery to application is becoming much shorter"

Finn is no stranger to exploration. He is involved with data from the Tara Oceans expedition, which sailed a research schooner more than 300,000 kilometres in a four-year journey covering the world's oceans. Scientists on the voyage systematically collected samples of plankton from all the world's oceans and shipped them back to land for DNA sequencing and analysis.

"Sequencing the samples from Tara lets us 'see' some of the diversity of life in the oceans," continues Finn. "The first set of 40 million genes identified in Tara Oceans samples are mainly from prokaryotes – bacterial species we haven't seen before. But in the second wave of data, we have identified over 117 million eukaryote genes so far – and there is still a long way to go. There's a huge amount of genetic data to study out there. What do all these genes do, what species do they belong to? How does it all fit into the bigger picture? Those are the really intriguing questions we'll be exploring for years to come."

Mapping the life sciences

In light of this ever-growing influx of data, what are the big challenges facing biology in the coming years? "The big change I see in biology is that molecular scientists now have the capacity to look genome-wide and species-wide," says Janet Thornton, Director Emeritus of EMBL-EBI and Senior Scientist. "Before open data, a scientist worked on one protein, gene or experimental system, possibly for their entire career. Seeing the bigger picture was practically impossible. Today, we can make genome-wide and species-wide observations.

"It's like before the world was mapped – we are only just properly mapping biology now"

"This shift also poses the biggest challenge, which is that, despite the unity of biology (in that all living systems are coded by the genetic code), truly important discoveries in biology still lie within the nitty gritty details. In genomics, we have seen the impact of technological development to drive innovation. Certainly, recent developments in imaging for cell biology will allow researchers to develop high-throughput experiments that change the questions we can ask.

"Biology is still in the discovery phase, and slowly moving into the theoretical explanation phase. There is so much left to understand. As always, our science will follow the 'Map, Quantify and Model' roadmap. It's like before the world was mapped – we are only just properly mapping biology now. Initiatives like the Human Cell Atlas are shedding light on some of the missing details we need to understand before we begin to explain how things work. The next step will be to translate this knowledge into everyday areas, such as medicine, agriculture and biodiversity."

Tools for a curious mind

Much like the collectors who set up the first cabinets of curiosities, scientists are still meticulously cataloguing everything they learn about the form and function of life. But at EMBL-EBI, the work is about more than just recording and describing data. Linking it all up to facilitate further discovery is another area of intense focus.

By working with users, helping set standards and curating data, EMBL-EBI creates resources that other scientists can build on well into the future. EMBL-EBI's 'smart' cabinet of curiosities spans all of molecular biology. From microbes to population-scale, genome-wide studies, the institute makes data from biological discoveries open and accessible to anyone with an Internet connection and a curious mind.

MORE ONLINE:
BIT.LY/emblebiservices

CSSB: A new approach to studying infectious disease

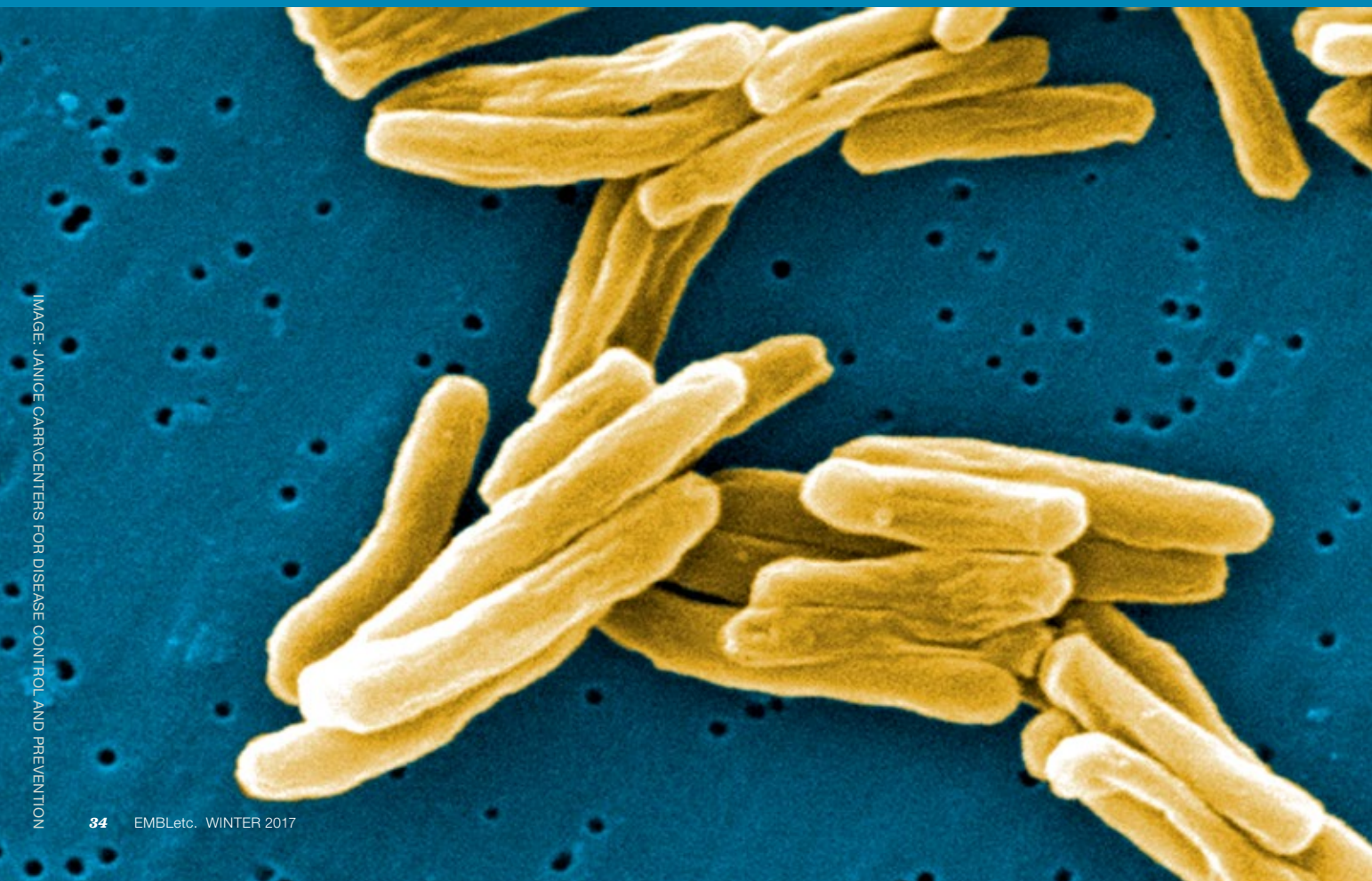


IMAGE: JANICE CARR/CENTERS FOR DISEASE CONTROL AND PREVENTION

After years of design and construction, the Centre for Structural Systems Biology (CSSB) is now ready to make its mark as the new kid on the block and tackle some of the most important questions relating to how infections take hold in our bodies

BY ROSEMARY WILSON

Around a quarter of all deaths every year worldwide can be attributed to infectious diseases. Malaria alone results in half a million deaths per year. Other infectious diseases can be even more devastating: tuberculosis claims the lives of around 1.8 million and HIV around 1 million people per annum. A lack of vaccines and increasing resistance of pathogens to antibiotics and anti-viral drugs, mean that the battle to reduce deaths and cut instances of infectious disease is becoming ever more intense.

"Infectious disease is one of the greatest challenges the world faces today," says Matthias Wilmanns, Head of EMBL Hamburg and Centre for Structural Systems Biology (CSSB) scientific director. "From multidrug resistant bugs in our hospitals, to tropical diseases, there is so much we don't know about how pathogens such as viruses and bacteria infect humans."

PHOTO: ROSEMARY WILSON/EMBL

Christian Löw is an EMBL group leader at the CSSB.

Complementary expertise

Taking further steps towards understanding how pathogens hijack cellular machinery and wreak havoc on human health needs large collaboration efforts. Wilmanns and colleagues wanted to take this a step further by bringing together computational, structural and wet lab researchers in a single building with access to state-of-the-art infrastructures. The opening of the CSSB building in June was the realisation of a vision first set out a decade ago.

CSSB is presently a collaboration of nine academic partners from north Germany, each active in different areas of infection biology research. The partners are represented by one or more research groups within the new building on the DESY campus in Hamburg. Together, they will use a combination of structural and systems biology approaches to unravel the fundamental mechanisms of how pathogens infect their hosts. "It is not enough to understand the structure of the miniscule tools that a pathogen uses to infect its host, for example," says Wilmanns. "In order to eventually inform the development of urgently needed new drugs, we need to understand how the tools are built, what other molecules are required to build it and how they all interact with each other. We need to throw all the knowledge and know-how we have together to understand this whole process."

One of EMBL's representatives within the CSSB is group leader Christian Löw. He was among the first to move into the new building after its inauguration. His cosy office on the second floor of the building looks out to a patch of woodland at the heart of the DESY campus. Löw has been heavily involved in shaping the concept and structure of CSSB since he joined EMBL three years ago, an experience he has very much appreciated. Now it's time to focus on the science.

"CSSB is unique in that researchers have access to a simply breath-taking range of different techniques to study the structural details of molecules and cells at different scales of resolution," Löw says. "We have the tools to zoom in to the position of an individual atom within a cellular protein using X-ray crystallography and electron microscopy. We are also able to zoom out and see how components interact within cells and organisms using the latest fluorescence microscopy methods. We want to piece all this information together to get a complete picture of what happens during infection across time and resolution scales."

State-of-the-art

CSSB scientists will use bioinformatics analyses to interpret those snapshots within the context of how infections operate within a host. And researchers housed in the new building are perfectly situated to make use of the immense research infrastructures on its doorstep. "The parallel X-ray beams provided by the EMBL beamlines at the PETRA III synchrotron on campus are extremely intense and precise – ideal for studying the tiny delicate crystals of large proteins," explains Wilmanns. "The development of the CSSB will enable structural biologists to further focus their collective expertise in order to get the most out of these incredible infrastructures." >>

PHOTO: CSSB

Left to right: At the grand opening of CSSB: Oliver Grundei, Helmut Dosch, Bärbel Brumme-Bothe, Matthias Wilmanns, Gabriele Heinen-Kljajič and Olaf Scholz.

>> The building will also host four core facilities using state-of-the-art technologies and equipment. Protein characterisation and crystallisation facilities at EMBL next door have been expanded and upgraded in order to serve both EMBL and CSSB. An advanced light and microscopy facility will be run in cooperation with leading microscope manufacturer Leica microsystems. A protein production facility is in the process of being set up. In addition, an in-house electron-microscopy facility will also become available, with four microscopes set to come online before the end of the year.

Interdisciplinary collaboration

Löw is fascinated by membrane transporters. These large protein complexes sit astride the cell membrane and regulate the traffic passing in and out of the cell – letting important nutrients in and keeping nasty invaders out. Their size and shape mean they are tricky to study using methods such as X-ray crystallography alone. Löw has spent the last few years optimising methods for handling these proteins for crystallography experiments. "Now that we understand how to work with these proteins, we will help other CSSB groups optimise their protocols, as well as widening our horizons to look at how they are regulated and interact within the cell," he explains. Working together with CSSB group leader Tim Gilberger of the Bernhard-Nocht-Institute for Tropical Medicine, Löw plans to investigate a membrane complex that allows the malaria parasite to invade the red blood cells of a human host.

"This membrane complex is fascinating," Löw explains. "It sits across multiple layers of the pathogen cell membrane and is very large. To visualise its atomic structure in high-resolution, we will use multiple techniques including crystallography and electron microscopy supported by Kay Grünewald of the Heinrich Pette Institute. The membrane complex is crucial for the survival of the malaria parasite, so a complete understanding of its structure and biology would enable us to design small molecules to block it, thereby halting the disease."

Even before groups moved into the building, interdisciplinary collaboration within the network – developed during the CSSB's formation – started bearing fruit. Thomas Marlovits, CSSB group leader from the University Hospital Hamburg Eppendorf, uses a range of structural biology methods to study groups of proteins called secretion systems that certain types of bacteria such as *Salmonella* and *E.coli* use to infect their host. Wilmanns teamed up with Marlovits to study a secretion system found in the tuberculosis pathogen *Mycobacterium*. Using a combination of small-angle X-ray scattering and electron microscopy

techniques complemented by biochemical and biophysical studies, the groups were able to reveal the unusual shape of the system and the unexpected position of the complex within the *Mycobacterium* cell membrane. "The results advance our knowledge of how tuberculosis pathogens function," says Wilmanns. "It shows how powerful interdisciplinary studies can be for infection research."

Modelling systems

In addition to space for research groups from the CSSB partners, around one fifth of the building is reserved for a 'research hotel'. Through the initiative, the CSSB provides young group leaders – irrespective of their research organisation – lab and work spaces including access to the core facilities and integration into the CSSB network for an average stay of five years. "Making the transition from postdoc to group leader is not easy," says Löw. "Like at EMBL, the CSSB's research hotel allows young scientists to focus on their science and group members without worrying about financing lab equipment at the same time." Applicants are selected on the grounds of scientific excellence and how their research interests complement the CSSB research portfolio.

A short walk down the hall from Löw, EMBL's Jan Kosinski has just moved into his office as the latest recruit to the research hotel. "I was really attracted by CSSB's vision of integrating structure and systems biology approaches, because this is exactly what I want to do in my own research," he says. Kosinski's expertise is in combining and integrating data from different structural biology methods to develop models of molecules otherwise too large to determine with experimental methods alone. His work is a clear fit for the CSSB. As a postdoc at EMBL in Heidelberg Kosinski used a collection of different structural data to model the atomic structure of one of the biggest molecule components of the cell. "The nuclear pore complex is an important gateway to the cell nucleus, regulating which molecules can pass in and out," explains Kosinski. "We want to know how it does this and how pathogens manage to pass through it."

At the CSSB Kosinski will continue to integrate various data sources to model difficult to study molecules. He's also excited about applying his methods to modelling entire infection pathways in collaboration with other CSSB group leaders. For example his studies will include the influenza virus, the malaria parasite (together with Tim Gilberger) and the herpesvirus (in collaboration with Kay Grünewald). For this he plans to integrate various sets of structural information and systems biology 'big data' from high-throughput experiments such as studies of protein-protein interactions and RNA interference screens. Kosinski only joined CSSB revcently, but has wasted no time getting started. "The CSSB has opened up a whole new range of collaboration opportunities," he says.

Incubating ideas

Kosinski and Löw are keen to put the very special workspace at the CSSB through its paces and get everyone mixing and talking. "We have introduced communal coffee breaks and we plan joint seminar series, a graduate school for CSSB's PhD students, as well as an opening symposium," says Löw.

Communal kitchens, open plan office spaces, shared labs and a large modern lecture theatre – it is clear that the CSSB is a communicative and welcoming space. "It was always important for us to have a physical, rather than a virtual, place to work together," says Wilmanns. "Good communication between groups, as well as to the outside community, was an important part of our vision from the beginning. We hope this common space will act as an incubator, fuelling innovations that build on our combined expertise and lead to knowledge that will pave the way for drugs and therapies in the fight against infectious diseases."

CREDIT: MARIETTA SCHUPP/EMBL

EMBL's Jan Kosinski is integrated into the CSSB through the 'research hotel'.

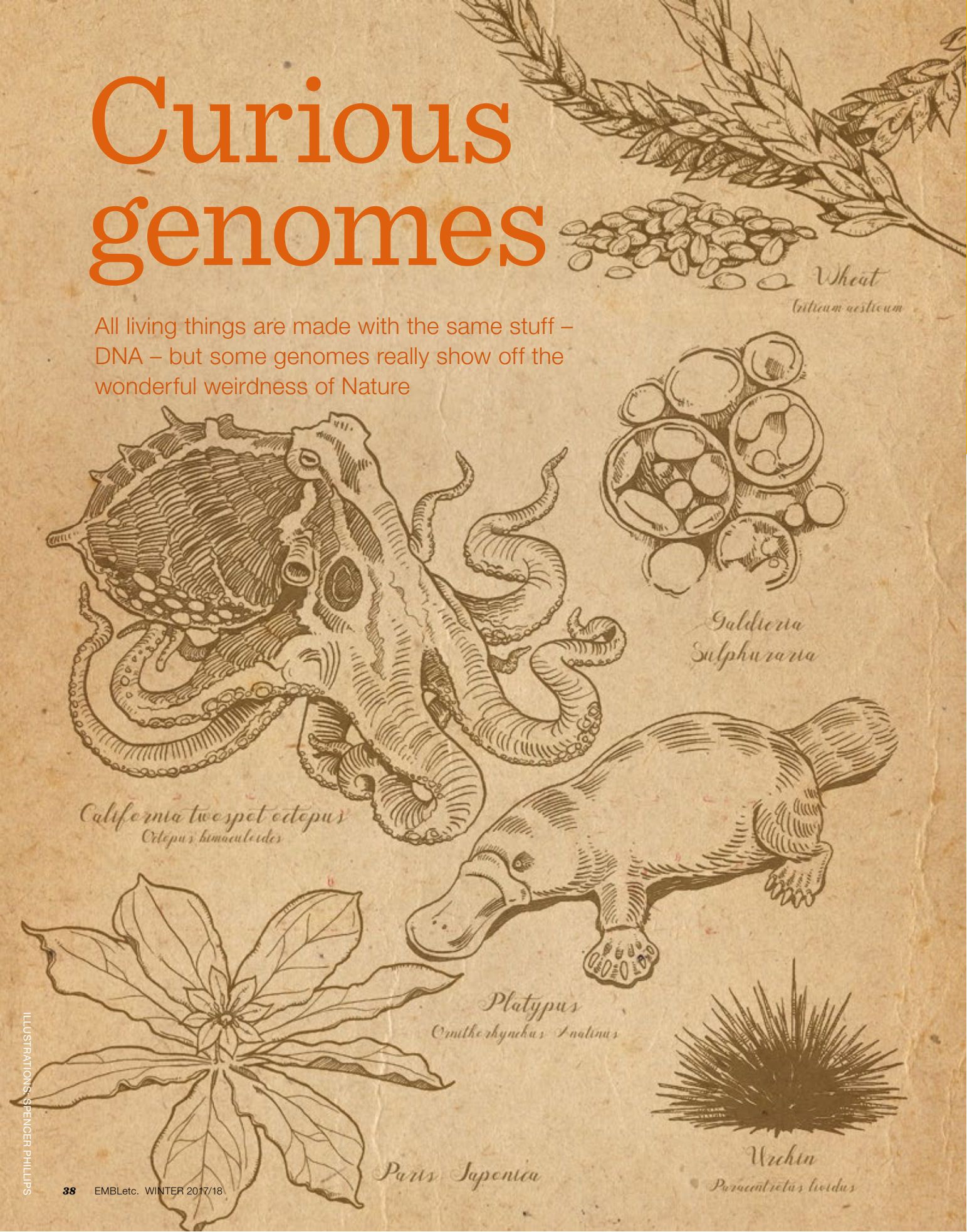
MORE ONLINE:
CSSB-HAMBURG.DE

CSSB is a joint initiative of ten research partners from northern Germany, including three universities and six research institutes.

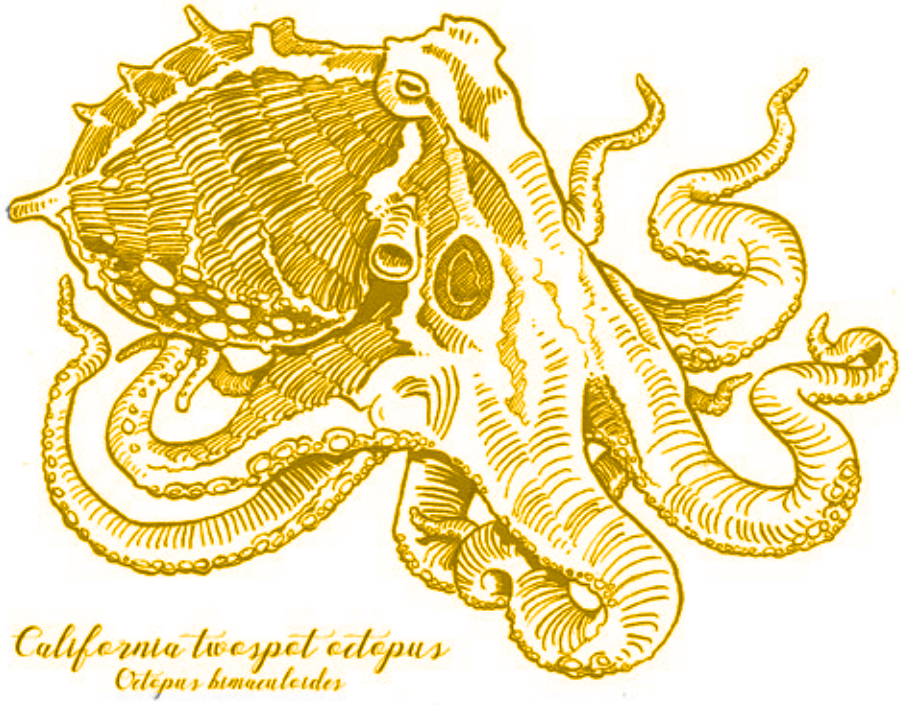
- EMBL
- Bernhard Nocht Institute for Tropical Medicine (BNITM)
- Deutsches Elektronen-Synchrotron (DESY)
- Forschungszentrum Jülich (FZJ)
- Hannover Medical School (MHH)
- Heinrich Pette Institute, Leibniz Institute for Experimental Virology (HPI)
- Helmholtz Centre for Infection Research (HZI)
- Research Center Borstel (FZB)
- Universität Hamburg (UHH)
- University Medical Center Hamburg-Eppendorf (UKE)

Curious genomes

All living things are made with the same stuff – DNA – but some genomes really show off the wonderful weirdness of Nature



ILLUSTRATIONS: SPENCER PHILLIPS



BY MARY TODD BERGMAN

People sequence the genomes of living creatures for lots of reasons: to see how we could make them more nutritious (plants) or tastier (animals), to see if they can be useful to us (bacteria) or to find out why they're sick (humans). Sometimes we sequence them just because we're curious, and we can.

There are millions of species living with us on this planet – too many to fit in a family album, and quite enough to show how little we know. For example, the Tara Oceans expedition gathered plankton samples from a couple of hundred stops on the 360 million square kilometers of ocean covering our world. Sequencing those samples has revealed 40 million novel genes so far. Analysing them and trying to figure out which new species they belong to is an exercise in wonder and humility.

When people publish genomics research on any species, they send their results to public databases like the European Nucleotide Archive (ENA). Scientists working for the Ensembl genome browser combine hard-earned knowledge from many studies carried out by laboratories around the world into a single, integrated resource. They carefully plot new information against a reference sequence for each species, and make it available for anyone to use, any time, free of charge.

The Ensembl team comes across weird genomes every day. For this special issue on curiosity, they were kind enough to share a selection of their favourites.

Animals

Platypus, *Ornithorhynchus anatinus*
The platypus gets plenty of attention for its odd appearance, egg laying and venomous legs. But did you know it also has five pairs of sex chromosomes? One pair is similar to the single pair of sex-determination chromosomes found in humans, and another is similar to that found in birds. That link between birds and mammals is certainly food for thought… but why so many chromosomes, do you think?

Article: bit.ly/platypuspaper
Platypus genome: bit.ly/platypusgenome
Platypus venom: bit.ly/platypusvenom

California two-spot octopus, *Octopus bimaculoides*
This boneless, clever creature has massive expansions in two 'families' of genes, one of which regulates – unsurprisingly – neuronal development. Genes involved in such complex functions often have copies (gene families), which gives a bit of genetic wiggle-room when things go wrong. Scientists used to think the protocadherin and C2H2 gene families (involved in neuronal development and gene regulation, respectively) were only expanded in vertebrates. Is it the beautiful coordination of eight arms, or the highly developed escape artistry that has demanded these expansions?

Article: bit.ly/octopusgenomepaper
Octopus genome: bit.ly/octopusgenome
>>

>> Sea urchin, *Strongylocentrotus purpuratus*
The genome of this spiky, slow-moving 'hedgehog of the sea' has an unusually large number of gene families involved in its immune response. It also has a vast collection of pathogen-recognition proteins. Like the two-spot octopus, it has genes that you'd normally think were just for vertebrates – including orthologs (gene cousins) to human genes associated with disease, vision, hearing, balance and sensing chemical stimuli. Applications for health, anyone?

Article: bit.ly/seaurchinpaper
Sea urchin genome: bit.ly/seaurchingenome

Algae

Galdieria sulphuraria
This species of red algae is an acid- and heat-loving extremophile. It gives an interesting example of 'horizontal gene transfer'. What's that? Well, say you were swimming in a lake, and as you glided along your genome collected some new genes from the lily pads in the water. Pretty weird, right? That's horizontal gene transfer. It doesn't usually happen between animals and plants – it's more common among unicellular organisms, like bacteria. To survive in hostile environments, extremophiles need specialised genes that have not evolved in the *Galdiera suphuraria* lineage. Instead, this alga has gained its ability to resist acid and heat by borrowing genes from extremophilic bacteria.

Article: bit.ly/redalgaepaper
Galdieria sulphuraria genome: bit.ly/redalgaegenome

Plants

Wheat, *Triticum aestivium*
You may not think wheat is particularly weird when you're tucking into your toast, but did you know that wheat is hexaploid? That means it has six copies of each chromosome (humans have two of each). This brings its genome to a whopping 17 giga base pairs (17,000,000,000 bp) long: five times the size of the human genome. How did it get this big? Modern bread wheat is actually derived from three different species that have cross-bred – and it retains the genetic material of all three ancestors. Because of that, most of its genes exist in several copies, which have similar sequence and function. That makes the bread-wheat genome one of the most difficult to decipher and modify, for example to make it resistant to drought.

Article: bit.ly/GRwheatgenome
Bread wheat TGACv1 genome: bit.ly/wheatgenome

Ensembl is waiting for...

Paris japonica
This slow-growing, octoploid mountain flower has the largest genome of all: 149 giga base pairs (or 50 times larger than a human genome) and 40 chromosomes. Scientists don't fully understand why some organisms have evolved huge genomes, or what has enabled these species to survive in spite of the hard work of maintaining a huge genome.

Article: bit.ly/genomesizepaper
Genome: Eagerly awaiting the Paris japonica genome in Ensembl

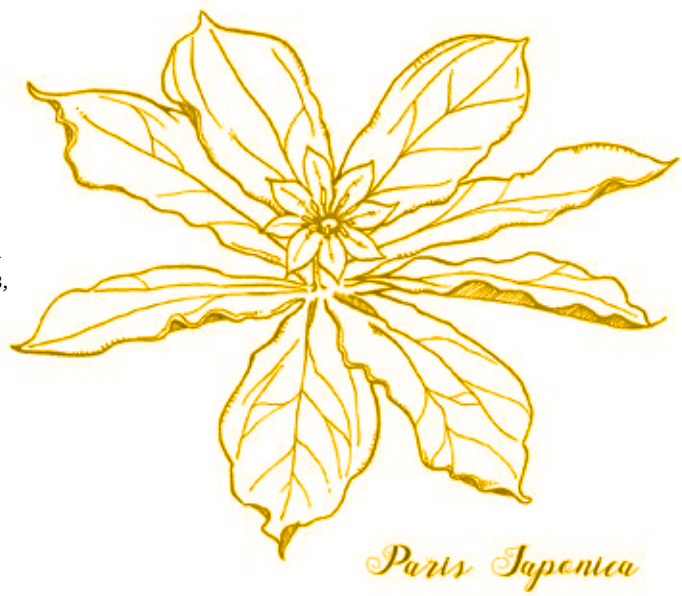


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PHOTO: NICOLA ROMAGNA (CC BY 2.0)

Humans of EMBL

EMBLers across all sites share how their curiosity about the world shapes their everyday life

BY BERTA CARREÑO

I play rugby on the side

I arrived at EMBL Rome a year ago and as soon as you arrive you meet everyone. It's like a little family and you start doing things together, you get invited everywhere. But I have a second family, because I play rugby on the side! I found a team to join last month, so I've just started – cool guys, cool team, so I'm going to join.

I started playing rugby during university, in Clermont-Ferrand in France. There's a famous rugby team called ASM, who reach the finals almost every year – it's a big event. It looked like so much fun that I kept wondering what it would be like to try it. That's how I started playing, and later I discovered other advantages.

Rugby is my way to 'de-contract' – there's also a yoga club here, but that wouldn't be enough for me, I need to express my frustration sometimes. Every experiment that went badly during the week. With rugby you can relieve the stress with someone who agrees to that. You go and play and have fun with someone who also wants to play like that: running into each other and at the end everyone is exhausted and happy! Then we can go back to work. That's the way I see it. It has to be something physical, and at the end when you just want to lie somewhere, it's such a good feeling.

Tom Boissonnet

PhD Student, EMBL Rome

PHOTO: ANASTASIIA VLASIUK

PHOTO: HUGO NEVES\EMBL

I got into singing through BlaBlaCar

A few years ago, I was dedicating all my time to work. Apart from that I just went to the gym – which I do for health reasons mainly – so I thought: "I need something for my soul, something different, something that enriches me more." That's why I went for singing.

Back then my husband – who at the time was still my boyfriend – was living in Italy, so we were commuting every weekend to see each other. I joined BlaBlaCar, the ridesharing community where drivers and passengers agree to travel together and share the costs of the journey. Through BlaBlaCar I met an Italian girl who was part of a choir. Eventually we discovered that I was attending the same church where her choir rehearsed and she invited me to join. I said, "Why not? Let's start!"

At first it was difficult, because even though I had played the piano as a kid and learnt how to read music, I couldn't read the notes and sing directly. I always need to go to the piano first. Eventually it also got more difficult because I'm an alto, which often involves singing an accompaniment to the main melody while you can hear most people singing something else. I also think it's easier to be a soprano because there are more of those, but my voice doesn't go that high. Still, I really like it, and now I'm going to start a new challenge: making the congregation in a church sing with me. I think I'll enjoy it!

Erika Pellegrini

Postdoc, EMBL Grenoble

Nature soothes me

Rome is surrounded by mountains. I've been looking at them for over 16 years. I wondered what it would be like to walk them, though I never did – until now. I'll be moving to Finland in January for family reasons, so I told myself, "Before I leave, the least I can do is go and see these beautiful places!"

So, it's a recent thing: I started in March. I've started many things over the years, but I'm not very good at continuing. I like taking pictures too. Now I try to combine photography and hiking, but so far I haven't captured anything exceptional. I take the camera but I almost forget I have it: I prefer looking around with my eyes!

The mountains here are small, but full of history. They were busy places during medieval times, full of anchorites – people who decided for religious reasons to retire from the world and live in isolation. You can still visit the caves where they lived. I also enjoy walking in the woods. The landscape and the quietness really satisfy me: you feel in harmony with nature and it's so beautiful. While I walk my mind empties, I detoxify and when I reach the top I'm almost clean. The mountaintops soothe me: the beautiful landscape has a really good effect that lasts for over a week.

This is the reason why I started in a rush: until January I want to make the most of my sudden enthusiasm. I wish I'd started doing this when I moved here: I really like it and soon I'll have to give it up.

Flavio Zizzo

Administrative and Purchase Officer, EMBL Rome

PHOTO: TALO ROSARIO

PHOTO: YANN MILEWSKI

The science of soap

I find regular shampoo very harsh on my hair and skin, so I began to think about whether I could use my lab background to create a soap bar that would work better for me. It's something I do for myself and as a present for family and friends – the soap bars smell nice and you can decorate them!

I experiment with my soaps, adapting the recipe every time. Now I've started making soaps for my hair and also for my skin. The ones for the skin need to have some extra oil, so you put in less sodium hydroxide to make sure there's still some fat left to treat your skin. For me it works out fine, because I don't need to use lotions any more – a really nice side-effect!

I used nettles for my last soap – you can grow them yourself in the garden. They're supposed to make your hair shine. For this one I will also use dandelions. I collected some last spring and macerated them in oil for a few weeks. They colour the soap yellow and they're also supposed to be good for the skin.

Unfortunately I don't have very much time to do this – I have to do it when the kids are in bed so they don't jump around on all my things. But I really like to do something for me, and it's great to use products where you know exactly what's in there!

Morlin Milewski

Research Technician, EMBL Hamburg

I need to dance!

In high school talent shows I used to recite poetry, but a guy who did hip-hop was getting all the girls' attention. I thought, "I need to dance!", so I joined lessons at school and now I'm a hip-hop teacher. Dancing – like science – is a fantastic way to explore things and grow as a person. As a grown-up, you don't fully explore your curiosity that often. Dancing allows you to do that.

The thing I like most about dancing is the philosophy around it. First, you get the chance to play and be a child again. You keep exploring and playing with the music, being creative. That's really nice, not only as a dancer, but as a person: to explore and try things out without knowing what the outcome will be. Maybe also failing sometimes!

Another thing I like is that it's a very intense activity. You need a lot of control over your body: strength, flexibility, endurance – you need discipline to be that fit. Communication with yourself is really important: when you try to move part of your body in a way you haven't tried before, you get this feeling like, "What is my body doing?!" The more comfortable you feel with your body, the more comfortable you feel overall. It's definitely a mental thing too, not only physical.

Dmitry Richter

Master's Student, EMBL Heidelberg

PHOTO: COURTESY OF DMITRY RICHTER

I feel at home anywhere

I come from a small town in the south of Spain with 5,000 inhabitants: Fuente de Cantos. I was always the unusual one – I wanted to travel, see the world! Neighbours asked me: "Why do you want to leave? We eat well here, and it's sunny! Isn't it cold where you're going?" I kept thinking, "Well, weather will not determine my whole life!" Luckily my parents encouraged me to go out and try new things. They thought I would leave for a year and then come back, but it's been 13 now since I first left!

When I started working in Luxembourg at the European Court of Justice I got the feeling that I had found my place, because when I work in international organisations – like EMBL – I have this feeling of belonging. Most people are like me: they've moved a lot, lived in several countries, speak several languages. I know I'm lucky – I studied international law and specialised in international organisations, so I will always be in such environments.

It was clear to me that I wanted to live in other countries and learn languages. I speak six now: Spanish, English, French, German, Italian, Portuguese – even if I'm not completely fluent in all of them. I've also just started to learn Catalan. I started living abroad during college: I studied in Lubbock, Texas and then Brussels. After that I started working in Madrid, then Luxembourg City, then Heidelberg, and now Barcelona. I love beginnings, the feeling that everything is yet to be discovered, getting lost in the streets. That feeling of novelty is very joyful to me!

Amaranta Amador Bernal

Head of Administration and Senior Legal Advisor, EMBL Barcelona

PHOTO: MARIETTA SCHUPP/EMBL

PHOTO: MAMUT SLOVENIJA

In the wild in Europe

I like being outdoors. I grew up on a farm near Brisbane, Australia, so I spent most of my childhood outside and now I always seek out the sunshine. I'm also trying to see as much of Europe as I can while I'm here. Over the years, I've visited France, Sweden, Denmark, Croatia, Iceland, Germany, Italy, Spain, and Slovenia. There are still many things I need to see – Portugal is pretty high up the list – but Slovenia is definitely one of the top ten places I've visited!

In Slovenia, it feels like they have a culture of being outside and being active. It was sunny while I was there, so it was perfect for enjoying the wilderness and doing something other than sitting in a chair in an office for the whole day. I went there alone – I've tried travelling with my friends, but they usually have other things going on and I think: "If I don't do it now, I'm never going to do it." Because I was alone, I joined day trips here and there: hiking and white water rafting were my favourite.

Rafting was really fun: being in a big inflatable boat and going down the rapids in the river, trying to avoid all the rocks. Halfway down, the rafts get pulled out of the river next to a big boulder. We climbed the side of the boulder and jumped off it into the water: it was really fun! It sounds crazy when you sit in an office and talk about it, but on the spur of the moment it was just wonderful. I would definitely do it again!

Melissa Burke

Scientific Training Officer e-Learning, EMBL-EBI

Science + X: The science behind *The Matrix*

PHOTO: EMBL

EMBL researchers separated fact from fiction at a Friends of EMBL Science Movie Night

BY ANNIKA DUDA

Separating fact from fiction, EMBL researchers Ina Huppertz and Thomas Schwarzl explored the science behind *The Matrix* at an EMBL Science Movie Night held in Heidelberg, in May. Speaking to more than 200 science fiction enthusiasts ahead of a screening of the 1999 classic, their talks covered areas ranging from our perceptions of reality to the blurring of lines between humans and machines. In the first of a series of articles on the impact of extracurricular activities on research, we spoke to Ina and Thomas about their experience.

Ina Huppertz is a postdoc in the Hentze group. Her projects focus on the interface between metabolism and gene regulation.

Tom Schwarzl is an EMBL Interdisciplinary Postdoc (EIPOD) working for the Hentze, Huber and Krijgsveld groups. He's studying the binding dynamics of RNA-binding proteins.

Why were you interested in taking part in the science movie night?

Ina: I think it's very important that we explain to the public what we're working on. I really wanted to get in contact with non-scientists to get feedback on what they think about science. Additionally, I love science – I enjoy being in the lab and thinking about scientific problems and I hope that this might inspire other people.

Tom: Talking to an audience about science can be very inspiring because we're working in a very complex and competitive field and it can be really helpful to step out for a while and remind yourself why you do what you do.

Did the event give you new inspiration for your own research?

Ina: To a certain extent, yes. One of the themes that I considered during my presentation was: what does the human body need to survive and maintain itself? *The Matrix* considers this in a very surreal and philosophical context, but this question is also central to what we're trying to understand as life scientists. It's helped me to think about the bigger picture of my research and I've developed some new ideas for my projects.

Tom: It won't change my immediate research projects, but thinking about the scientific and philosophical issues in *The Matrix* raises fascinating questions about the future of fields such as artificial intelligence.

How do your personal interests influence your research?

Ina: I love reading science fiction and literature in general. One of my favourite authors is Terry Pratchett. I find it amazing how he describes phenomena in such colourful, vivid and descriptive language – something that's really important when communicating science to the public. I also enjoy running – I know a lot about the molecular details of how exercise impacts your body, but sometimes feeling the effects personally can give you another perspective on things!

Tom: In my free time I like to relax by making music. Creativity, which is essential for innovation, more often than not comes from a calm rather than a busy mind.

Would you encourage others to take part?

Ina: It was great to have so much positive feedback. Sometimes it can be difficult to comprehend the impact of your work but this experience motivated me to go back to my projects and say. "Yes, it is really important what I'm doing!" I would recommend it to anyone.

Tom: Definitely! Breaking down scientific topics so that they're easily understandable to non-experts is tricky but very rewarding.

Friends of EMBL is the network for members of the public interested in the life sciences, and in supporting EMBL's research and mission. Friends are invited to engage in a closer relationship with the Laboratory and its researchers through a dedicated website, a quarterly newsletter, and a series of special events, among them the Science Movie Night. For more information write to Barbara Solich at friends@embl.de or visit:

EMBL.ORG/FRIENDS

Science is a universal language – we must stand up for it

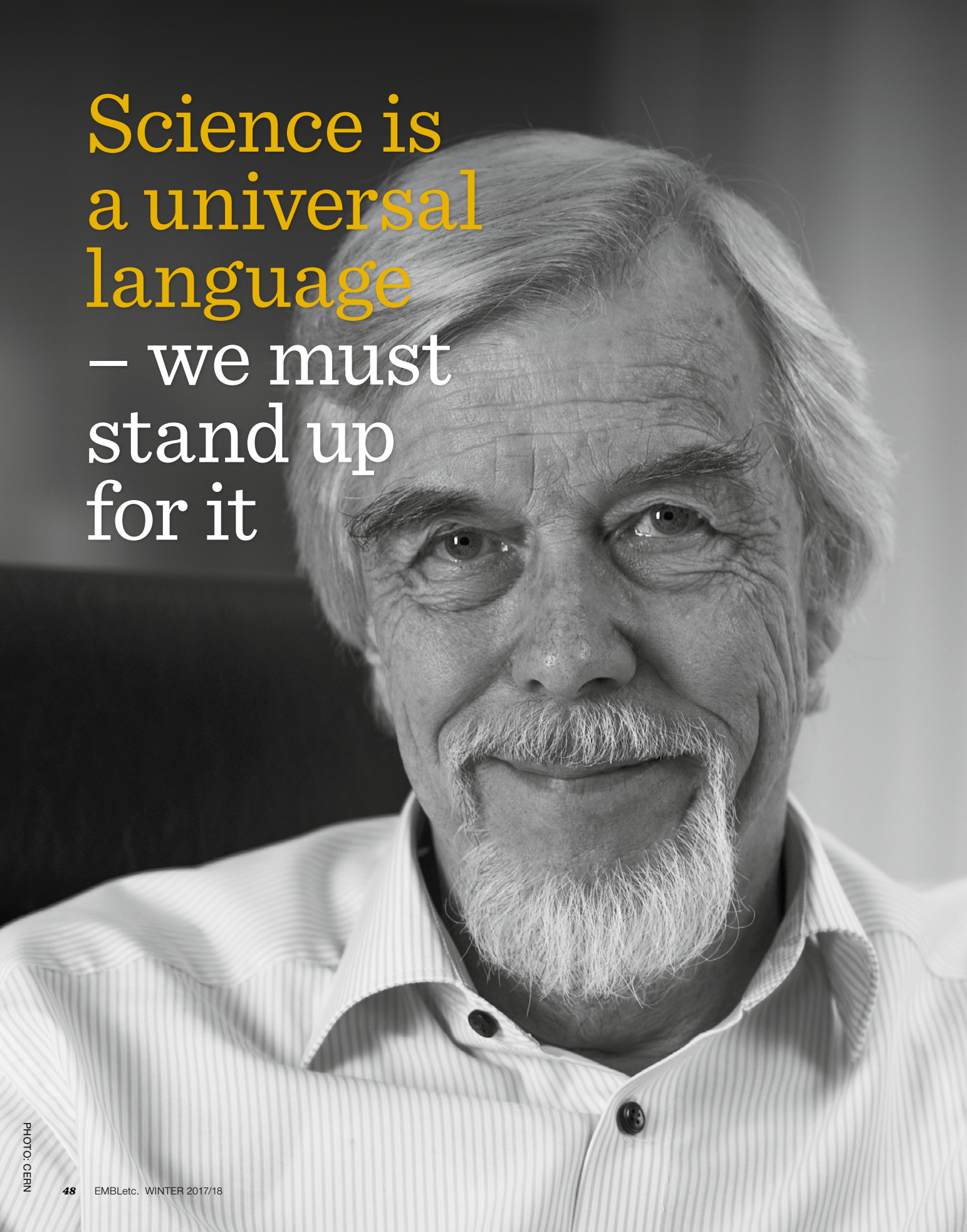


PHOTO: CERN

An interview with Rolf-Dieter Heuer, President of SESAME Council, who was guest speaker at EMBL's 2017 Annual Reception

BY BERTA CARREÑO

What were the key messages of your talk?

The world needs science. Not just applied science or technology, but the whole spectrum of research. Sometimes there is pressure to design projects that can be used immediately by society. However, all science has roots in fundamental research and it is important to have a combination of focused research and basic science – just a few examples being the World Wide Web, smartphones, GPS, solar panels and many innovative medicines.

You need a virtuous circle of basic research, driving innovation, which drives focused research, which drives more innovation, and ultimately feeds back into improved basic research. If you break this virtuous circle then at some stage you will have no science and we must by all means avoid that.

At the same time, science bridges cultures and nations because it's a universal language. In today's globalised world this is even more important than it was 40 or 60 years ago. Research brings people together – united by science rather than divided by politics. Science needs an open atmosphere: open to argument, open to suggestions and open to everybody. I saw the benefits of this first hand during my time as CERN Director General and now at SESAME, a new synchrotron that has recently opened in the Middle East.

Rolf-Dieter Heuer is president of SESAME Council, advisor to the European Commission and former CERN Director General.

What are your hopes for the SESAME project? What is your role?

The SESAME project is a project of hope. The idea, born 20 years ago, was to create a world-leading scientific institute in the Middle East with the participation of researchers diverse in expertise, nationality and background. A synchrotron is the ideal facility to achieve these goals. The facility will be used to do research in biology, medicine, archaeology, environmental studies, physics, material science, chemistry and many other fields. SESAME's governance is modelled along the same lines as EMBL and CERN, meaning there is a Council where members are represented – I am now the President of that Council.

Science projects are getting ever larger, like the big accelerators needed in modern particle physics or initiatives such as the human genome project and its successors. These huge projects implicitly require collaboration, and to achieve this you need to build trust, sustainability and long-term support from funders. International organisations such as EMBL and CERN are fantastic examples of what Europe can achieve when it works together with its partners and our hope is that the model – and the spirit of science and collaboration it creates – will drive similar success at SESAME.

You are also an advisor to the European Commission – what are your priorities in this respect?

We provide the EC with scientific advice on policy issues, where such advice is critical to the development of EU policies or legislation. Policy makers can play an important role in connecting science and society, especially when explaining the role of science in decision making – I encourage them to explain science as if they were with friends in a bar. But it is equally crucial for scientists to use a language that politicians and the general public understand.

EMBL is now chairing EIROforum. From your experience, what do you think are the benefits of this kind of organisation?

I think scientists need to join forces and speak out. The global movement that led to the March for Science is an example where researchers identified a problem and spoke out in numbers. Another example is EIROforum, which brings together eight of the largest intergovernmental research organisations in Europe. Together we look to find synergies in areas like computing, instrumentation and technology transfer. Where possible we also aim to express a unified voice in key areas of European science policy. Eight together is much stronger than one alone, especially if one combines many disciplines.

What do you think is the most important skill the next generation of scientists needs to learn?

To question everything, be critical – but positively critical – and to appreciate the art of collaboration.

To laugh and then think

Meet Ig Nobel emcee Marc Abrahams, who gave an EMBL Science and Society talk in December

BY MARGAUX PHARES

PHOTO: NICOLA ROMAGNA (CC BY 2.0)

One of this year's Ig Nobel Prizes was awarded for a study arguing that cats can technically be regarded as simultaneously solid and liquid.

The Ig Nobel Prizes are renowned as a spoof alternative to the Nobel Prizes. The annual Ig Nobel awards ceremony is a celebration of curious, imaginative studies that make people laugh. Yet while studies of cats behaving like liquids or frogs levitating inside a magnet might have you chortling, the founder Marc Abrahams, has an equally important purpose in mind for the prizes: to get you to think. Abrahams is also editor of the *Annals of Improbable Research*. He gave a Science and Society talk at EMBL in Heidelberg, on 4 December. We caught up with him to find out more.

What does it mean to call research improbable?

Improbable, like many words, can have different meanings. The meaning that I choose to concentrate on is: not what you expect. The studies that win Ig Nobel Prizes all have this element in common. In 2015, for instance, the Ig Nobel Prize for Mathematics was awarded for a study that tried to apply mathematical techniques to determine whether and how Moulay Ismael, an emperor of Morocco (who now has the nickname 'the bloodthirsty'), fathered 888 children over a 32-year time period. In the end, they not only found it was possible, but they also found some unexpected things: according to their computer simulations, Ismael could have fathered 600 sons, and the harem size needed to achieve that number ended up being far smaller than what the historical reports asserted!

PHOTO: COURTESY OF MARC ABRAHAMS

Marc Abrahams awarding an Ig Nobel Prize at this year's awards ceremony.

Do you have a favourite improbable study?

This is a very hard question and one that I get a lot! If I had, say, six studies to choose from, it might be easy. But since 1991, we have awarded hundreds of different Ig Nobel Prizes and to pick out my favourites is just too difficult!

Is there a difference between "silly" and "serious" science?

Those are words that get twisted up very easily. Once something becomes generally understood and accepted, it comes to be seen as serious and important. Almost everybody either forgets or doesn't become aware that this thing started out as something that everyone else regarded as nuts! Any scientific discovery seems like such an easy thing after it has been discovered, and it almost never was. Your understanding of a study might change – drastically! – if you spend time looking at its details.

We do something in the Ig Nobel ceremony called the 24/7 Lectures, in which we bring in scientists to explain

their research in twenty-four seconds of intense jargon followed by seven clear words. For Ig Nobel Prizes, we choose studies that have that quality: that it's not possible if you just see a seven-word summary to know whether it's real or fake. You've got to spend another few seconds – and preferably more than that! – actively looking at something you come across, say in the news or in a research study.

Can we ever find a way to make even the most serious of people laugh?

Yes, we can! Because scientists spend a lot of their time thinking about things that not many other people are thinking about, they're often stereotyped in a certain way – but then you realise that's not really who they are. I like to think most people have a sense of humour!

Ig Nobels have two criteria: to make people laugh, and then make them think. Is it important they be in that order?

When a study wins an Ig Nobel Prize, there's something about it so surprising that the only initial reaction you can have is to laugh. This makes you stop and pay attention to the study. At this point you may start to realise, "Wow, I'm going to keep thinking about this thing because I want to know more about this." The other direction – to think and then laugh – is slower and more contemplative. When you've got that gut feeling to laugh at something, you can train yourself to – even for an instant – think about it, and not move on to something else right away. If you can do that, I think that's a valuable skill you've given yourself, in science and beyond.

Awards & Honours

EMBL researchers awarded prestigious ERC grants

Takashi Hiiragi, a group leader in the Developmental Biology Unit in Heidelberg, has been awarded a grant of more than two million euros to study how early mouse embryos break their initial symmetry and self-organise to generate well-defined asymmetrical forms and patterns. Combining biology and physics, Hiiragi aims to identify the mechanisms by which cells communicate and behave to determine their future function from the sub-cellular scale to the whole organism. Despite extensive studies of how genes in the early mouse embryo are expressed, the molecular and physical signals driving these processes are still poorly understood. The project will also go into other uncharted territories, examining how fluid cavities within the embryo help coordinate the development of cells' lineages, and therefore their functions.

EMBL senior scientist **Lars Steinmetz**, who is part of the Genome Biology Unit at EMBL Heidelberg, has been awarded an ERC Advanced Investigator grant worth 2.5 million euros, for a project that will improve our understanding of how variation in the genetic code leads to differences in individual cells. Using state-of-the-art genome editing technology, Steinmetz aims to uncover how subtle variation affects evolution and influences an organism's adaptation to different environments. This study, which will be the largest of its kind, will provide important scientific insights and drive the development of new tools to model the effects of genetic variation. Ultimately, Steinmetz hopes that his study will result in guiding principles that improve diagnosis and treatment of human diseases.

Alumni

For the future

PHOTO: EMBL

Curiosity is a fitting theme for this edition as we celebrate the achievements of EMBL alumnus – and now Nobel Prize winner – Jacques Dubochet (pages 5 & 7), announce the launch of the alumni portal, share the alumni impact report and showcase community events that have taken place in recent months (pages 53-55). We also profile the work of two physicists-turned-biologists who won this year's prestigious John Kendrew and Lennart Philipson alumni awards (pages 56-57). In the features section, you will find profiles of alumni whose curiosity has led them literally to the ends of the Earth and beyond (page 15). And finally, we invite you to get ready for the year ahead and to mark your diaries for our events in 2018 (see back page and online).

Mehrnoosh Rayner
Head of Alumni Relations

New alumni portal – keeping the community connected

EMBL is delighted to announce the launch of a new EMBL alumni portal which replaces the old alumni update form and directory. Designed to keep EMBL's alumni community connected, the portal allows you to share contact, employment and biographical information, search EMBL's Alumni Directory and to specify the types of information you would like to receive from EMBL and EMBO. You can also upload a profile photo and send email directly to other members of the alumni community. As before, EMBL staff can access and use the Alumni Directory using EMBL's intranet. This has taken us over a year to build, and we look forward to the feedback of users to help us maintain, enhance and further develop the portal. We also thank alumni for making the effort to keep their information up-to-date for the benefit of the whole community. Thank you!

THE EMBL ALUMNI PORTAL IS AVAILABLE AT:
ALUMNIPORTAL.EMBL.ORG
CONTACT THE ALUMNI RELATIONS TEAM FOR YOUR LOGIN: ALUMNI@EMBL.ORG

New team members for alumni relations

The Alumni Team welcomes new alumni volunteer officer, Peter Papagiannis, and alumni relations officer, Joe Murray. Peter is from Vancouver Island in Canada and most recently worked at the University of Victoria for the Alumni Relations and Development department. Joe is originally from Seattle in the United States and joins EMBL from Montefiore Medical Centre, a large hospital and health system in New York City.

Left to right: Peter Papagiannis, Mehrnoosh Rayner and Joe Murray.

PHOTO: EMBL

Connecting at community events

PHOTO: ROBERT SLOWLEY

EMBL alumni events have been taking place all over Europe and the world – including the UK, Italy, France, Australia, Norway and the USA. We catch up with just a few of those involved (for more see page 59).

Italy – Gennaro Ciliberto

Now: Professor of Molecular Biology at the Magna Graecia University of Catanzaro and Scientific Director of the Regina Elena National Cancer Institute
At EMBL: 1979-1987, Staff Scientist, Cortese Group, Heidelberg

At EMBL... My time at EMBL was the best time in my life – and not just because I was young! Back when I started in 1979, EMBL had been very recently established and was coloured by a very enthusiastic and collaborative atmosphere. I had no other duties besides research – no teaching duties and a fully-funded lab without the need to seek additional funding. I was lucky to have a great lab head, Riccardo Cortese, and an excellent relationship and productive collaboration with Lennart Philipson, who went on to become EMBL's second Director General.

Since then... I became associate Professor of Genetics at the University of Pisa and then Professor of Molecular Biology in Naples. I was then asked by Riccardo Cortese to become Director of the Cellular and Molecular Biology Department at the Institute of Molecular Biology Research (IRBM), a position I accepted with great enthusiasm. I also founded a small biotech company called Takis, dedicated to cancer research.

And now... As a scientific director of a cancer institute, I enjoy fostering translational research between different groups of investigators. Together with my wife Rita Mancini, who is also a professor, our research focuses on the mechanisms of drug resistance in cancer.

Gennaro was speaking at the EMBL in Italy event at TIGEM on 5 May.

The UK – Miriam Hock

Now: Senior Scientist at Immunocore Ltd, Abingdon, Oxfordshire, UK
At EMBL: 2010, Visiting Scientist, Grenoble

At EMBL... My time at EMBL and my PhD helped me understand what really made me tick. I did structural work that I enjoyed, but I was really interested in understanding disease. More than anything else, I wanted a product – a practical application for my work.

Since then... After finishing my PhD, I felt a bit uncertain about what I wanted to do. I took a step back and refocused my efforts. I've always been in love with Oxford. It's one of Grenoble's twin cities and has a similarly vibrant academic, cultural and scientific life. Not to mention it boasts the legacy of Inspector Morse, a series that absolutely fascinated me when I was growing up. So when I saw a job advert at Immunocore, I couldn't help but apply.

And now... I'm working on developing a new class of immunotherapeutic drugs, based on proprietary T-cell receptors. The company uses soluble T-cell receptors that redirect a person's immune system to treat diseases and infection. We focus heavily on cancer, viral infections and autoimmune diseases. Our science and strong intellectual property has attracted collaborations with major pharmaceutical companies including GSK and AstraZeneca. I'm enjoying every minute of it!

Miriam was speaking at the EMBL in the UK event at Oxford University on 22 May.

Alumni Impact Report 2017

The opportunities and resources that EMBL offers are for life. The Alumni Impact report reveals the impact of EMBL through its alumni: highly trained individuals who share their EMBL networks, training and resources with new communities. It also explains how alumni can continue to benefit from and support EMBL and identifies measures EMBL has taken in response to feedback from a survey for this report.

BIT.LY/alumniimpactreport2017

Where are you now?

EMBL in Norway

Meet EMBL alumnus Rein Aasland, who co-organised a recent EMBL in Norway event

BY ANNABEL DARBY

PHOTO: ANNABEL DARBY

Rein Aasland was a postdoc at EMBL (1992-1995) in the Gene Expression Programme. Today, he is Head of the Department of Biosciences at the University of Oslo. In September, he and EMBL alumnus Gareth Griffiths co-organised an EMBL in Norway event.

What did you work on during your postdoc?

I worked in the group of Francis Stewart, in the Gene Expression Programme. We studied how chromatin changes in Hox gene clusters during cell differentiation, a topic which introduced me to the ideas of the mechanisms for epigenetic gene regulation.

What do you feel you gained from your time at EMBL?

So much! Just being there, and the exposure to such a rich and dynamic learning environment was incredibly valuable for me. The connections I made and the opportunities offered to me were vast. For example, during my time, gene expression shared a coffee room with computational biology, meaning we often got talking to one another. Through these connections, I had the opportunity to learn lots of methods and ideas in applied bioinformatics, which allowed me to develop a bioinformatics-focused side-project that ended up being very successful. Some of the findings from this work formed the basis of my later research.

How did it feel to go back to Norway?

Of course, moving away from EMBL was a huge change. Adapting to a new setting and taking on new responsibilities was a challenge. Yet I felt ready, and was able to put all of the knowledge and training I had acquired to good use. There have been quite a few people trained at EMBL who have brought their knowledge and expertise back to Norway, and the Nordic countries more widely. These people have definitely helped to positively influence the path of molecular biology here. I think anyone who has been to EMBL takes a piece of it home with them – both in terms of scientific expertise and in terms of the culture.

What does your work involve today?

Today I manage a large department at the University of Oslo, which keeps me very busy. I am actually continuing the chromatin and gene regulation work I started at EMBL, although the focus has shifted towards the chromatin of enhancers and long-distance gene regulation, still with epigenetics in mind.

What was the mission of the EMBL in Norway event?

Gareth and I wanted to try and promote EMBL on a larger, more coordinated scale. We felt that by organising a dedicated information day that targeted PhD students and postdocs, with current students and various alumni as speakers, we could really show what it's like to study or train at EMBL.

FULL ARTICLE ONLINE:
BIT.LY/emblinnorway

PHOTO: COURTESY OF MICHAEL PARKER

EMBL alumnus Michael Parker was a staff scientist at EMBL in Heidelberg (1986-1991)

Where are you now?

EMBL in Australia

EMBL alumnus Michael Parker discusses his career, research highlights and how EMBL has played a role

BY MARGAUX PHARES

What did you work on when you were at EMBL?

I solved two protein structures, both in collaboration with the group of Franc Pattus. The first was colicin, which comes from *E. coli*. The second was called aerolysin, which comes from a bacterium called *Aeromonas*, which infects fish. Both proteins are particularly interesting because they are pore-forming toxins and yet have a water-soluble nature.

And what are you working on now?

Rather than just focusing on how pore-forming proteins pass through membranes, as at EMBL, we have extended our studies to examine the structures of proteins that are already bound to membranes – that is, channels and receptors. With this knowledge, we're seeing if we can design drugs to treat a variety of diseases. Of the three areas I'm working on, the one I'm particularly passionate about is Alzheimer's disease. We're trying to understand how antibodies interact with toxic proteins that interact with membranes, and in turn designing molecules that can stop these toxins accumulating in the brain.

Another exciting project is on *Rhinovirus*, a major cause of the common cold. By working with the three-dimensional structure, we visualised how a drug that was developed by a local biotechnology company stops the virus from multiplying. We're also developing anti-cancer drugs based on the structures of membrane receptors. These drugs are now entering clinical trials.

What is your interaction like with the EMBL community in Australia?

The recent alumni event was great for networking – not only alumni took part, but also students. EMBL's alumni are diverse in terms of what they do. An important common topic that arose is the problem of working with big data. For example, how best to visualise and analyse vast amounts of information to discover new biological insights and to develop clinically useful drugs. EMBL has influenced my career very strongly – both the people and the science. I've kept connections with people at EMBL to this day, all around the world.

MORE ONLINE:
BIT.LY/michaelparker

PHOTO: COURTESY OF VIVID SYDNEY

The event coincided with the Vivid Sydney light festival.

The EMBL community spans the globe and there is perhaps no greater illustration of this than EMBL's extensive connections in Australia. To further engage and inspire these networks, 74 EMBL alumni, colleagues and collaborators convened on 9 June in Sydney for the first official EMBL alumni in Australia event. Speakers from EMBL, alumni and representatives from partner institutions outlined the impact of partnership and collaboration on research at EMBL, and on research in Australia, as well as highlighting opportunities for the future.

A physical revolution

EMBL physicist-turned-biologist win 2017 Kendrew and Philipson awards

BY MARGAUX PHARES AND SARAH B. PUSCHMANN

This year, two physicist-turned-biologists received alumni awards from EMBL for achievements in the life sciences: Matthias Mann, who received the Lennart Philipson Award, and Philipp Keller who received the 2017 John Kendrew Award. As their work demonstrates, physics informs biology – across generations.

Mass spectrometry master

Mass spectrometry (MS) enables researchers to identify molecules such as proteins and nucleic acids quickly and accurately. Yet while the technique has been used by physicists for the past century, it was not until the 1990s that biologists began to make use of its potential. One of the people driving this biological revolution was EMBL alumnus Matthias Mann, a physicist who led the development of methods that helped bring MS from the margins to the mainstream.

MS, a technique for sorting unknown molecules by their mass and electric charge in order to identify them, requires the molecules to be both electrically charged and in the form of a gas. In order to get them into this state, Mann's former advisor, John Fenn, developed a technology called electrospray ionisation – a method for producing charged particles, for which Fenn was awarded the Nobel Prize. Mann then took his advisor's method one crucial step further.

Electrospray ionisation requires a quantity of sample that, in the case of samples containing proteins and amino acids, often isn't available. Along with his group, Mann found that by decreasing the size of the tip through which the solution is sprayed and lowering the rate of liquid flow through the needle, this new technique, called nanoelectrospray, could be used even on biological samples in tiny quantities.

PHOTO: MAX PLANCK SOCIETY

Matthias Mann was a group leader at EMBL in Heidelberg (1992-1998).

Still, nanoelectrospray had its limitations – it could only be used to identify peptides with different masses. Peptides, like proteins, are compounds composed of amino acids arranged in a set order. To distinguish peptides of the same mass, he and his team developed another technique. They found that peptides could be identified by determining only a tiny stretch – a few amino acids long – plus

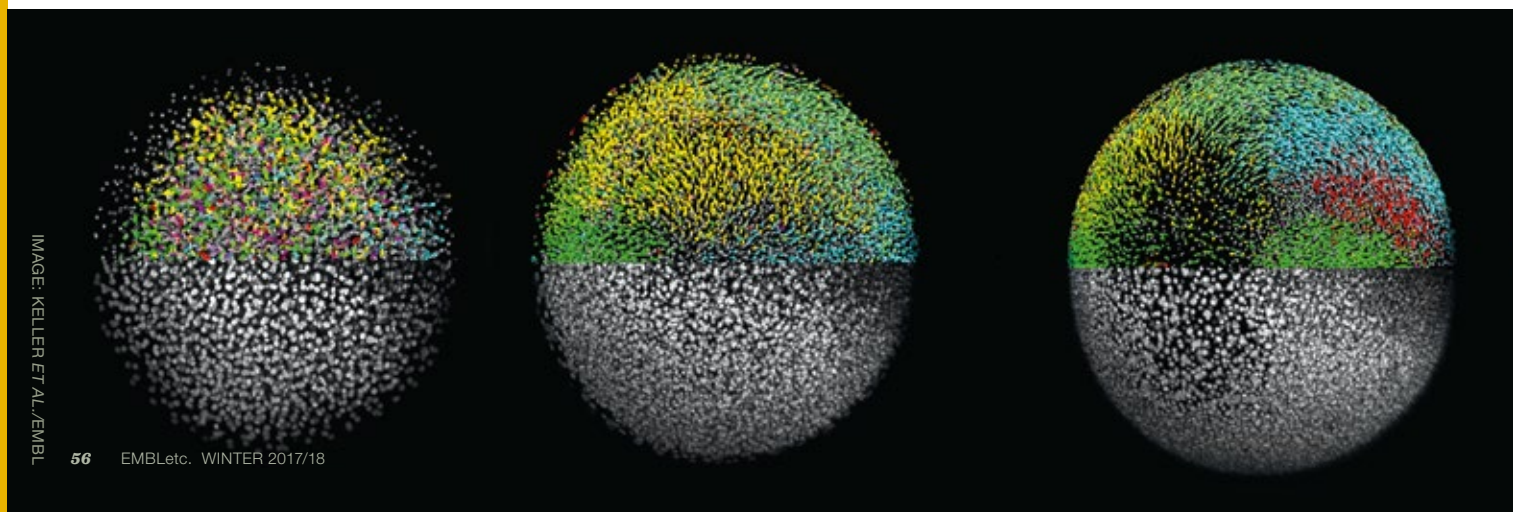


IMAGE: KELLER ET AL./EMBL

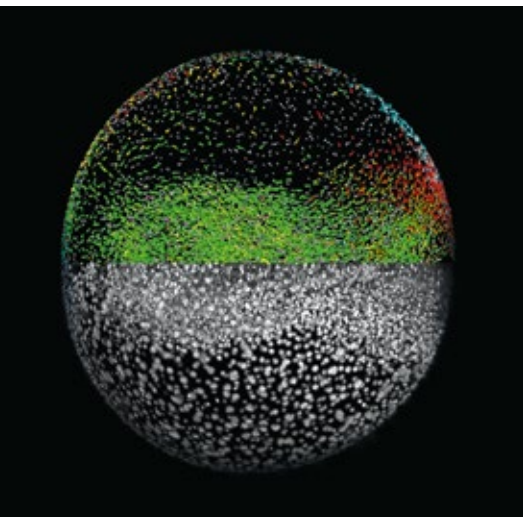
the masses of the surrounding amino acids. This characteristic chunk provided researchers with a unique fingerprint for the peptide, which they could then compare in a database to determine the peptide's identity.

Mann's postdoctoral student, Andrej Shevchenko, further improved the sensitivity for identifying peptides by developing a technique to prepare samples containing proteins for nanoelectrospray. By staining the proteins using silver rather than the standard dye, the proteins of interest could be distinguished to a greater degree of sensitivity from the wash of background proteins in the sample.

These three achievements have made it possible for Mann's team and others to identify important proteins, making key contributions to the field of proteomics – the mapping of all proteins in a particular organism.

Driving development

Philipp Keller's fascination with animal development dates back to his training as a physicist. But it wasn't until working on his PhD at EMBL that he had the opportunity to combine physics and biology studies, as well as being able to work in three different labs and with three different advisors – an interdisciplinary experience that helped direct and shape his research.



Philipp Keller's work imaged the early development of a zebrafish embryo using light sheet microscopy.

"I could see the developing fish right in front of my eyes!"

First Keller worked in Joachim Wittbrodt's group on a project focused on visualising and reconstructing how a zebrafish forms from a single cell. They wanted to know how the single cell divides, migrates, and develops into other tissues to form an embryo. It had never been seen before and it was technically difficult to study a vertebrate embryo at the cellular level.

Keller then began work in Ernst Stelzer's lab on a new kind of microscope, which he called the Digital Scanned Laser Light-Sheet Microscope (DSLM). While the group awaited some parts Keller needed in order to build the new microscope, Keller joined a third project headed by group leader Michael Knop: spore formation in yeast.

Once the parts to create the DSLM in Stelzer's lab arrived, Keller found that the skills he'd learned in computational modelling came full circle in the zebrafish project. The DSLM was faster and produced higher quality images than existing microscopes, which made it possible to image a developing zebrafish embryo for the first time.

"Rather than trying to work through a bunch of text and numbers, I could see the system – the developing fish – right in front of my eyes!", Keller says. This gave him better insight into how biologists think about development at the cellular level.

After Keller completed his PhD at EMBL, he set off to map complex systems in the body as a group leader at the Janelia Research Campus of the Howard Hughes Medical Institute in Virginia, USA, where he is currently based. He continues to research developmental biology, in particular the nervous system and how it develops and first starts to function in the course of emrbyogenesis.

PHOTO: HHMI

Philipp Keller was a PhD student at EMBL in Heidelberg (2005-2010).

But in order to see such minute and speedy activity, which can be measured by monitoring calcium concentrations in the neurons, his lab needs sensitive microscopes. Neurons are flooded with calcium when they fire, and are emptied when they reset. It's possible to detect this activity with an indicator sensitive to calcium concentrations or even by measuring the electrical signals themselves, but neurons can spike one hundred or even one thousand times per second. "If you want to get the timing relationship right between cells, you need to match these timescales," Keller explains. "That's why we're building a new generation of microscopes to be as fast as possible."

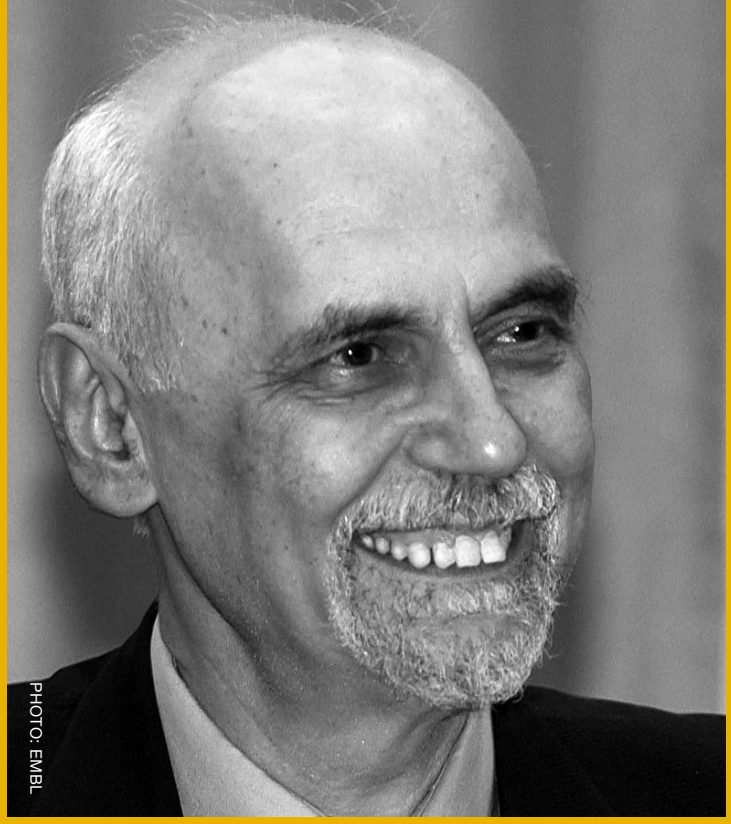


PHOTO: EMBL

Fotis Kafatos was EMBL's third Director General.

Obituary
Fotis Kafatos

Fotis Kafatos, EMBL's third Director General, has passed away

It is with great sadness that EMBL learned of the passing of Fotis Kafatos, former EMBL Director General, who died on 18 November at the age of 77.

Fotis was EMBL's third Director General from 1993-2005 and afterwards became the founding president of the European Research Council (ERC), as well as a member of its Scientific Council from 2005-2010. Fotis' contributions to science and the scientific community over five decades in the US and Europe had a significant influence on the advancement of molecular biology on both sides of the Atlantic.

Before joining EMBL, Fotis became a professor of biology at Harvard University at the age of 29, the youngest full professor in the University's history. In particular he was among the first to apply molecular biology along with genetics to study animal development. His group also developed important techniques in DNA synthesis, cloning and sequencing that were widely adopted. While at Harvard, Fotis remained very committed to European science, founding the Institute for Research and Technology, Research Centre of Crete in 1982 and directing it until 1993.

Fotis had a rare ability to bring together people, ideas and disciplines. During his time at EMBL he applied his skills to work passionately towards accomplishing three major goals: excellence, inclusiveness and cooperation. Fotis led the establishment of the Developmental Biology Unit at EMBL in Heidelberg and the Mouse Biology Unit in Rome (now the Neurobiology and Epigenetics Unit). He also pursued the conversion of the Data Library into EMBL-EBI, a move that had been decided under his predecessor but was largely implemented under Fotis' leadership. He drove the development of core facilities, training, outreach, technology transfer, industry collaboration and many ground-breaking pan-European research initiatives, which have transformed the way life scientists around the world work together.

During his tenure at EMBL, Fotis continued to carry out his own research, focusing on the study of malaria and its major insect vector, *Anopheles gambiae*. This work led to the sequencing of the A. gambiae genome and opened new avenues of study regarding the malaria parasite and its interactions with its insect host. Fotis also led studies on the *Drosophila* genome and is recognised as a pioneer in the development of comparative and functional genomics. In 2005, Fotis took up a position at Imperial College London, where he held the Chair of Insect Immunogenomics. He was elected as the first President of the ERC in 2007.

"Fotis had a huge impact on EMBL and the life sciences in general – the scientific community has lost a deeply caring colleague, friend and leader," says Iain Mattaj, EMBL Director General. "Fotis established two new EMBL units, he drove the reorganisation and expansion of PhD training and introduced the EMBL partnership scheme, amongst a multitude of other successes. But he was also a very approachable person, and what struck me most about him was his warmth, a feeling that was returned by all who knew him. Our thoughts are with Fotis' wife Sarah and his family at this time."

Colleagues of Fotis have created the Fotis Kafatos Prize for Excellence in Biology, which is to be awarded to the most promising young Greek researchers working in the life sciences anywhere in the world.

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EMBL alumni in pictures

Catching up with alumni around the world

←
EMBL in France took place on 9 June at the European Institute of Chemistry and Biology in Bordeaux.

↓
EMBL in Italy, dedicated to the late Riccardo Cortese, took place on 5 May.

→
EMBL alumni and their guests gathered in the University of Oxford's Lady Margaret Hall on 22 May.

↓
An EMBL in the USA weekend symposium took place in Gloucester, Massachusetts, 3-5 November.

Events

March
11-14

EMBL Heidelberg
EMBO | EMBL Symposium: Tissue Self-Organisation: Challenging the Systems

Upcoming meetings
Alumni

2 February
EMBL Staff and Alumni Reception, EMBL-EBI

23 March
EMBL Annual Pensioners' Coffee, EMBL Heidelberg

3-4 May
EMBL in Italy, IFOM, Milan

21 May
EMBL in the UK, Edinburgh University

20 July
Alumni Awards Ceremony & Dinner, EMBL Heidelberg

21 July
EMBL Summer Party, EMBL Heidelberg

March
16-17

EMBL-EBI
EMBL Course: Bioinformatics for Discovery

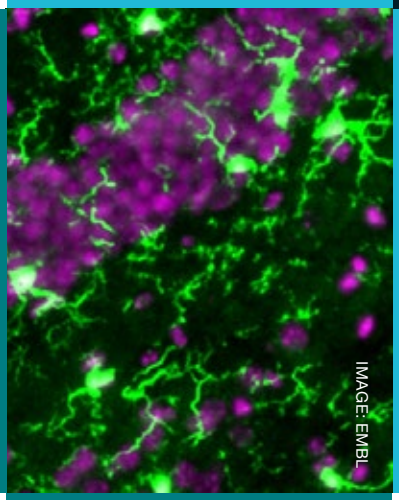
IMAGE: EMBL

March
18-21

EMBL Heidelberg
EMBO Workshop: Microglia 2018

April
15-17

EMBL Heidelberg
EMBO Workshop: Integrating Systems Biology: From Networks to Mechanisms to Models

April
25-27

EMBL Heidelberg
EMBL Conference: The Epitranscriptome

May
7-10

EMBL Heidelberg
EMBO | EMBL Symposium: DNA Replication: From Basic Biology to Disease

May
12-19

EMBL Grenoble
EMBO Practical Course: Characterisation of Macromolecular Complexes by Integrative Structural Biology

VIEW THE COMPLETE LIST OF EVENTS ONLINE: EMBL.ORG/EVENTS