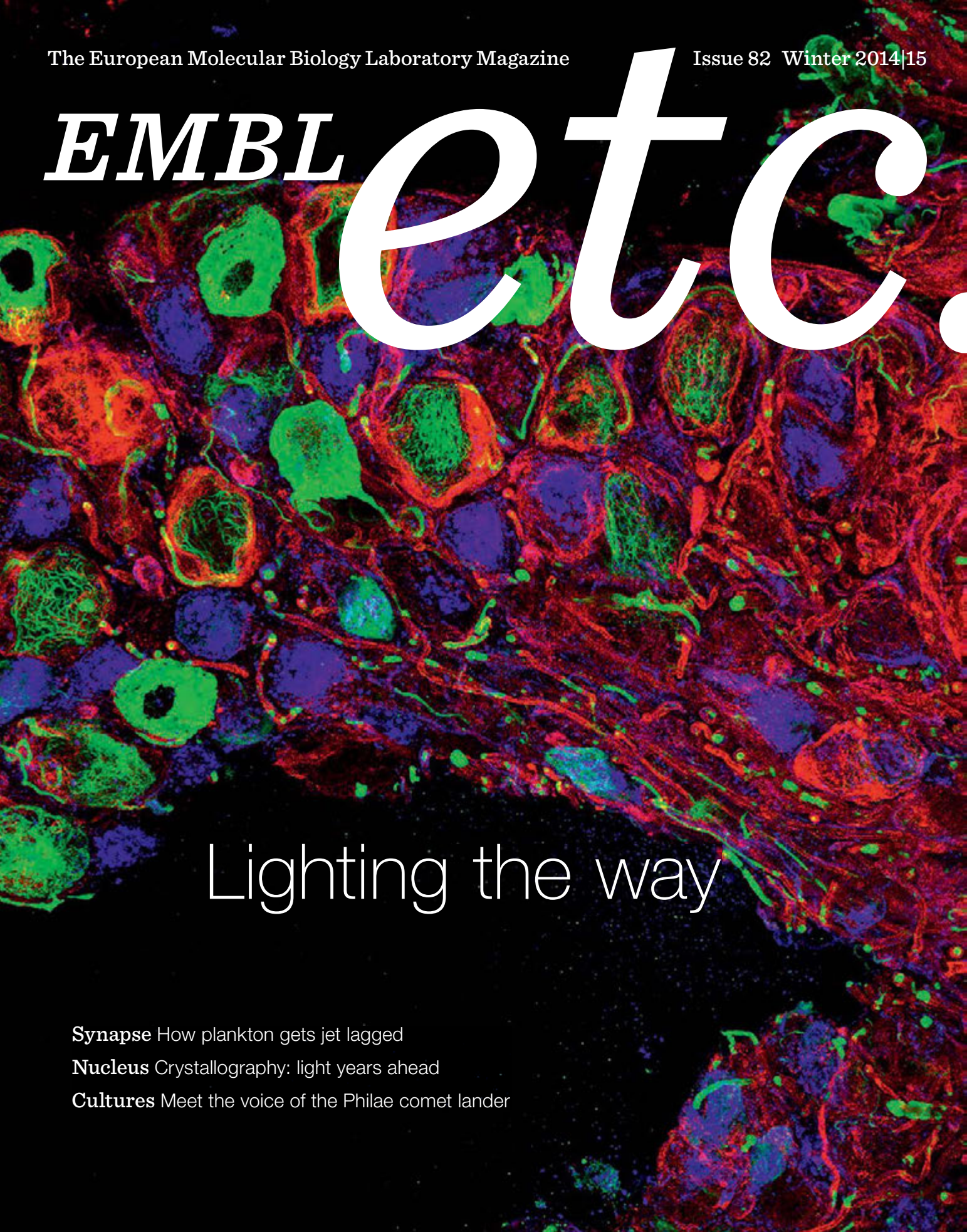
The European Molecular Biology Laboratory Magazine

Issue 82 Winter 2014|15

EMBL etc.



Lighting the way

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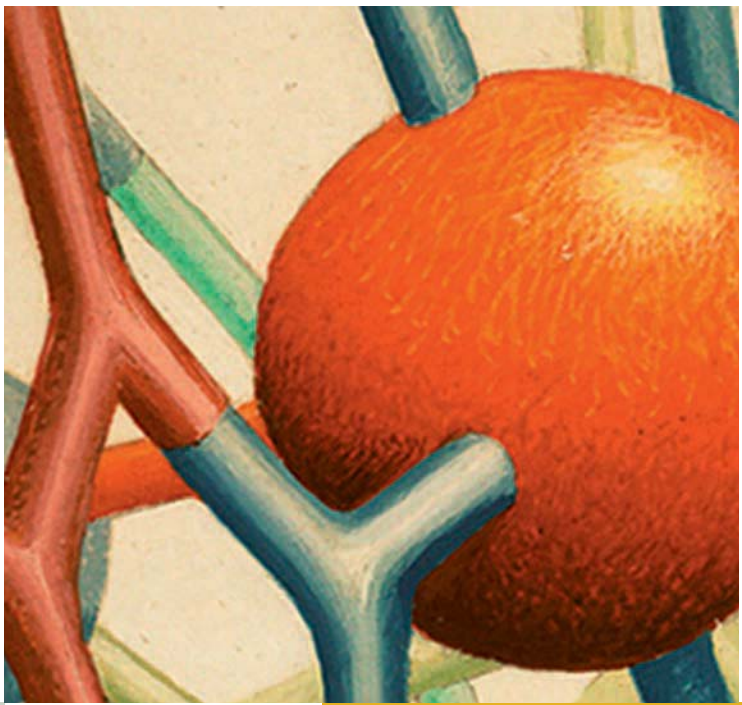

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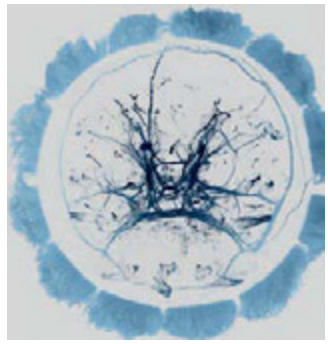

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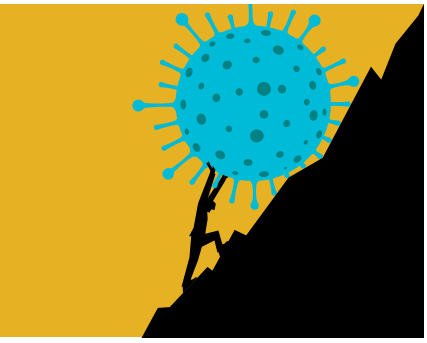

PHOTO: EMBL PHOTOLAB/MARIETTA SCHUPP

Editorial

It is a millennium since mathematician Ibn al-Haytham penned his revolutionary theory of optics, combining experimentation, geometry and psychology to deliver an alternative to Euclidean and Ptolemaic ideas of "visual rays" emanating from the eyes. Today, our understanding of light continues to cut across disciplines, and this edition, which coincides with the beginning of the United Nations' International Year of Light, looks at some of the ways light is informing, inspiring and illuminating work at EMBL and beyond.

We start this journey with EMBL Hamburg's recent 40th anniversary celebrations – an opportunity to explore the past, present and future of the revolutionary technique of X-ray crystallography (page 11). Another ingenious way of manipulating light is super-resolution microscopy – using fluorescence to extend the limits of the light microscope – a method pioneered by alumnus Stefan Hell (page 16).

Whether as tool, trigger, or messenger, light-related stories could be found almost everywhere we looked. From understanding the sleep patterns of plankton (page 5), the evolutionary origins of the eye (page 30), and new approaches using optogenetics (page 32), to celebrations (page 41), comet connections (page 44), and stunning animations (page 49), it is clear light is central to how we understand, interpret, and communicate science. And like our stunning cover image, which has captured media attention around the world (page 22), we can anticipate many more dazzling stories to come in this very special light year.

Adam Gristwood
Editor

Word to remember

Ommatidium

Noun, pronunciation: ˌɒməˈtɪdɪəm

One of the individual, light-sensitive units that together form a compound eye in arthropods such as insects and crustaceans.

Exploring the functions of different photoreceptors (page 30).

Publisher
European Molecular Biology Laboratory, Heidelberg
Office of Information and Public Affairs

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Director International Relations

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Design
Edenspiekermann, Amsterdam

Printed by
ColorDruck Solutions, Leimen

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Cover photo
EMBL/Laura Castaldi

EMBLetc. ONLINE
NEWS.EMBL.DE

How plankton gets jet lagged

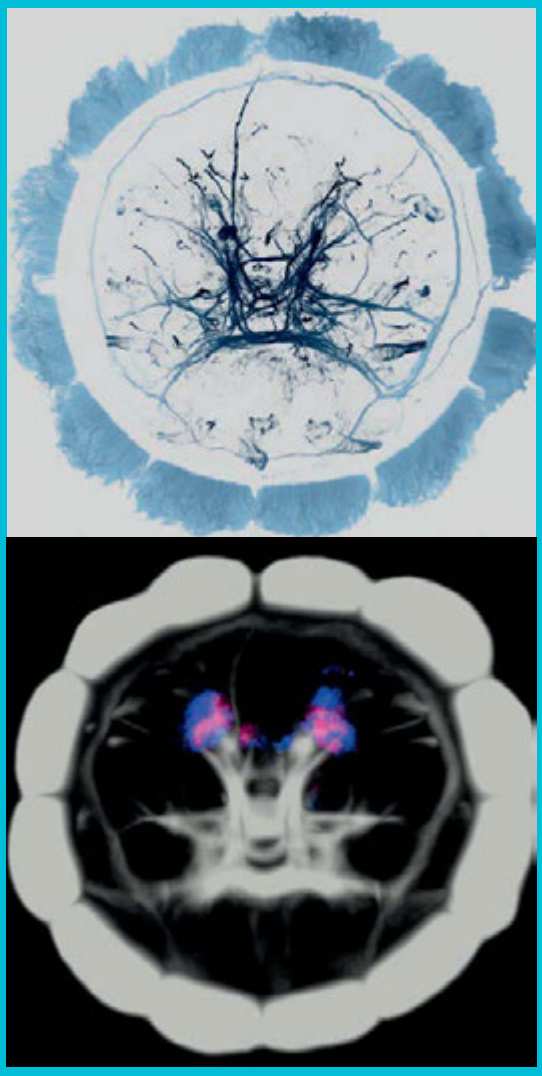
One of the world's largest migrations is probably driven by a hormone that governs our sleep patterns, scientists at EMBL Heidelberg have found. BY SONIA FURTADO NEVES

A hormone that governs sleep and jet lag in humans may also drive the mass migration of plankton in the ocean. The molecule in question, melatonin, is essential to maintain our daily rhythm, and scientists in the Arendt group have now discovered that it governs the nightly migration of a plankton species from the surface to deeper waters. The findings indicate that melatonin's role in controlling daily rhythms probably evolved early in the history of animals, and hold hints to how our sleep patterns may have evolved.

In vertebrates, melatonin is known to play a key role in controlling daily activity patterns – patterns which get thrown out of sync when we fly across time zones, leading to jet lag. But virtually all animals have melatonin. What is its role in other species, and how did it evolve the task of promoting sleep? To find out, the team turned to the marine ragworm *Platynereis dumerilii*. This worm's larvae take part in what has been described as the planet's biggest migration, in terms of biomass: the daily vertical movement of plankton in the ocean. By beating a set of microscopic 'flippers' – cilia – arranged in a belt around its midline, the worm larva is able to migrate toward the sea's surface every day. The larvae reach the surface at dusk, and then throughout the night they settle back down to deeper waters, where they are sheltered from damaging UV rays at the height of day.

"We found that a group of multitasking cells in the brains of these larvae that sense light also run an internal clock and make melatonin at night," says Arendt. "So we think that melatonin is the message these cells produce at night to regulate the activity of other neurons that ultimately drive day-night rhythmic behaviour."

Maria Antonietta Tosches, a postdoc in Arendt's lab, discovered a group of specialised motor neurons that respond to melatonin. Using modern molecular sensors, she was able to visualise the activity of these neurons in the larva's brain, and found that it changes radically from day to night. The night-time production of melatonin drives changes in these neurons' activity, which in turn cause the larva's cilia to take long pauses from beating. Thanks to these extended pauses, the larva slowly sinks down. During daytime, no melatonin is produced, the cilia pause less, and the larva swims upwards. "When we exposed the larvae to melatonin during the day, they switched towards night-time behaviour," says Tosches. "It's as if they were jet lagged."



IMAGES: EMBL/MARIA ANTONIETTA TOSCHES

Top: Every night, an increase in melatonin levels in this larva's brain makes it move away from the sea's surface. Bottom: Multi-tasking neurons sense light, run an internal clock, and produce melatonin.

Tosches, M.A., *et al. Cell*, 25 September 2014.
DOI: 10.1016/j.cell.2014.07.042

FULL REPORT ONLINE
NEWS.EMBL.DE/?p=1885

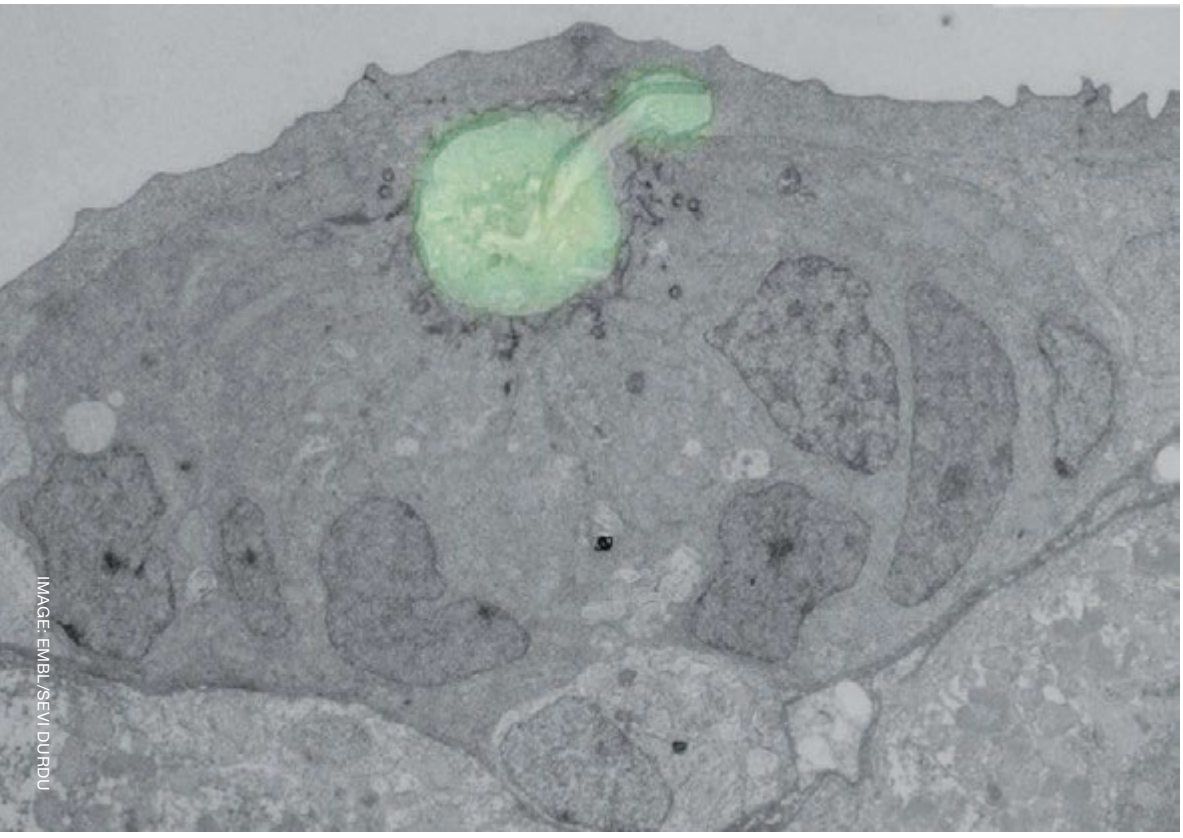


IMAGE: EMBL/SEVI DURDU

By huddling together, groups of cells can trap a signal molecule (green), to communicate within a restricted group

Chamber of secrets

Like sports teams agreeing their tactics in secret, cells, too, can huddle to communicate within a restricted group.

BY SONIA FURTADO NEVES

A study by Darren Gilmour's group at EMBL Heidelberg is the first demonstration that the way cells organise themselves influences their ability to communicate. The researchers propose that this strategy, which they discovered in developing zebrafish, could be much more widespread, influencing processes like wound repair, organ formation and even cancer.

Sevi Durdu, a PhD student in the Gilmour lab, found this behaviour in specific groups of cells in the zebrafish: the cells that will develop into a sensory organ called the 'lateral line'. She discovered that these cells, which migrate along the developing fish's flank, form groups that huddle around a shared space, or lumen, in which they trap a molecule called FGF.

Trapping the signal

"Normally, FGF acts as a long-range communication signal, and in the lateral line we find that most of this signal is normally just wafting over the cells' heads," says Gilmour. "But when cells get together and huddle they can trap and concentrate this signal in their shared lumen, and make a decision that the others can't: they stop moving. All epithelial cells – and that's the cells that make up most of the organs in our bodies – can do this, so you could imagine that this type of local chamber could be forming transiently in many different parts of the body, whenever cells need to self-organise and communicate."

Durdu, S. *et al. Nature*, 22 October 2014. DOI: 10.1038/nature13852

FULL REPORT ONLINE
NEWS.EMBL.DE/?p=2339

European Variation Archive launches

Detailed information about genetic variation is now simpler to explore in the new European Variation Archive.

BY MARY TODD BERGMAN

With the launch of its new, open-access European Variation Archive (EVA), EMBL-EBI is making it easier to explore detailed information about genetic variation. The EVA is the first archival resource at EMBL-EBI to provide a single access point for submissions, archiving, and access to high-resolution variation data of all types.

"We are launching the EVA with data from 15 high-profile studies that describe well over one billion submitted variants," says Justin Paschall, who leads variation archives at EMBL-EBI. "It lets you download the data from each study, individually or in bulk, and search it dynamically. That will be a big help to researchers working in this area."

EVA's 1.7 billion submitted variants are from large-scale efforts including the 1000 Genomes Project, Exome Variant Server, Genome of the Netherlands Project, and UK10K. The data in EVA is linked with external resources including Ensembl to display each variant in its genomic context. You can search the EVA by species, project, chromosomal location and many other fields. It supports complex queries based on gene, study, genomic location and variation type. It also lets users calculate allele frequencies across submitted studies and populations – a feature unique to EVA.

Digging deeper

The submission process is simple: researchers submit a VCF file of their data (and metadata), and the EVA team does the rest. Because the EVA's workflow is aligned to partner databases in dbSNP, dbVar, and ClinVar, data submitted to EVA is also shared with the National Center for Biotechnology Information (NCBI) in the US, forming the world's largest open genetic-variation dataset. The EVA provides data-mining and visualisation tools for exploring at the level of an individual study or variant. It is deeply linked in underlying read and alignment data available in the European Genome-phenome Archive (EGA) and European Nucleotide Archive (ENA), so users can follow the evidence chain from sequencing to variant calling.

The EVA is open source, and can be accessed programmatically. Users are invited to test the new EVA to its limits, and EMBL-EBI welcomes all feedback.

WWW.EBI.AC.UK/eva

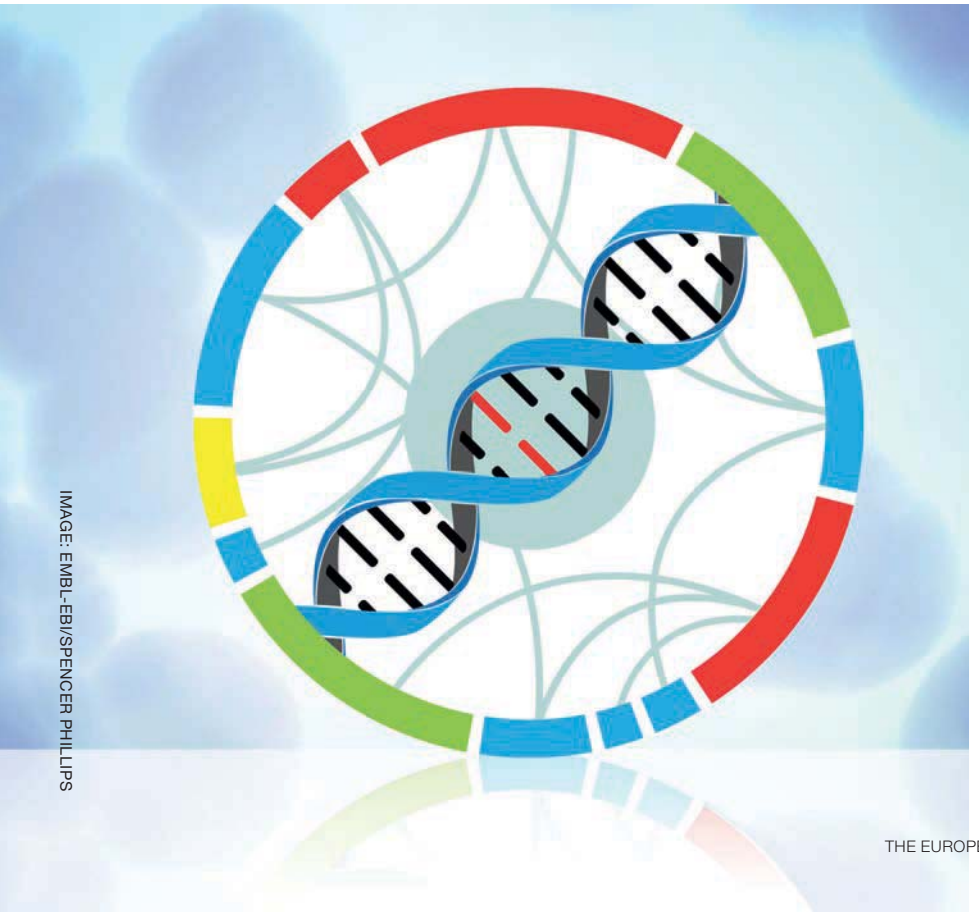


IMAGE: EMBL-EBI/SPENCER PHILLIPS

The European Variation Archive launches with data from 15 studies, describing well over one billion submitted variants

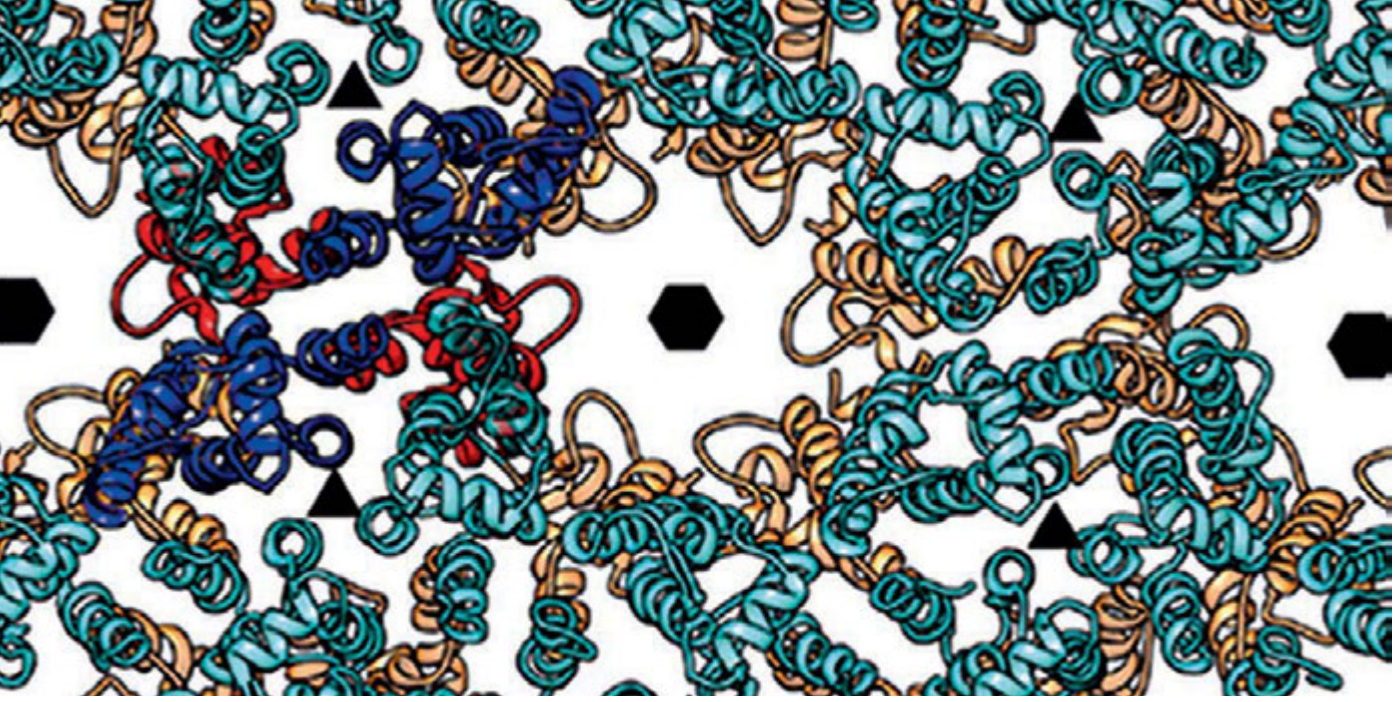


IMAGE: EMBL/FLORIAN SCHUR

An unprecedentedly detailed look at immature HIV revealed a surprise

Same pieces, different picture

Imagine you are putting together a puzzle, all your pieces align, and when you finish you have a completely different picture from what's on the cover. An unprecedentedly detailed look at the immature form of HIV has turned up a similar surprise.

BY SONIA FURTADO NEVES

This is not the first time the virus has challenged scientists' expectations. In the 1990s, Stephen Fuller at EMBL Heidelberg and colleagues obtained the first cryo-electron microscopy images of immature HIV, and found that the virus's protein lattice was surprisingly irregular.

Two decades on, Florian Schur, a PhD student in the Briggs group at EMBL Heidelberg, has obtained the first structure of the immature form of HIV at a high enough resolution to pinpoint exactly where each building block sits in the protein lattice. Working with colleagues at the Heidelberg University Hospital, in the joint Molecular Medicine Partnership Unit, he discovered that – like the puzzle forming an unexpected picture – those building blocks are not arranged in the pattern scientists had assumed.

"We assumed that retroviruses like HIV and Mason-Pfizer Monkey Virus – which we had also studied before – would have similar structures, because they use such similar building blocks, but it turns out that their immature forms are surprisingly different from each other," says Briggs. "At this point, we don't really know why."

Scientists can now use this structure to decide where to focus efforts for achieving the even greater detail needed to explore potential drug targets. It will also enable researchers to understand how mutations might influence how the virus assembles.

Schur, F. *et al. Nature*, 2 November 2014. DOI: 10.1038/nature13838

FULL REPORT ONLINE
NEWS.EMBL.DE/?p=2448

Building an EMPIAR

EMBL-EBI has just launched EMPIAR: a resource that lets researchers browse, download and reprocess thousands of raw, 2D electron microscopy images used to build 3D structures.

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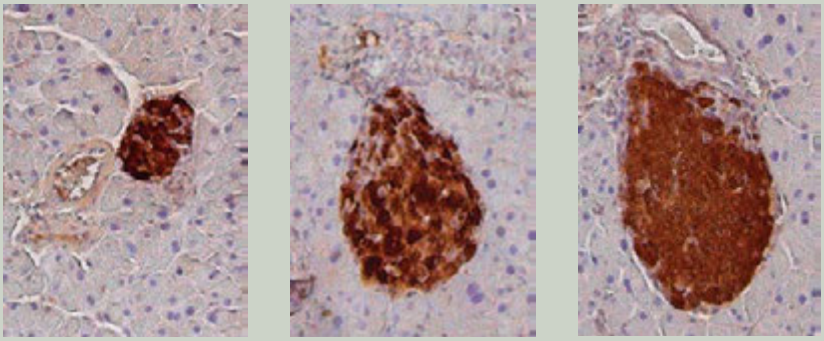

IMAGES: EMBL/DANIEL BILBAO

Treatment with IGF-1 (middle) brings the pancreas of mice suffering from diabetes (left) close to normal (right)

Protecting us from our cells

Therapy already approved as treatment for other conditions could help fight auto-immune diseases such as type-1 diabetes and multiple sclerosis.

BY SONIA FURTADO NEVES

Our immune system defends us from harmful bacteria and viruses, but, if left unchecked, it can turn on the body itself, causing auto-immune diseases like type-1 diabetes or multiple sclerosis. A molecule called insulin-like growth factor-1 (IGF-1) boosts the body's natural defence against this 'friendly fire', scientists at EMBL Monterotondo have found.

"To me what was really striking was the survival rate for multiple sclerosis," says Daniel Bilbao, who conducted the research with Nadia Rosenthal's lab at EMBL. "We went from less than 50% survival in untreated animals to over 80% survival in animals that received IGF-1."

In a separate study published earlier this year, Bilbao and Rosenthal had found that IGF-1 has the same effect on another condition in which the immune system goes awry: allergic contact dermatitis. "These studies have real clinical significance, because IGF-1 is already an approved therapeutic, which has been tested in many different settings, so it will be much easier to start clinical trials for IGF-1 in auto-immune and inflammatory diseases than it would if we were proposing a new, untested drug," says Nadia Rosenthal, former Head of EMBL Monterotondo, and now at Imperial College London and Monash University, where she is Scientific Head of EMBL Australia.

Bilbao, D., *et al. EMBO Molecular Medicine*, 22 October 2014.
DOI: 10.15252/emmm.201303376

FULL REPORT ONLINE
NEWS.EMBL.DE/?p=2322

Model(ler) collaborations

A new repository from the Drug Disease Model Resources (DDMoRe) consortium helps researchers share computational models of disease used in pharmaceutical research and development. This open resource will make it easier for researchers to refine and reuse models of drug action and disease progression.

FULL REPORT ONLINE
NEWS.EMBL.DE/?p=2416

Fixing cellular powerhouses

Lars Steinmetz's lab at EMBL Heidelberg and collaborators have identified a compound that can restore the cell's powerplants – mitochondria – when they fail, raising the possibility of new treatments for mitochondrial disorders.

Aiyar, R. *et al., Nature Communications*, 18 December 2014.
DOI: 10.1038/ncomm6585

FULL REPORT ONLINE
NEWS.EMBL.DE

MASSIF step forward

A new era of automation has dawned at the ESRF in Grenoble. In September 2014 the first of the Massively Automated Sample Selection Integrated Facility (MASSIF) beamlines opened – but users will never physically come to the beamline.

BY MATTHEW BOWLER

MASSIF1, operated by the EMBL/ESRF Joint Structural Biology Group, offers a unique, fully automated service for sample evaluation and data collection from crystals of macromolecules. The new service is not designed to replace all user visits to the synchrotron but rather to do the hard work of screening crystals through the night, freeing researchers to spend time on more challenging data collection problems and study the underlying biology. In less than two months of operation, more than 2.3 million diffraction images have been collected from 1422 samples – ranging from initial hits from crystallisation experiments to large-scale data set collection for drug discovery programmes.

As MASSIF1 is fully automatic, data are collected for the first time in a consistent manner and should allow the accumulation and comparison of a large amount of information that was previously unknown, including the exact dimensions of crystals and deeper information about their quality. Once the beamline has been running for an extended period, it will provide a treasure trove of additional information to feed back into crystallisation experiments and the software used to collect the data.

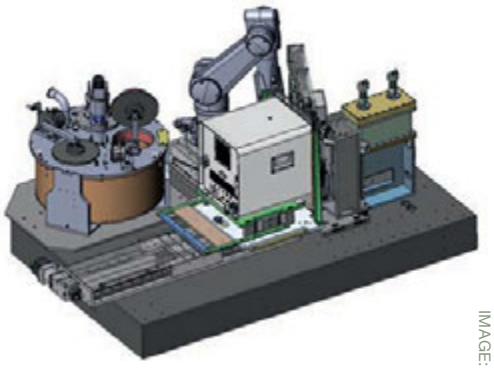

IMAGE: MATTHEW BOWLER/EMBL

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NEWS.EMBL.DE/?p=2791

Shaping up

A new study led by Sarah Teichmann's group at EMBL-EBI describes a fundamental mechanism regulating a protein's shape. Working in much the same way as a hair clip, the mechanism involves mutations acting on one side of a protein to open or close the configuration of amino acids on the other.

BY MARY TODD BERGMAN

The findings, published in *Science*, have implications for the manipulation of proteins, with potential applications in biotechnology and drug development.

The shape of a protein determines its function, but that shape can change under different conditions. Understanding how that works is key to figuring out how to manipulate a protein's function, for example its interaction with a drug. In this study, the group explored proteins that control a basic process in metabolism to determine how a protein morphs from one configuration to another.

"These proteins provide a very good example of a fundamental biophysical phenomenon that we think can happen in many proteins, regardless of which organism," says Teichmann. "We believe our findings will help future research into manipulating proteins, which has potential applications across the life sciences."

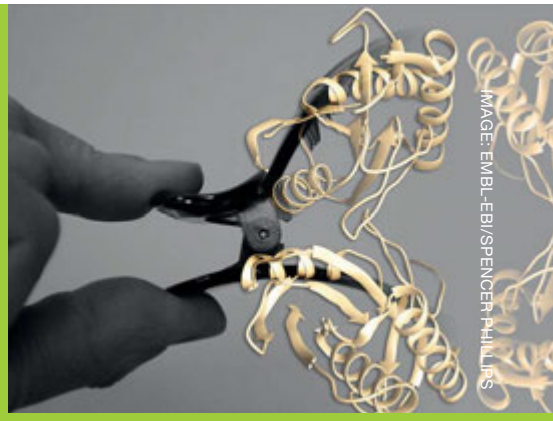


IMAGE: EMBL-EBI/SPENCER PHILLIPS

"We were really pleased to do the elastic network modelling for this study, because it helps you see the dynamics of how the protein goes from one configuration to another," adds Nathalie Reuters of the University of Bergen, Norway.

Perica, T., *et al. Science,* 19 December 2014. DOI: 10.1126/science.1254346

FULL REPORT ONLINE:
NEWS.EMBL.DE/?p=2860

Light years ahead

As EMBL Hamburg celebrates its 40th anniversary, we explore the past, present and future of the incredible world of crystallography.

BY ROSEMARY WILSON

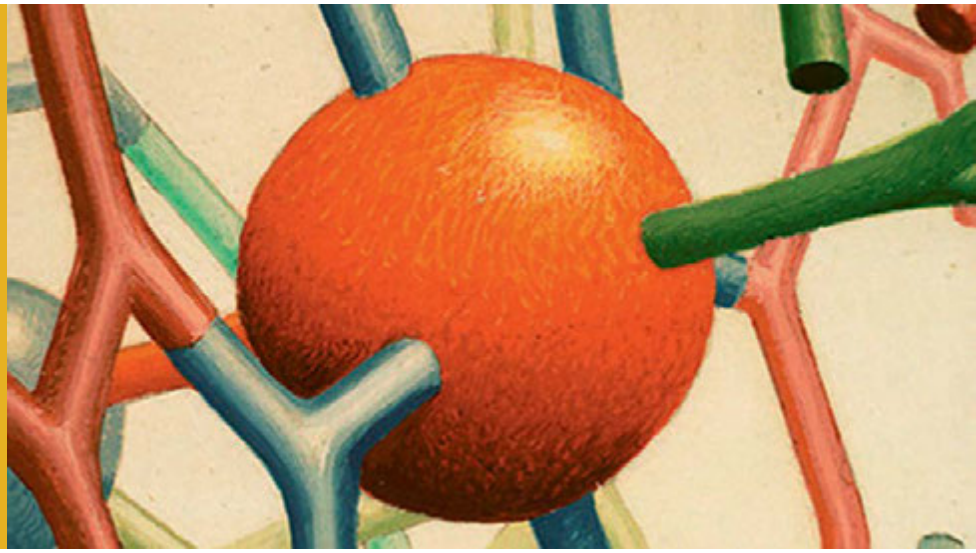
Just over a century ago, physicist Max von Laue pioneered a discovery that shone new light on the structure of our world. By firing X-rays at crystals, he revealed a pattern of remarkable spots that proved that X-rays are high-frequency waves. But by doing so, he also unearthed another puzzle: why did the X-rays scatter in such a regular fashion? The race was on to make sense of the story that von Laue's two-dimensional pattern told. The father-and-son team of William and Lawrence Bragg focused their attention on the nature of the crystals themselves, and they realised that by studying the way the X-rays reflected, the pattern could be transformed into a three-dimensional model of the molecules constituting the crystal. They found that these molecules formed a lattice with atoms arranged in layers throughout, describing them as "like soldiers in a parade or the pattern of a wallpaper". By working backwards from the pattern they were able to mathematically reconstruct the structure of the molecule, each ray relaying a tiny package of information about the molecules within. Crystallography was born.

Fast forward 100 years, and it is difficult to imagine where natural science would be without the field of structural analysis. Since the initial experiments that revealed simple >>

IMAGE: EMBL/GLEB BOURENKOV

In 1958, Sir John Kendrew and colleagues published the first X-ray crystallography-generated atomic structure of a protein – myoglobin.

Illustration: Detail of "Crystal Structure of Myoglobin", Irving Geis, 1961. Image from the Irving Geis Collection. Rights owned and administered by the Howard Hughes Medical Institute. Reproduction by permission only



Today, biologists are amongst the greatest users of synchrotrons

>> structures of molecules such as salt and diamond, the technique has been used to analyse those of increasing complexity, not just matter that is naturally crystalline, but anything that can be induced to be crystalline – including proteins and viruses. Understand the structure of a molecule, and you can begin to understand its function, and the technique provides a means to learning why and how genes are turned on and off, how cells defend themselves against invaders, and the nature of the switches that initiate cell division. Indeed, crystallography has played a key role in countless stunning discoveries, including the structures of DNA, penicillin, myoglobin, the ribosome and, more recently, whole viruses.

In sync

Just as when Galileo first trained his primitive telescope on the night sky and so changed the way we view and understand the cosmos, X-ray diffraction allows scientists to see what was previously invisible, at the molecular level. But as with the development of early telescopes there were many hurdles still to come, and as molecular biology advanced, the limitations of early light sources such as laboratory X-ray tubes were exposed. But a crucial breakthrough came in 1970, when Ken Holmes and Gerd Rosenbaum of the Max Planck Institute for Medical Research in Heidelberg published a study in *Nature* that investigated the mechanisms of insect flight muscles (see page 50). The work, which was carried out at the German Electron Synchrotron (DESY) in Hamburg, included a smudgy photograph of a diffraction pattern that sparked worldwide interest: proof that synchrotron radiation can be used to study biology.

What was previously the toolbox of physicists became useful for molecular biologists too, and many more biological secrets were set to come within the firing range of structural analysis. Holmes mobilised some of the biggest names in science, and his vision led to the establishment of facilities to run structural biology experiments at the DESY campus – the birth of EMBL's first outstation in Hamburg in 1974 – and the beginning of a long and celebrated partnership with the research centre that continues to this day.

Accelerating biology

In a synchrotron, particles are first accelerated along a linear track before being passed into circular machines, where magnets force them to move around a circular path. As they do so, light in the form of X-rays is radiated outwards, much like how you might lose the contents of your pockets while sitting on a roundabout at the fair. This synchrotron radiation can then be channelled through a series of optics and mirrors known as a beamline, firing an extremely intense, narrow beam of X-rays at the crystal. This beam – many magnitudes brighter than sources used to take X-rays at the doctor's surgery – reveals much greater structural detail from weakly scattering samples such as protein particles. Today, biologists are amongst the greatest users of synchrotrons and the instruments used are larger, more complex and more precise than the pioneering scientists of yesteryear could ever have imagined.

Since 2009, DESY's campus has been home to PETRA III – one of the most brilliant storage ring-based X-ray radiation sources in the world. Here, structural biologists from around the world have access not only to top-level instrumentation, but also to sample preparation and characterisation facilities, small angle scattering beamlines, data analysis software, robotics, as well as scientific and logistical support. The structures of larger and more complex proteins can be tackled with greater precision, fewer resources and less time – many remotely from the comfort of the user's office.

Crystal maze

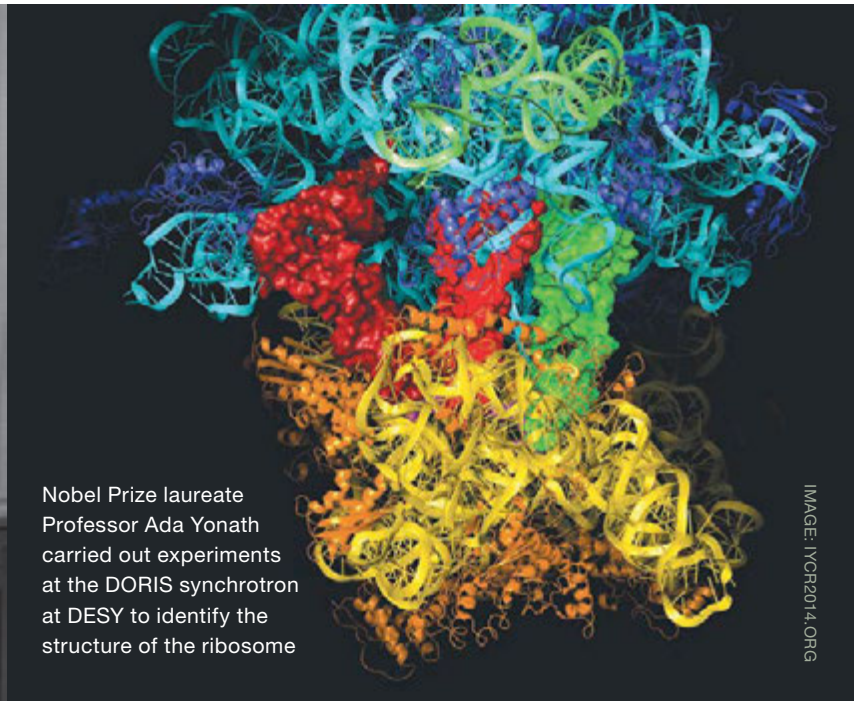
But for all these technological developments, there is still one crucial limiting factor when it comes to crystallography: crystals. Unfortunately, there is no universal recipe for producing them. Many crystallographers spend weeks, months or even years trying to crystallise a protein, gently tinkering with different concentrations of buffers and salts to seek out the optimal conditions. As our understanding of biology advances so too does our ambition to decipher the workings of larger complexes, such as membrane-bound proteins that mediate molecular traffic coming in and out of the cell. And it is exactly these molecules that are exceptionally difficult – if not impossible – to crystallise due to complexities in the scattering process that cannot be corrected using data analysis. Or, equally frustrating, some produce multiple microcrystals – too small to use in X-ray analysis or too weak to survive damage from radiation.

New techniques such as serial femtosecond crystallography are offering the tantalising prospect of overcoming some of these hurdles. Massive machines called free electron lasers (FEL) accelerate electrons along a linear track until they produce very short and intense X-ray pulses. From this, pulses of light lasting just 50 femtoseconds (20,000 times shorter than a nanosecond), and with a peak energy one billion times greater than the most powerful synchrotrons, smash crystal samples down to a micron in size to smithereens almost instantly. But crucially, if the X-ray pulse is short enough, it can pass through the crystal before it has time to explode – producing a clear diffraction pattern, with no radiation damage.

Researchers using the FLASH FEL on the DESY campus – a smaller version of the future European XFEL due to power up in 2017 – demonstrated this 'diffraction before destruction' principle, meaning that images can be collected faster than the X-rays destroy the sample. Studies using the Stanford-based SLAC National Accelerator Laboratory FEL have taken this a step further, with researchers recently solving previously unknown structures such as cathepsin B – an enzyme found in the sleeping sickness parasite *Trypanosoma brucei*. But availability of beam time is very limited, and a huge challenge lies in producing the massive amounts of sample needed for experiments to succeed. >>

In 1975 EMBL and DESY entered into a formal agreement to set up an EMBL outstation at DESY in Hamburg

PHOTO: DESY



Nobel Prize laureate Professor Ada Yonath carried out experiments at the DORIS synchrotron at DESY to identify the structure of the ribosome

IMAGE: IYCR2014.ORG

On the pulse

These were challenges EMBL Hamburg group leader Thomas Schneider had in mind when leading a study to solve the structure of cathepsin B for a second time. But a simple replication exercise this was not. Instead of using a FEL, he wanted to explore the complementary potential of the latest generation of synchrotrons. Back when EMBL began to plan the construction of the next generation of beamlines at PETRA III, Schneider's vision was to develop instruments capable of measuring micron-sized crystals, mobilising the power of third-generation synchrotrons to determine the structures of the tiniest crystals composed of the largest repeating units. Some six years since the construction of the beamlines began, they managed to do exactly that. In a paper published in 2014 in the *International Union of Crystallography (IUCr) Journal*, the team of scientists from EMBL, the Centre for Free-Electron Laser Science (CFEL) and the universities of Hamburg and Lübeck, resolved the crystal structure of cathespin B by analysing microcrystals of the enzyme, this time using synchrotron radiation.

A typical serial femtosecond crystallography experiment at a FEL involves flowing a suspension of microcrystals across a fine and intense X-ray laser beam – much like the flow of ink from an inkjet printer – which results in hundreds of thousands of single diffraction images. This principle was adopted for use on the EMBL microfocus beamline P14 at PETRA III. But instead of shooting the crystals across an X-ray beam, a small volume of cryo-cooled crystalline solution containing around 5000 crystals was mounted in a standard nylon loop, which was then scanned by the PETRA III beam.

The results are hugely encouraging: although the resolution doesn't (yet) quite match that of the data collected at the FEL, the team is convinced there are many other benefits, including less resources needed, and greater availability and accessibility of equipment. "Our experiment used a lot less sample than that needed for the FEL and measuring the crystals at the synchrotron could be a useful first step to check and optimise the quality of your sample, before having to produce large amounts for FEL experiments," Schneider explains. "The set-up is conceptually simple and can be applied to other state-of-the art synchrotrons – in comparison to the restricted access to FEL facilities," adds Gleb Bourenkov, EMBL Hamburg staff scientist and project leader at beamline P14.

Crucial for the success of the project was the high precision diffractometer developed together with colleagues at EMBL Grenoble and the micrometer-sized high intensity X-ray beam produced at PETRA III. "We have just made optimal use of what we had available, but none of this would have been possible without our close and productive working relationship with colleagues at EMBL Grenoble

"Since 2009, DESY's campus has been home to PETRA III – one of the most brilliant storage ring-based X-ray radiation sources in the world"

PHOTO: DESY

German Chancellor Angela Merkel attended a naming ceremony in 2012, with the PETRA III experimental hall given the name "Max von Laue"

and DESY," says Schneider, who points out that background "noise" can be countered by reducing the beam size to exactly that of the crystal, delivering a clearer signal and higher resolution data. The technique, known as serial synchrotron crystallography, will be available as a standard method on P14 for visiting users later in 2015.

Bright future

This work has added to the palpable sense of excitement ahead of the opening of the European XFEL in two years time. On the other side of the DESY campus, stretching some 3km through underground tunnels into the neighbouring federal state of Schleswig Holstein, the most powerful FEL in the world is currently under construction. "The ultra-fast flashes produced by the European XFEL could make it possible to take pictures of single protein molecules without the need for crystallisation, or watch molecular reactions in real time," says Matthias Wilmanns, Head of EMBL Hamburg. "For example, international teams have already managed to stimulate and record structural changes in light sensitive proteins involved in photosynthesis. The possibilities are seemingly endless and truly mind boggling."

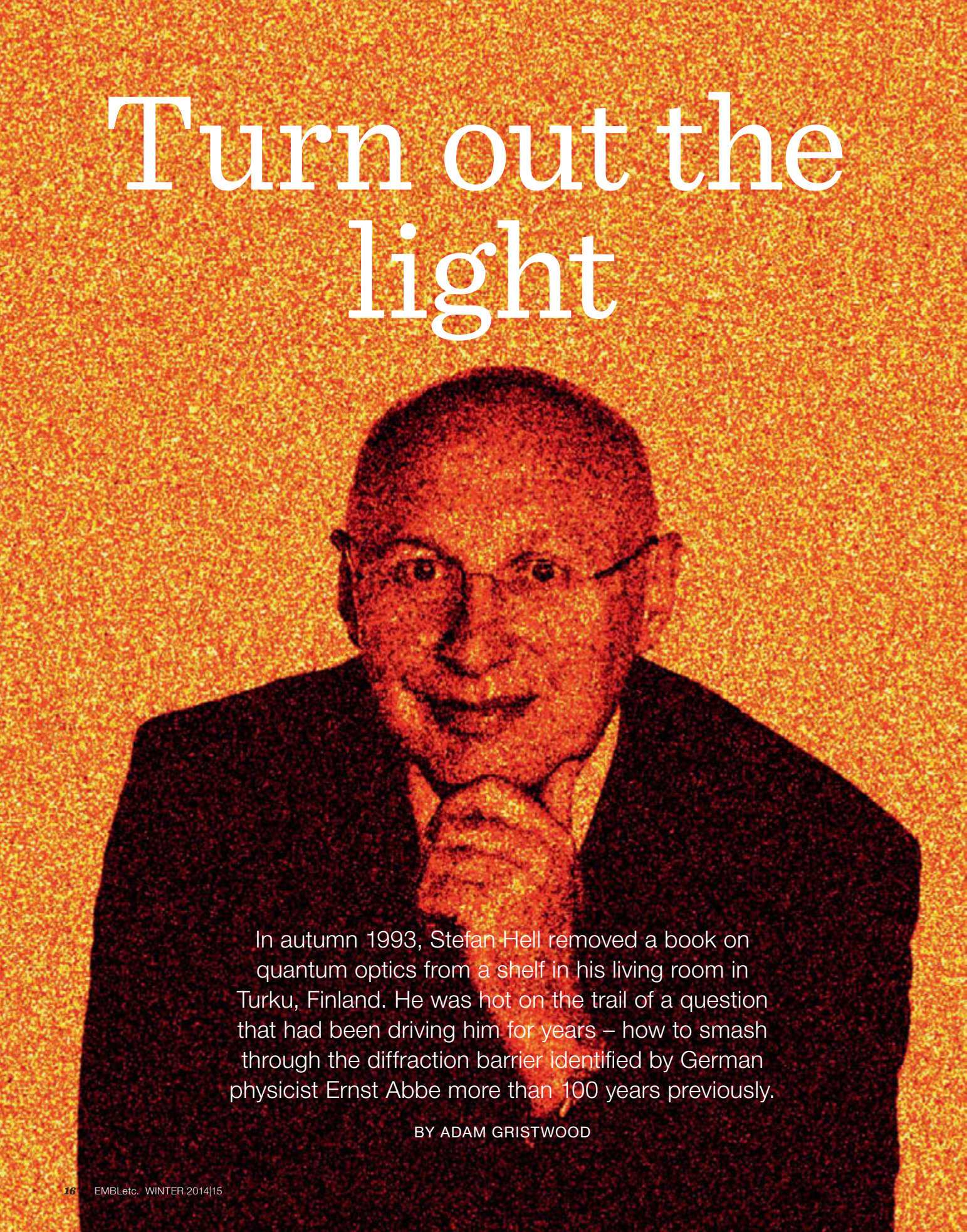
Collaborative projects in anticipation of this new research arsenal have already begun to exploit the remarkable potential for measuring three-dimensional structures and dynamics of single bioparticles. One example is an initiative to standardise protocols for sample preparation, provide novel sample delivery methods, and develop the first comprehensive software package to interpret the data is being coordinated by EMBL Hamburg group leader Victor Lamzin. Called "Laseromics", it brings together experts from EMBL Hamburg, University of Osnabrück and Moscow institutes – including Moscow State University and the Kurchatov Center.

Another sees Wilmanns and Schneider team up with Henry Chapman, a physicist at CFEL, and two groups in Moscow, for a project aimed at developing combined applications for synchrotron radiation and FELs in molecular medicine. "We are seeing some great collaborations and innovative projects being established across the campus between groups working at the synchrotron and XFEL and we are sure this spirit will continue," adds Wilmanns. "During the past few years we have seen how important it is to have a sample preparation laboratory directly next to the PETRA beamlines to ensure effective and timely use of precious protein samples. We are eager to apply our knowledge gained from working at the synchrotron to new challenges ahead at the European XFEL."

PHOTO: EUROPEAN XFEL

Underground construction of the European XFEL was completed in 2013

Turn out the light



In autumn 1993, Stefan Hell removed a book on quantum optics from a shelf in his living room in Turku, Finland. He was hot on the trail of a question that had been driving him for years – how to smash through the diffraction barrier identified by German physicist Ernst Abbe more than 100 years previously.

BY ADAM GRISTWOOD

Hell set about exploring ways that focused not on light and optics but on the molecules themselves being studied. Browsing the book, he struck upon the words "stimulated emission", and was stunned to read that molecules excited to fluoresce could be 'turned off' temporarily. It provided him with the lead he was looking for. Using chemistry to circumnavigate the laws of physics, he went on to develop stimulated emission depletion (STED) microscopy at the Max Planck Institute for Biophysical Chemistry in Göttingen, a technique that enables researchers to zoom in on the nano-world and watch life as it unfolds. Within a week of being awarded his Nobel Prize in Chemistry in October 2014, Hell visited EMBL Heidelberg, where he was a postdoc in the early 1990s.

When did you realise your idea would be possible?

I wondered whether there was still something profound that could be done with light microscopy, which seemed to me like 19th Century physics, and I saw that the diffraction barrier was the only important problem that was left. It was not feasible to break the barrier by changing the way light is focussed, so I started thinking about quantum optical effects or – more promisingly – the idea of playing with molecules and changing their molecular states. One approach I considered involved re-exciting fluorescent molecules from an excited state, to see if this could lead anywhere. Then, a book chapter on stimulated emission caught my attention. I immediately thought: why excite the molecules? Why not de-excite them and keep them in the dark? If I could find a way of turning off all but a nano-sized area of light emitted by a source, then it would be possible to get rid of the light that creates blurriness and thus

PHOTO: EMBL PHOTOLAB/MARIETTA SCHUPP. SUPERRESOLUTION PROCESSING: JONAS RIES (BASED ON PALM TECHNIQUE DEVELOPED BY ERIC BETZIG)

"When I was at EMBL in the early 1990s, it was the unrecognised cradle of a revolution in light and electron microscopy"

enhance the resolution. This was the moment when it dawned on me that I had finally found a concrete thread to pursue this idea. What happened next was the most exciting time of my professional career – I sat there with the incredible feeling that I might know something that no one else in the world knows.

What were the biggest challenges you faced?

A strong impression had developed amongst the scientific community that Abbe's barrier could not be broken – doing something against it was seen as kind of crazy, or unrealistic. Indeed, since its discovery, ideas had been repeatedly proposed to overcome it, but none had really succeeded and it was natural that there would be scepticism towards STED and related ideas. But I was convinced it would work as I could not find a basic flaw in my concept – basic problems will probably remain, but technical ones can be overcome. Still, there were many hurdles: support and funding was often in short supply – first the idea had to be proven in principle, then in practice – and even then, many doubted its broad applicability. But because I knew the idea was fundamentally correct, I held onto it and did not allow myself to be misled when people said it could not work.

What advice do you have for young researchers?

Employ a healthy disregard for scientific paradigms. Institutions should support young researchers in pursuing unusual research topics and to take risks – the most exciting science happens when questions are asked in the context not of careers but of discovery. The work that earned me the Nobel Prize was about overwriting one paradigm, but there are undoubtedly many others out there waiting for someone to think about them in a different way.

What are your memories of your time at EMBL?

When I was there in the early 1990s, EMBL was the unrecognised cradle of a revolution in light and electron microscopy. The Laboratory is open-minded, international, and quality-driven and places significant trust in young researchers. In many respects I began my scientific career here – at first I felt a bit alien as a physicist in a biology institute – but I very much enjoyed collaborations with biologists, chemists, medical scientists, and researchers from other disciplines. In the end, interdisciplinarity held the key to cracking the barrier. I would have loved to stay if it had been possible.

What now?

The ability to see and image at the nanoscale is critical to further advances in nanoscience. Work today is opening up possibilities in a vast number of areas, including improved diagnostic tools, studying the impact of medicines directly within the cell, and deeper insights into the nature of disease. My own work is now largely focused on neurobiology. We are interested in how cells interact with each other in tissues, especially in the brain, and how memory works at a molecular level. I was fascinated by the idea of delving into an old question of physics that everyone thought had been answered once and for all – it was a matter of principle – and we have seen just the tip of the iceberg in terms of what we can learn. It is very exciting to think about where this may lead in the coming years.

Breaking boundaries

Alumnus Stefan Hell jointly received this year's Nobel Prize in Chemistry, for breaking barriers in light microscopy. This pioneering discovery shapes the work of EMBL scientists – how, why, and what's next?

BY SAM LEMONICK

In the 1600s, the first microscopes allowed people to see a world hidden until then by the limits of the human eye: amoeba, sperm cells, the details of insects' wings. It took almost 400 years for researchers to push the optical microscope deeper, bringing into focus individual molecules and the inner workings of cells.

The Royal Swedish Academy of Sciences awarded the 2014 Nobel Prize in Chemistry to three of the researchers responsible for inventing what is called nanoscopy or super-resolution microscopy, recognising Eric Betzig, William Moerner and Stefan Hell.

The three were able to circumvent something called the Abbe limit, once considered a hard minimum on the smallest object an optical microscope could distinguish. An equation formulated in 1873 by Ernst Abbe showed it was impossible to resolve two objects closer than half of light's wavelength, about 200-350 nanometers. That's enough to clearly see a whole human cell or bacterium, but not a virus or a protein. While electron microscopes – developed in the 1920s and 30s – can see much smaller than that, they require samples to be set in preservative or frozen and sliced into thin layers, and therefore cannot be used to look at living cells.

Ingenious solution

Working first at the University of Turku in Finland and then at the Max Planck Institute for Biophysical Chemistry in Göttingen, Hell was one of the first to show that this boundary on optical microscope resolution could be circumvented if dyes with special photochemical properties are used, raising the tantalising possibility of a microscope that achieved a level of detail close to that of electron microscopy without its drawbacks. He did it by limiting the area in which the dyes responded to light to a region narrower than the resolution limit, circumventing the Abbe limit.

First, Hell used fluorescent dyes – compounds that glow when exposed to light – to tag specific molecules within cells. Then, he shined two lasers on the sample, one that made the dye glow in a focused point, and a second in a doughnut shape around that point which cancelled out fluorescence from most of the area except for a nanometre-sized central spot. By moving this effectively 'sharpened' laser beam across a sample, Hell could piece together clear images of structures below Abbe's theorised limit. Betzig and Moerner achieved a similar result by selectively activating single fluorescent molecules a few at a time, then combining many such images to get a clearer, more highly resolved picture.

"We all learned in high school that you cannot use a microscope beyond half the wavelength of the light the specimen emits," says Rainer Pepperkok, head of the EMBL Core Facilities and Advanced Light Microscopy Core Facility, and Team Leader in the Cell Biology and Biophysics Unit. "We are just now getting beyond this barrier and therefore we are able to see

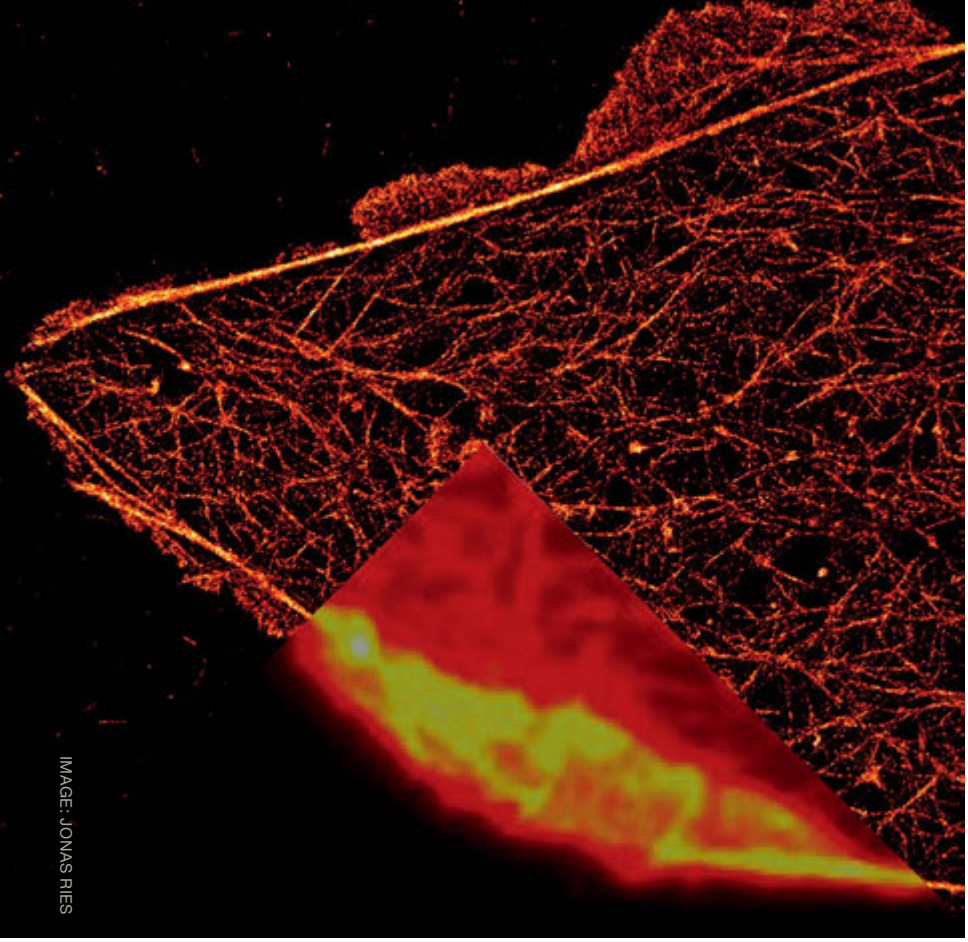


IMAGE: JONAS RIES

Zooming in on an actin meshwork: a comparison of confocal and STED microscopy demonstrates the stark difference in resolution

"We are able to see structures that we have never been able to see before"

structures and the dynamics of structures that we have never been able to see before."

Watching life move

Pepperkok is among many EMBL scientists who use microscopy in their work. His group studies how molecules move across the membranes of cells and between organelles. The structures that control movement between organelles are only 50 to 60 nanometers across – about 2000 times smaller than the thickness of a human hair – while other structures are within a few nanometers of each other, well below the limit of ordinary optical microscopy. "Live cell imaging is a must for us," he explains, "because we want to study how these things move." That's why electron microscopy – which can pinpoint such nanostructures but only works well with very thin slices of fixed cells – is also out of the question.

His group needs to see how the molecules interact in functioning cells to truly understand what is happening. "Work in a living cell was hampered for many years because an ordinary light microscope does not provide the resolution that is required to resolve the structure that we are interested in," he says. With super-resolution microscopy, observing live cells at that level of detail is now possible.

That capability has allowed Edward Lemke, group leader in the Structural and Computational Biology Unit, to better understand the proteins that control traffic in and out of a cell's nucleus. Lemke explains that the proteins that regulate this process are disordered in their natural state inside the cell, meaning they don't have a rigid three-dimensional structure that computers can predict or that can be easily determined by structural biology techniques, such as those used at EMBL Hamburg and EMBL Grenoble. In future, Lemke and his group would like to use super-resolution microscopy to see how such proteins act in the dynamic conditions inside a cell.

"The idea of moving biochemistry into the living cell is dramatically facilitated by super-resolution microscopy," he says. By turning cells into test tubes, scientists can learn much more about the way protein interactions and other biochemical processes unfold in the real world.

Lemke's group have also used the quantitative capabilities of super-resolution microscopy. "There were estimates that the nuclear pore protein complex had around 1000 proteins, but no one really knew exactly how many there were," Lemke explains. From the intensity and frequency of the dye-tagged proteins' glow, the group was able to determine exactly how many proteins the complex contained. "This was something we couldn't have done before super-resolution microscopy, something I don't know any other way we could have done."

Expanding into space

Jonas Ries is another young scientist pushing the boundaries of microscopy. A group leader in the Cell Biology and Biophysics Unit, Ries is working to improve the >>

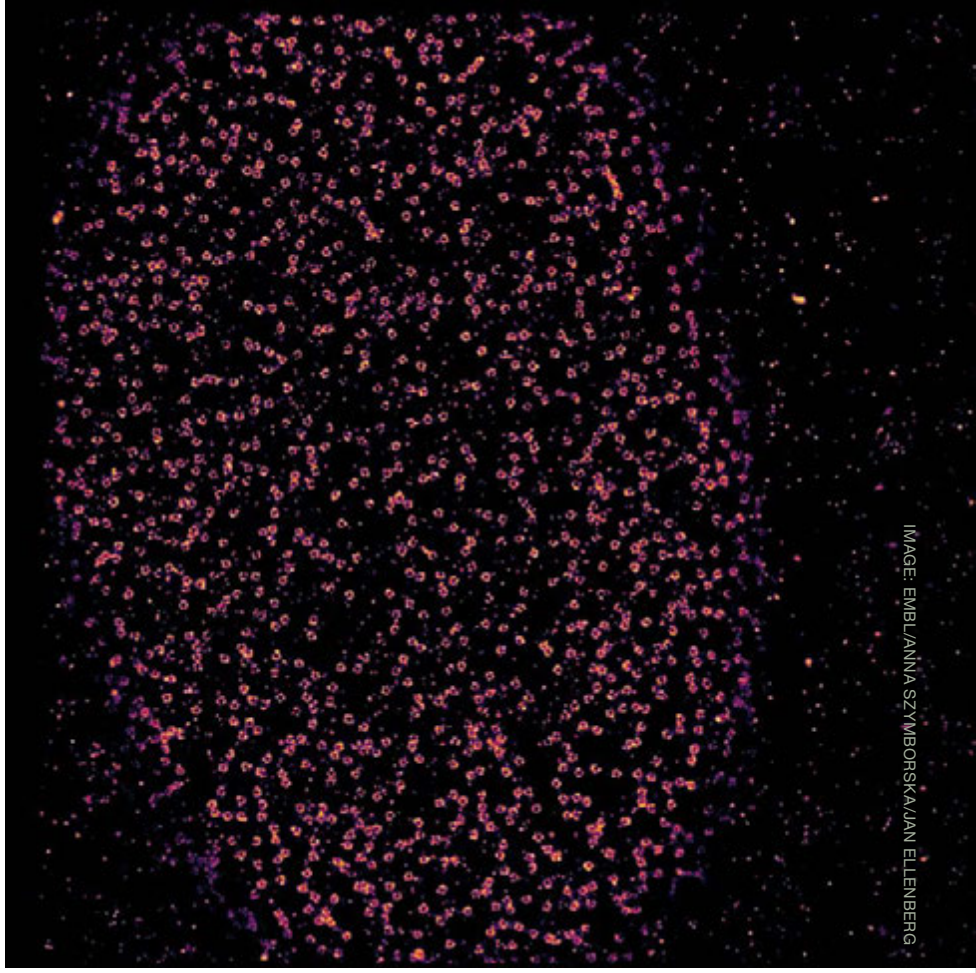


IMAGE: EMBL/ANNA SZYMBORSKA/JAN ELLENBERG

Nuclear pores imaged through super-resolution microscopy

>> three-dimensional capabilities of super-resolution microscopy. His group has found a way to determine a glowing molecule's position in space. By looking at fluorescence generated by a molecule's interaction with the glass plate behind it in addition to its normal fluorescence, they can pinpoint each molecule's location, allowing them to make a three-dimensional model of the structure they're studying.

He's also exploring what can be gained by combining super-resolution microscopy with other imaging technology, like electron microscopy or light sheet microscopy, which excites fluorescence only in a thin slice of a sample. For instance, Ries envisions learning more about endocytosis – which is how cells engulf and 'swallow' molecules – by looking closely at each of the 50 or so proteins involved using electron microscopy and then determining their positions relative to one another from the more zoomed-out view super-resolution microscopy allows.

Jan Ellenberg, Head of the Cell Biology and Biophysics Unit, points to Ries' work as an example of how researchers are using super-resolution microscopy in inventive and ever more useful ways. He utilises the technique himself to study the organisation of the cell's nucleus. Last year, his group was among the first to demonstrate super-resolution microscopy's power for structural biology when they published how the different proteins inside nuclear pore protein complexes are arranged. "With super-resolution microscopy you can start to see the internal molecular organisation of individual large protein complexes," Ellenberg says.

"That was a very controversial matter before: we could not directly visualise that inside a cell."

More to come

One thing he says will make super-resolution microscopy more useful is better fluorescent dyes – his colleagues agree: "Super-resolution microscopy in principle can make clear images down to a few nanometers," Pepperkok explains. "However, this is at a price; you need a lot of energy, and living cells cannot cope with that." With dyes that produce better, more distinguishable signals and are more tolerable to living cells, he and other EMBL scientists say that they will soon learn more about structural biology, cellular division, and more.

That could mean a whole new depth of understanding in biochemistry when it's occurring inside living matter. And, even though super-resolution microscopy is still the domain of fundamental – rather than applied – research, Pepperkok points out that work already under way by Stefan Hell's group at the German Cancer Research Center could help answer important questions about disease. For researchers at EMBL and around the world, super-resolution microscopy has lifted the veil further on the once-mysterious inner workings of our cells.

"With super-resolution microscopy you can start to see the internal molecular organisation of individual large protein complexes"

Miraculous microscopes: a brief history

BY MICHELE CRISTOVAO

It is impossible to imagine where cell biology would be without the invention of the light microscope. But what is now a complex network of lasers, optics and mechanics, started off as a simple brass plate, with a small glass sphere serving as an objective – while the only light needed was sunlight. And we have Dutch scientist Anton van Leeuwenhoek to thank for that.

Back in 1673 van Leeuwenhoek, then a curious young trader, began to take an interest in lens making – and from there, microscopes. Developing his ingenuously simple contraption to zoom in on the micro-world, he stepped into a completely different dimension, discovering what he called "animalcules" – or as we know them today, microorganisms.

Fast-forward two centuries, and Carl Zeiss, struggling with his lens-making workshop, decided to switch to microscope making. A collaboration with physicist Ernst Abbe provided the spark for microscopy to take another giant leap. Abbe postulated the Abbe sine condition, which had to be fulfilled by a lens to produce sharp, undistorted images. Calling in glass chemist Otto Schott, the trio put their heads together to design and build the first apochromatic objective – a powerful device allowing clearer images with minimal colour distortion – lenses that are still used in science today.

Abbe's astonishing contribution to microscopy did not stop there. Crucially, he also defined the theoretical resolution limit of the microscope – roughly 100 times smaller than a human cell. This resolution limit held up for more than a century, until Stefan Hell, Eric Betzig and William Moerner smashed through the diffraction barrier to make super-resolution microscopy a reality.

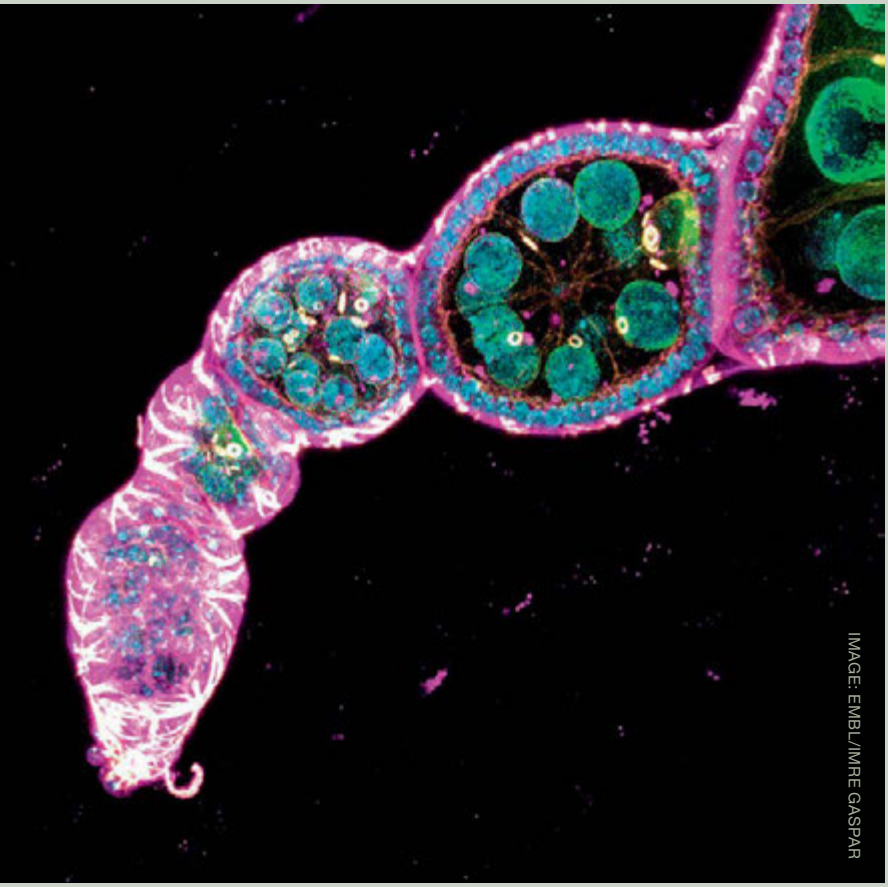


IMAGE: EMBL/IMRE GASPAR

Mesmerising microscopy: Imre Gaspar, staff scientist in the Ephrussi group at EMBL Heidelberg, imaged these *Drosophila* ovarioles using a Leica SP8 confocal laser scanning microscope

Delighting in detail

A bundle of nerves that relays information from touch receptors on the skin to the spinal cord and ultimately the brain, has been imaged by Paul Heppenstall's group at EMBL Monterotondo. The method, called SNAP-tagging, relies on a small protein that binds to a specific small chemical structure – and once bound, it won't let go.

Yang, G., *et al. Nature Methods*, published online 8 December 2014.
DOI: 10.1038/nmeth.3207

FULL REPORT ONLINE:
NEWS.EMBL.DE/?p=2860

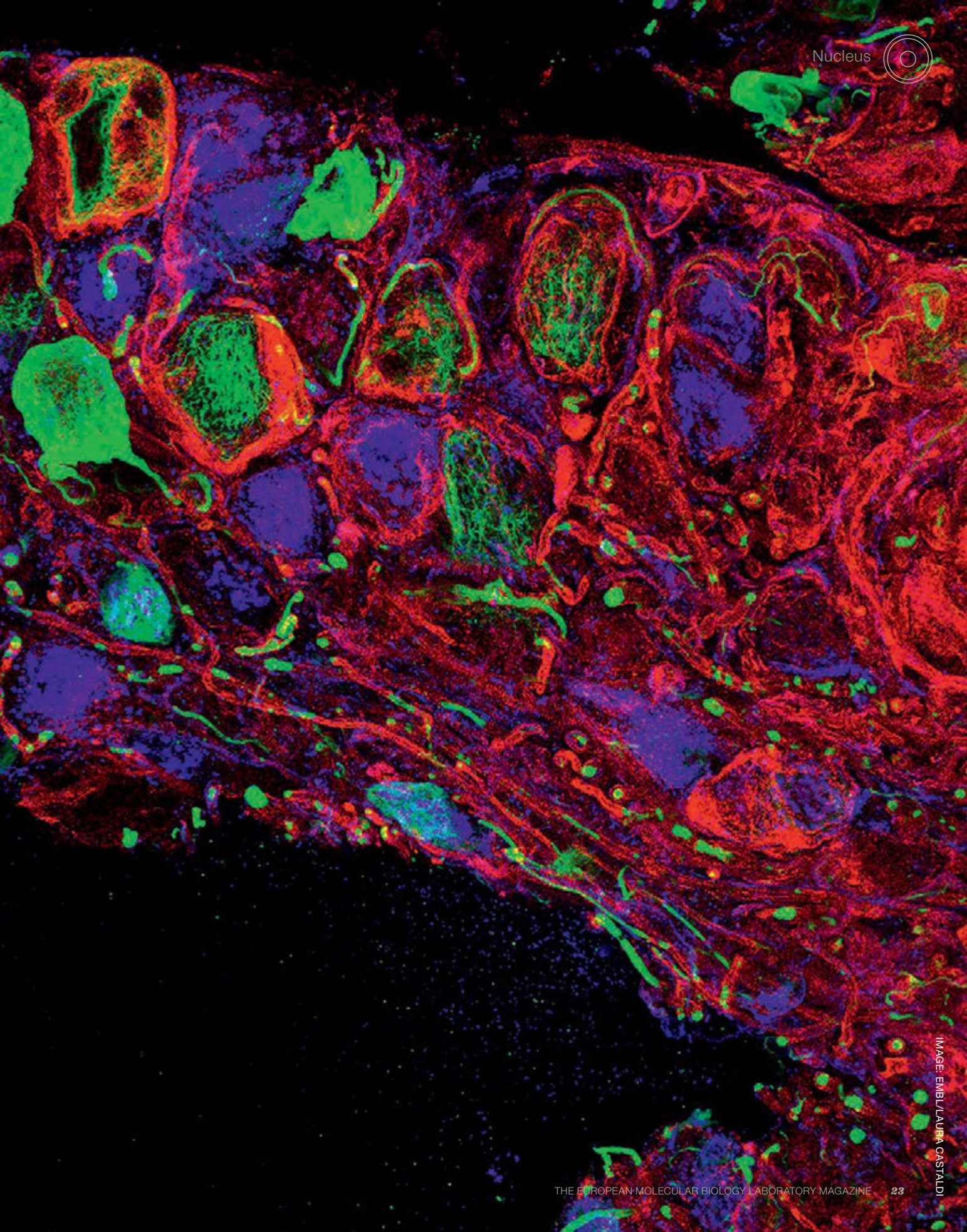


IMAGE: EMBL/LAURA CASTALDI

Two decades in the making

"This has taken 20 years of my life," smiles Head of EMBL Grenoble Stephen Cusack, "and for the first 15 years we had almost no results!" Cusack's perseverance, determination and vision have now been duly rewarded as he and his team published the first crystal structure of an influenza polymerase in the journal *Nature*.

BY ROSEMARY WILSON

Influenza is a major infectious disease, but despite its common occurrence the virus is still not really well understood at the molecular level. The results represent a revolution in the field of flu research and will help to answer a vast number of questions about the virus' replication but, as Cusack says, "we also have a lot of new questions too."

During the cold winter months, the annual wave of coughs, colds and bugs lurks around the corner waiting to work its way through schools and workplaces and send us to our beds. And while the majority of us will be able to shake off a bout of the flu without any medication other than hot drinks, painkillers and rest, for some it represents a real health risk. For babies, the elderly and patients with weakened immune systems, it can mean serious health complications such as pneumonia, or even prove fatal. Even during the relatively mild winter of 2013/2014, the Robert Koch Institute reported an estimated 430,000 cases of flu-associated sick leave and some 3100 cases of hospitalisations in Germany alone.

Not all flu is created equal

The flu – or influenza to give it its full name – is a virus that comes in two main guises. Influenza A infects humans, certain other mammals (including pigs, horses, bats and seals) and birds (such as water birds and poultry) and gives rise to seasonal epidemics and, occasionally, serious pandemics. Influenza B infects only humans and, while causing seasonal sickness, does not present the same global health risk as influenza A. Although infection generally occurs via the transmission of droplets carried in the air from one person to the next, some occasional – but severe – highly pathogenic bird strains have been known to transmit to humans.

In 1918, a worldwide pandemic caused by a strain that made this leap from birds to humans, probably via pigs, killed some 50 million people worldwide. In 2009, a variant of the same strain, H1N1, caused the so-called 'swine flu' pandemic that originated in pigs, resulting in an estimated 284,500 deaths worldwide. Highly infectious avian strains of influenza A – H5N1 and H7N9 – have recently caused several serious outbreaks, devastating poultry industries in Asia and infecting a significant number >>

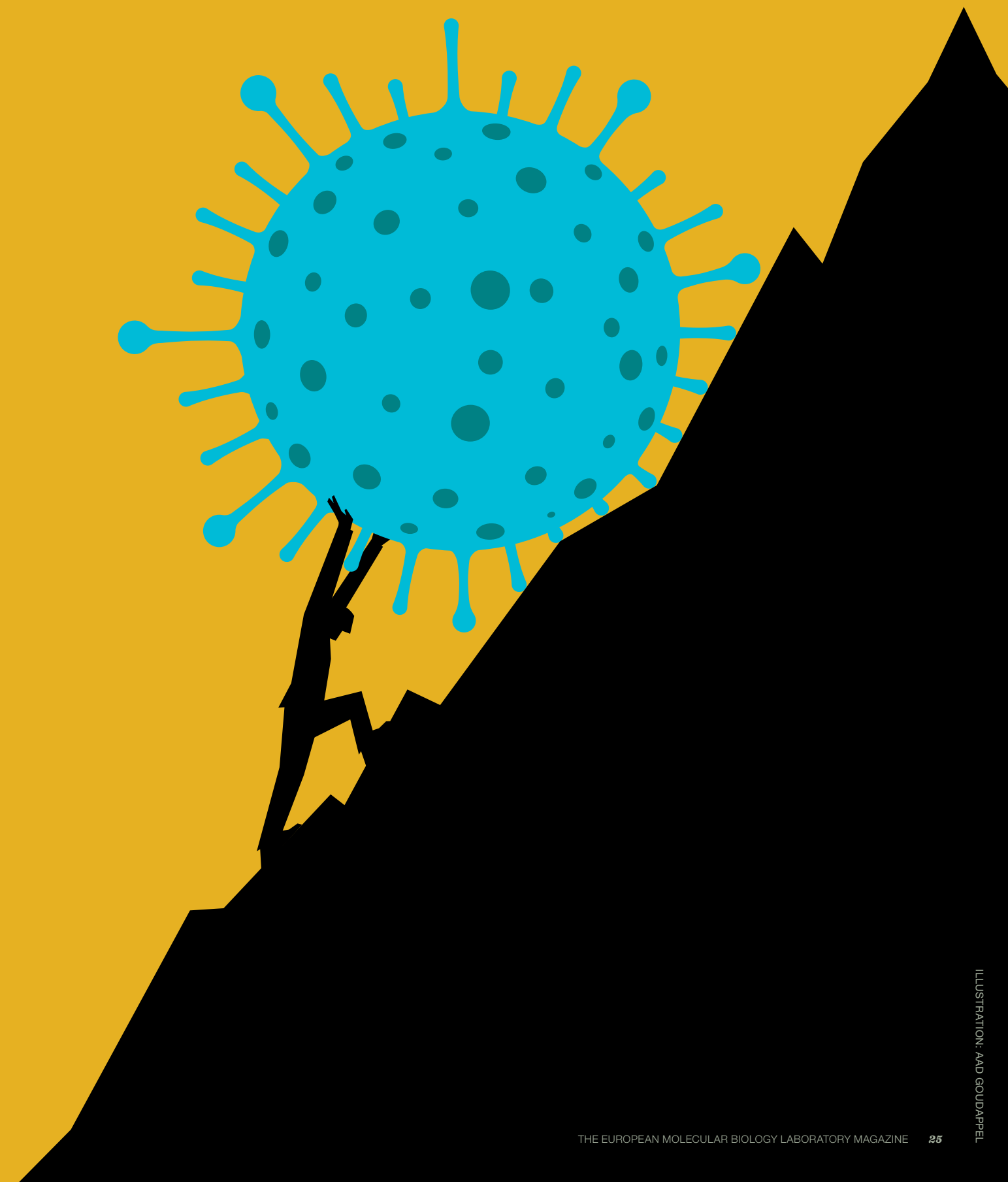


ILLUSTRATION: AAD GOUDAPPEL

"The high-intensity X-ray beamlines at the ESRF were crucial for getting high-quality crystallographic data from weakly diffracting crystals of the large polymerase complex"

>> of people. The World Health Organization estimates that annual epidemics of influenza A strains result in roughly "3-5 million cases of severe illnesses and about 250 to 500 thousand deaths" worldwide.

Although the virus has been well studied, annual outbreaks have been documented and surveyed, and the high economic cost has been chronicled, there is still no cure and eradication of the virus is as yet inconceivable. Seasonal vaccinations are recommended for high-risk groups such as the elderly and health workers, but vaccines comprise only those strains predicted to be the most prevalent in that season, and so do not protect against other variants. Current antiviral drugs, such as Tamiflu, can reduce and alleviate the symptoms and prevent serious health consequences, but they cannot completely cure the patient and the virus will often develop resistance to these treatments.

Final piece of the puzzle

Twenty years ago, Stephen Cusack started working on the polymerase of influenza A – one of the 'holy grails' of influenza research. "That's the one everyone really wants to understand," Cusack says, "since it's the essential machine that replicates the viral genome." When the virus infects and enters the host cell, it sets about reproducing: replicating its genomic material and transcribing it so that it can be read by the host's protein production machinery, which is then tricked into making viral proteins. It is the polymerase that is responsible for both the transcription and replication of the virus and is therefore crucial to its virulence and survival. Understanding how this key enzyme works would pave the way for the development of new antiviral drugs.

The plan was to resolve the structure of the enzyme using structural biology approaches, such as X-ray crystallography. "The polymerase has been known about for some 40 years," explains Cusack, "so there is 40 years' worth of literature on biochemical and genetic studies trying to understand how it all works." Having the structure of the enzyme would help to put all previous studies into context and finish the puzzle. And the polymerase seems to be particularly puzzling. It consists of three entwined subunits, making it difficult to decipher and to find out which subunit does what. "Not only does it bind viral RNA, transcribing it to messenger RNA, but it also replicates the RNA to be packaged into new virus particles," Cusack emphasises. How can it do both things with only one active site? How does it switch from one task to the other? How does it bind to viral RNA in the first place? These questions have long been debated in the field, but without a complete structure, it has been difficult to put everything into place.

Switching to plan B

To determine the enzyme's structure, the scientists needed samples in crystalline form: repetitive arrangements of the molecule that they could then analyse by measuring how they interfered with X-rays shone onto the sample. To produce crystals, the first task is to obtain sufficient amounts – measured in milligrams – of pure polymerase. But for the polymerase of human or avian influenza A virus, this turned out be impossible. Instead, from 2007, Cusack's group and collaborators contributed several significant insights into the workings of the polymerase by solving the structures of isolated, but functionally important, fragments of the enzyme.

These fragments included the two domains of the polymerase that are required for the unique 'cap-snatching' transcription mechanism. Both these domains, if blocked by small molecules, inhibit the working of the polymerase and are therefore good targets for anti-flu drug development, which Cusack has pursued with start-up company Savira, and Roche Diagnostics.

But the structure of the entire polymerase remained elusive. Cusack and his team decided to change tack and started looking at influenza B instead. "This was one of a number of significant breakthroughs," he says.

EMBL PHOTOLAB/MARIETTA SCHUPP

After 20 years' work by Stephen Cusack, the first complete structure of one of the flu virus' key machines – its polymerase – has been revealed

Although influenza B does affect humans, it only makes up a small proportion of seasonal epidemic infections and its slow rate of change means that most people acquire some state of immunity in their childhood. By contrast, the constant and rapid evolution seen in the influenza A virus makes it harder for the immune system and health agencies to keep up.

Having made the switch to influenza B, and with the help of techniques developed by group leader Imre Berger, also at EMBL Grenoble, Cusack and his team were soon able to produce enough of the enzyme for crystallisation experiments. Once they had managed to make crystals, the structure soon followed: "It all happened very quickly," says Cusack, still surprised by the dramatic turn of events. Shortly after, the group also managed to express a strain of influenza A from bats that was only discovered recently and is genetically very similar to human A strains. Key to the success of this project were developments in technology: "The high-intensity X-ray beamlines at the ESRF, equipped with state-of-the-art detectors available by this time, were crucial for getting high-quality crystallographic data from weakly diffracting crystals of the large polymerase complex," says Cusack. "We couldn't have got the data at this resolution without them."

The big picture

Now, with the information from the atomic structures of the influenza A and B polymerases, Cusack and his team can finally propose a more complete and detailed description of how it works. The new data show that the three subunits that make up the enzyme are heavily intertwined, with all three units intricately involved in the function of the polymerase. "Now that we can see how everything fits together, it's no wonder that the biochemical results produced over the past 40 years have been confusing," says Cusack.

The different structures also capture the polymerase in different states of activity, which helps to show the dynamics of the system. The team had already determined the structure of the subunit that 'snatches' a specific piece of host-cell RNA needed to kick-start the production of viral proteins. Now that they know the structure of the whole polymerase, they can see how that part of the enzyme moves relative to the others, revealing that it is able to rotate by a large angle to bring the 'snatched' piece of RNA in line with the polymerase's active site so that transcription can begin.

Although the structures are from different influenza species, Cusack does not believe this is significant when it comes to understanding how the polymerase works, and how we might be able to stop it in its tracks. "The functional areas of the polymerase are very similar, and we think this information will also shed light on understanding how the polymerases of other related viruses work – such as that from the Ebola virus, for example," he says.

So, what's next? "We need to crystallise the machine in different functional states so we can be sure how it works," says Cusack. "We have already begun high-throughput screening to try to find inhibitors for the active site based on this new information," he adds. Although the structures reveal a lot about how the viral polymerase works, the living cells that the virus infects are a lot more complex than the purified polymerase used in the laboratory. "There are a lot of other players in the infected host cell. What role do the host proteins play in helping, or hindering, the polymerase working? The viral RNA genome is protected by a coat of viral nucleoproteins. How are these removed and put back on again to allow the passage of the polymerase? There are a whole lot more questions to be answered, but at least we are in a much better starting position to answer them."

Pflug, A., *et al. Nature*, 19 November 2014. DOI: 10.1038/Nature14008
Reich, S., *et al. Nature*, 19 November 2014. DOI: 10.1038/nature14009

Kidney cancer: connection to a potent carcinogen

A large-scale genomic study of renal cell carcinoma has demonstrated a strong association between kidney cancer and exposure to aristolochic acid – a powerful carcinogen found in some herbal remedies.

BY MARY TODD BERGMAN

Kidney cancer kills more than 140 000 people every year and, in Central Europe, the incidence of reported cases is increasing. The Cancer Genomics of the Kidney consortium (CAGEKID) – part of the International Cancer Genome Consortium (ICGC) – has been studying the genetic causes of this disease in Europe. As part of this effort, researchers at McGill University in Canada and at EMBL-EBI have identified a connection between kidney cancer and exposure to aristolochic acid. The study, published in *Nature Communications*, could have important implications for public health.

The project partners sequenced the DNA and RNA of normal and tumour cells in approximately 100 renal cell carcinoma patients from the Czech Republic, Romania, Russia and the United Kingdom and confirmed the association between specific genetic changes and the

development of cancer. Their findings identify biological pathways and sets of genes that are affected by the mutations, and suggest that the main causes of kidney cancer vary between populations.

In the majority of Romanian patients, the researchers observed a high frequency of genetic changes associated with exposure to aristolochic acid. This carcinogen occurs in the plant *Aristolochia clematitis* – commonly known as birthwort – which is used in herbal remedies and has also been known to contaminate wheat crops in central Europe. It is more powerfully linked to cancer than cigarette smoking, and has long been known to cause kidney failure.

"The most striking observation was the high frequency of a specific type of mutation pattern found in the Romanian patients," says Yasser Riazalhosseini, assistant professor of genetics at McGill University, where the DNA data analyses were carried out. "The specific sequence context surrounding these mutations and their predominance on the non-transcribed strand of DNA enabled us to hypothesise that the mutation is due to exposure to aristolochic acid during the patient's lifetime."

Interpreting patterns

This same mutation pattern is found in people suffering from a cancer of the urinary tract associated with Balkan endemic nephropathy. This disease has been connected with the consumption of wheat flour contaminated with *A. clematitis* seeds.

"While the study included only 14 patients from Romania, the specific mutation pattern was found in 12 of them," says Mark Lathrop, scientific director of McGill University and the Génome Québec Innovation Centre. "As a result, we will analyse samples from more patients from Romania and elsewhere in the Balkan region. This follow-up research is now underway to assess the extent of exposure."

The study shows that the phosphoinositide-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) signalling pathway is significantly deregulated in kidney cancer and that a connected pathway, focal adhesion, is affected by molecular aberrations. The authors suggest that targeted therapies for PI3K/mTOR signalling may help kidney cancer patients and those affected by other abnormalities of the focal adhesion pathway.

"This tumour genomic project is unique in that it is based on samples from various countries"

EMBL-EBI's functional genomics team, led by Alvis Brazma, used new software developed by alumna Mar Gonzales Porta, to identify potential loss-of-function events caused by the change in transcript splicing patterns between the normal and tumour tissues. A different approach, led by Liliana Greger, identified six novel fusion genes – mutations that can be used to identify a cancer – out of a sea of potential candidates.

"Our group analysed the very large quantity of RNA data produced in the studies, and we saw some interesting abnormalities," says Brazma, who is senior team leader of functional genomics. "There was clearly a loss of gene function, due to changes in splicing patterns. We also saw novel fusion genes – pairs of genes that are fused together and create products that interfere with the proper functioning of the cell."

The study drew on data from the EU-funded Genetic European Variation in Health and Disease (GEUVADIS) consortium, which provides knowledge and resources on medical genome sequencing to help researchers explore the genetic basis of disease.

Finding unexpected causes

"We were very lucky to be working with one of the largest renal cell carcinoma sequencing datasets, with matched DNA and RNA genomes from the same patients," adds Greger. "Our analysis also made use of 'normal' data from the GEUVADIS consortium, which we used for filtering out false positive fusion events – so all in all the dataset was quite big and very well controlled."

"This tumour genomic project is unique in that it is based on samples from various countries, with potential diversity in risk factors," says Ghislaine Scelo, lead author of the study and part of the International Agency for Research on Cancer (IARC/WHO) at McGill University. "Our study illustrates that systematic exploration of tumour DNA via massive sequencing can identify previously unsuspected causes of cancer."

All data from the study are available in EMBL-EBI's controlled-access European Genome-phenome Archive (EGA) and ArrayExpress. The datasets will be incorporated into the ICGC's pan-cancer project, which uses the EGA for data management and EMBL-EBI's Embassy Cloud for storage and data analysis.

Scelo, G., *et al. Nature Communications* (in press), published online 29 October 2014. DOI: 10.1038/ncomms6135

WWW.EBI.AC.UK/ega

Let there be light

With topics ranging from how microbes influence our lives to the storage of data in DNA, EMBL Heidelberg hosted a unique brand of seminar in 2014 that gave young researchers the chance to give a popular science lecture on the big stage. Organised by outreach officer Angela Michel, the Sunday Matinee series *Mehr vom Leben* (More from Life) saw more than 1300 visitors fill the EMBL Advanced Training Centre to learn about the incredible work being carried out by EMBL fellows. Concluding the series was a talk on the evolution of photoreceptors by Silvia Rohr, a PhD student in Detlev Arendt's group.

BY ADAM GRISTWOOD

EMBL PHOTOLAB/MARIETTA SCHUPP

What was the key message you wanted to deliver?

Light is very important for us – in science, philosophy, culture and more. It irradiates the universe, illuminates how we see the world and is central to our own existence. The human eye is beautifully complex, and acts like a camera to collect and focus light. It converts this into an electrical signal that our brain then interprets into an image of the world in front of us. Evidence suggests that our eye evolved from a simple light sensor, and present-day primitive sea creatures hold important clues for understanding this process. Indeed, some of their features resemble the ancestor from whom we all evolved and in which photoreceptors initially developed. In a sense, we are all sea creatures – we depend on the oceans to provide our food and regulate the Earth's climate – but the ocean also holds secrets to our past and how we came to be.

Why do you do what you do?

Charles Darwin wrote in *the Origin of Species* that he was perplexed by the complexity of the eye – its functions, architecture, and how it works – yet he remained convinced it evolved in the manner he proposed. In recent years we have learned a lot more about the evolutionary steps that have occurred, particularly by comparing eye structures and genes across species to understand when key traits arose. But there is much more to learn. For me personally, the most striking aspect is the sheer diversity of light perception that is evident in animals, depending on where they live, what they do, and how they have adapted to their environment. Some insects, such as flies, have compound eyes made of thousands of hexagonal compartments, or ommatidia, that comprise a corneal lens, a crystalline cone and a light-sensitive organ at its base, all working in unison to deliver a picture of the world. The octopus, on the other hand, has camera-style eyes that at first glance resemble our own, but in reality its photoreceptors are more like those found in insects. The functions of different styles of photoreceptors vary between vertebrates and invertebrates, and can impact on day and night vision – for example, geckos can distinguish colours in dim moonlight, whereas humans are colour blind. There are countless examples of such diversity in nature and I am fascinated by what is out there, what it all does, and why it is as it is.

What are you personally working on?

I am defining the different types of photoreceptor cells in a fish-like marine chordate called amphioxus, which is usually found in shallow sands in temperate and tropical climates. Amphioxus has a very simple brain uniting invertebrate- and vertebrate-like features, and we believe its appearance has not changed in more than 500 million years. I am using modern molecular biology approaches, such as cell-type molecular fingerprinting, to try to understand the differences and similarities in photoreceptors between various species, including amphioxus, the marine annelid *Platynereis dumerilii* and the sea anemone *Nematostella* . By comparing species we can begin to ask questions such as: how did the first photoreceptor cells emerge? What was their function? Which environmental pressures push photoreceptors to take on new roles? We are a long way from understanding all the phenomena we see in nature, but even these initial steps are very exciting.

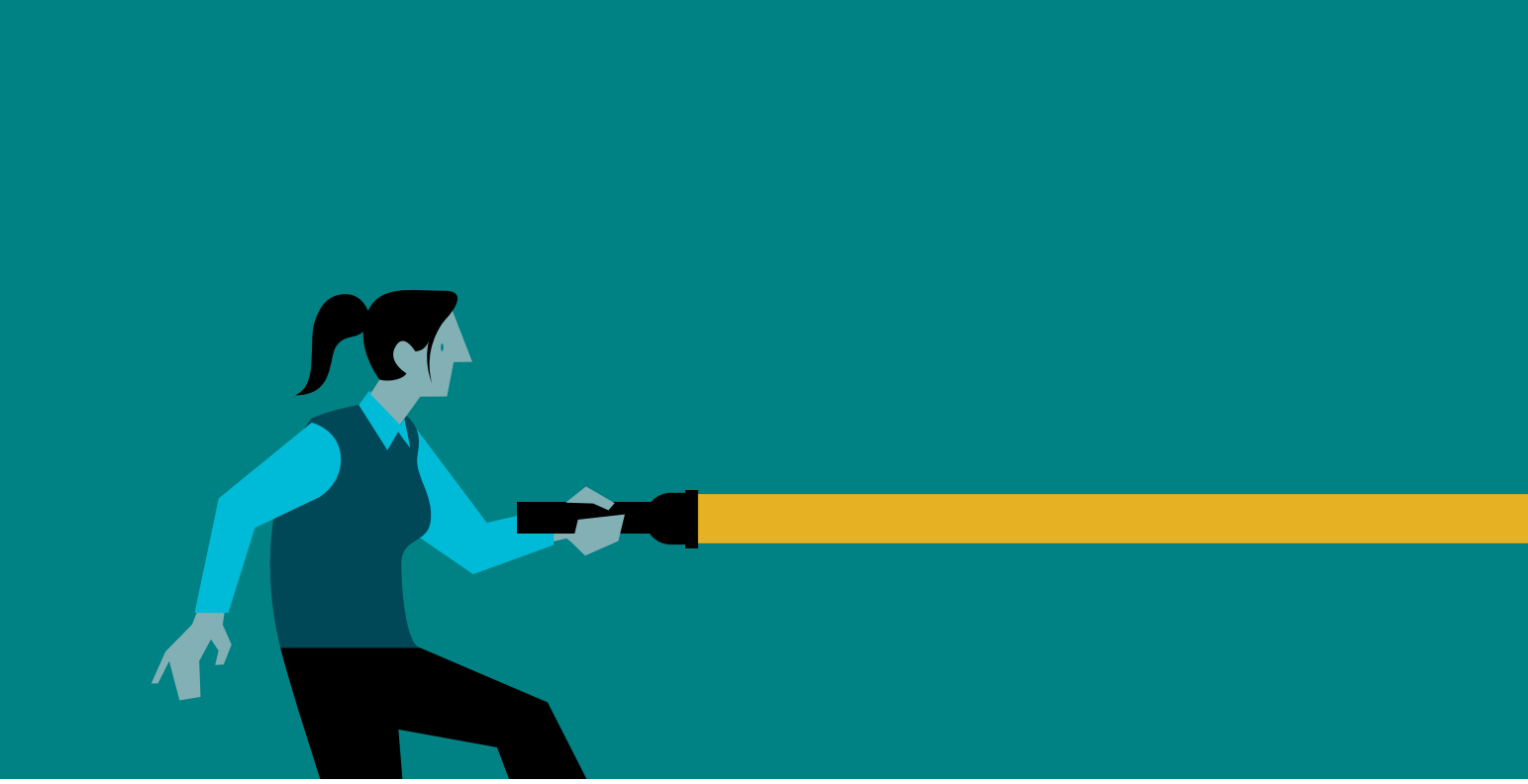
What is a typical week like for you?

In the summer months we plan our days – experimental work, caring for the animals and cleaning the tanks – around animal spawning, which happens one hour after an artificial "sunset" at 1pm each day. In winter, I spend more time at the bench as well as reading books and papers. We make occasional trips to find new animals at sea: some we locate easily, others are more like a treasure hunt that involves identifying possible habitats, travelling out there by boat, bringing up samples from the sandy water, and sieving through the contents. Often you can go days without finding anything at all, but when we finally locate the creatures we are looking for, it's all worth it.

"I am fascinated by what is out there, what it all does and why it is as it is."

Did the experience of giving a popular science lecture change the way you look at your own research?

It was a fantastic opportunity to share my passion for this subject with a large public audience – I would certainly do it again. I was impressed by the connections members of the audience made between this and other research areas, such as the evolution of the brain, and the role of photoreceptors in plankton. I realised that people other than scientists actually find my work really interesting. Many of my friends came to the lecture or watched the live stream because they wanted to know more about it. As we learn more about the ocean, it's like discovering a second world within our own. It is fascinating to think about what's been going on down there over the course of hundreds of millions of years, what is going on down there today, and what is still left to discover.



Cell control in a

Flick the switch, and illumination follows. The comical image of a light bulb pinging on when a brainwave occurs became remarkably prescient just a few years ago when suddenly, out of the dark, a brand new technique for controlling brain activity lit up the scene.

BY ADAM RUTHERFORD

Emerging in 2003, optogenetics was developed by several scientists across the globe, including Ernst Bamberg, Ed Boyden, Karl Deisseroth, Peter Hegemann, Gero Miesenböck, and Georg Nagel. The aim was to elicit control over ever-smaller neural pathways, trying to unpick the circuits of thought. But the simplicity of the idea betrays an impressive and imaginative technical feat. The principle is straightforward: a light-sensitive protein is incorporated into a specific population of cells, and a laser tuned to that protein's specific firing frequency is used to activate the cells with millisecond precision. The timing is crucial, as it mirrors the physiological response time, and the light triggers the neuron's action potential.

Standard techniques of genetic modification, such as the cre/lox system and lentiviral vectors, are used to target the gene encoding a phototransduction protein – often a microbial opsin – to specific neuronal cells. But the more fiddly aspect of this technique is that this has to be done in such a way that normal function is not upset. The use of optogenetics in the past decade has blossomed, and uncovered all sorts of revelations about brain function – for example, the circuits that modulate fear and the conditioning of cells involved in cocaine dependency. Speculation has been rife for some time that sooner rather than later, this is a tool that will bag a few Nobel Prizes.

In touch

Paul Heppenstall, a group leader at EMBL Monterotondo, has now adapted the system for use outside the darkness of the brain. "It was the ability to look through the microscope and image neurons under the skin that got me excited," he explains. Heppenstall's team work on our perception of touch and pain, which

ILLUSTRATION: AAD GOUDAPPEL

flash

means their targets are the cells at the periphery of the nervous system – neurons that react to mechanical or chemical stimuli, touch, heat and pressure. The specific populations for each of these are poorly understood, and not easy to disentangle.

"Traditionally we've used electrophysiology of single cells, which is tedious and slow," says Heppenstall. "It takes several months to put the data together, and at the end, you might see something. Or you might not."

Their new technique involves identifying a cell-specific marker, a gene that is active in a discreet population of skin neurons. They do this by scanning the literature, making educated guesses and also through a bit of luck. Once they find such a gene, they attach an optogenetic control switch onto it using the cre/lox system. Then they can activate the cells by shining blue light on a patch of skin and monitor the behaviour this evokes in mice, such as withdrawal for pain-sensing neurons and scratching for itch receptors. As a complementary experiment, they also use the same system to ablate specific populations of cells through a photosensitive dye. Once they've ablated the cell, a stimulus can be applied and changes in behaviour studied.

"It was the ability to look through the microscope and image neurons under the skin that got me excited"

Shaping up

Optogenetics offers cell-specific and microsecond precision. What's odd is that this powerful technique has always been about brain cells. Even in the 1970s, Francis Crick pondered light-controlled cells, but only for neurons.

At EMBL Heidelberg, group leader Stefano De Renzis is set to break that stranglehold. "The biggest surprise for us was that it's a technique that works so well for studying *Drosophila* morphogenesis," he explains. It was De Renzis' graduate student Giorgia Guglielmi who first suggested co-opting optogenetics from neuroscience to scrutinise basic fruit fly development. "I knew it would be great if it worked, but to tell you the truth, I was quite sceptical. Giorgia who had just started her PhD in my lab was immediately enthusiastic to try something new." >>

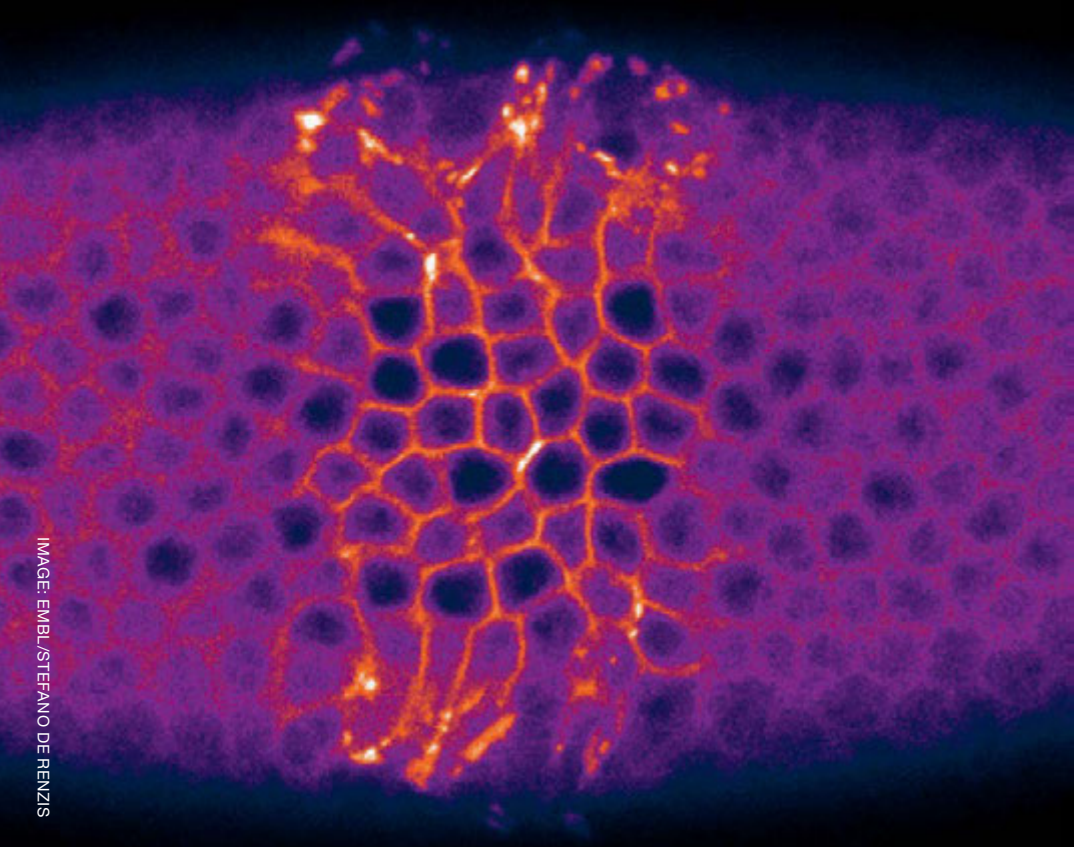


IMAGE: EMBL/STEFANO DE RENZIS

Surface view of a *Drosophila* embryo at the onset of gastrulation. Optogenetically activated cells lose their regular hexagonal shape and will fail to gastrulate

"Optogenetics enables us to look at immediate cellular and tissue responses"

>> Their work is centred on how proteins and other elements of the cell membrane regulate the shape of cells during *Drosophila* embryogenesis. This is crucial to overall tissue patterning as cells mature and take on specific shapes and sizes. Differentiation of individual cells affects their neighbours and ultimately the whole embryo. But these changes are highly temporal and spatial, and addressing the underlying mechanisms is a question that has been hampered by an inability to command the whens and wheres of gene expression. And there's no action potential to trigger.

Knocking down

"We were always looking for ways of controlling specific cells during development – to knock-down protein activity, but in a very temporal and spatial way," De Renzis says. "In the past we've used knock-outs, and temperature-sensitive mutants, but it takes time for the clones to grow, which complicates the interpretation of results. With optogenetics we can do it in a fraction of the time, enabling us to look at immediate cell and tissue responses."

In some ways, this seems a simpler proposition than eliciting complex behavioural changes in mammals, as has been the mainstay of optogenetics so far. The De Renzis team is looking at actin and membrane trafficking, and how they affect patterning and cell shape. They are quizzing the way the embryo invaginates – a process of folding in on itself to internalise mesodermal cells that run the length of the fruit fly embryo. This is regulated by molecules on the plasma membrane, and by simply turning these off using light in only a small population of cells, the effect is global. The targeted cells fail to contract, and the knock-on effect is the arrest of invagination across the whole embryo.

This first foray into using optogenetics in developmental biology is now submitted for publication and no doubt the technique is set to become a versatile tool in the future. "To control cellular activity experimentally has not been possible with conventional genetics so far," De Renzis says, "at least not at very precise resolution. Now, we are very excited about adding this new technique to our research arsenal and we look forward to sharing it with other labs interested in shedding light on the cellular and molecular mechanisms driving the development of organisms."

ONLINE EXTRA: CORNELIUS GROSS, DEPUTY HEAD OF EMBL MONTEROTONDO, DISCUSSES OPTOGENETICS POTENTIAL DURING THE 2014 ELLS INSIGHT LECTURE – GO TO EMBLOG.EMBL.DE/ells/eil

Foods are us!

Are we what we eat? This was the question that food experts and more than 350 participants from around the world came to EMBL Heidelberg to discuss in this year's EMBL|EMBO Science and Society conference, 6–7 November. Here is our bite-sized A–Z of some of the highlights.

BY ADAM GRISTWOOD

IMAGE BY GIUSEPPE ARCIMBOLDO. REPRODUCED WITH PERMISSION OF THE KUNSTHISTORISCHES MUSEUM, VIENNA, AUSTRIA

A is for appetite
Why are foods loaded with fat, sugar and salt so difficult to resist? asked Jason Halford, head of the Department of Experimental Psychology at the University of Liverpool. Halford, who has studied the impact of branding and food promotion on children's food preferences, argued "tackling obesity requires better understanding of the role of the modern food environment in influencing appetite," – and subsequently eating behaviour, food intake, and biology.

B is for breakfast
Chocolate sprinkled on toast, or 'Hagelslag' (a real tongue-twister in Dutch!), was the hook Ben van Ommen used to urge a 'systems view' of food and health. "Ultimately, the goal should be to deliver health advice that empowers individuals to switch from 'disease thinking' and towards 'optimal health thinking'," said van Ommen, who is principle scientist at the Dutch Organisation for Applied Scientific Research.

PHOTO: iSTOCK

C is for conversation
Can conversation trump consumption? asked Priscilla Parkhurst Ferguson, a sociologist from Columbia University. "The meal is a vehicle of socialisation," she said. "The real pleasure in eating comes from knowing how to talk about it – ultimately conversation creates culture, socialises food, and civilises appetite."

D is for digital seasoning
Inspired by research led by Charles Spence, a psychologist from the University of Oxford, London-based restaurant House of Wolf invited diners who had been served a dessert of cinder toffee lollies to use their mobile phones to ring one of two numbers should they find the delicacies not to their taste. On one line was music chosen to enhance the sense of sweetness, on the other a tune to bring to mind a feeling of bitterness. "It seems we associate higher notes, such as a tinkling piano, with sweetness and deeper more resonant tones with bitterness," Spence said.

E is for extremely large brains
The gradual transition from our earliest hominid ancestors, predominantly herbivorous gatherers, to modern humans, the ultimate masters of tools, happened not after, but before our energy-hungry grey matter began to expand at an unprecedented rate, explained Mark Thomas. Thomas, who is professor of evolutionary genetics at University College London, assessed evidence of the evolution of the human diet over the past three million years, and argued that subsequent increases in food security permitted us to afford "such a fundamentally expensive and extravagant organ".

PHOTOS IN MIDDLE AND RIGHT: EMBL PHOTOLAB/MARIETTA SCHUPP

F is for farming
"Apart from the invention of the first tools, there has been nothing more dramatic to change the way we eat than the onset of farming," added Thomas. He emphasised the relevance of evolutionary approaches to food in understanding mismatches between the diets we have evolved for – 'Palaeolithic' diets – and post-agricultural 'Neolithic' diets. While warning of the dangers of fad diets, he said: "by looking into the distant past, we may discover how to lead healthier lives."

G is for gut bacteria
One square centimetre of your lower colon contains more microbes than humans have ever been born, said Simon Carding, from the University of East Anglia – and we are only beginning to understand them. "But this is hampered by the fact that we cannot grow many microbial species outside the body," he pointed out, explaining how our gut microbiome helps us digest food, provides us with nutrients and safeguards our health.

H is for history
Focusing on nutritional epigenetics – which seeks to explain the effects of nutrition on gene expression – Hannah Landecker, a historian from the UCLA Institute for Society and Genetics, reflected on the writings of Huxley, Haldane, Marx and more to consider how our understanding of food has changed

over time. "In the present era food is still seen as fuel, but much more than that – it is being reconceptualised as a source of information," she said. Landecker put forward the idea that a contemporary view of food is not just about our bodies as factories for food processing, but also an intricate network of signals and biochemical pathways.

I is for insects

Whether it is boiled ant larvae, deep fried scorpions, or roasted water bugs – many in western societies will turn away in disgust at the mere thought of an insect supper. How to change these squeamish attitudes? Step forward Charles Spence. "We need to begin by emphasising the sensory qualities – for instance the flowery notes or great tastes of a bee brew," said Spence, who is an expert in sensory marketing.

PHOTO: MTSOFAN CC-BY-2.0

J is for journey

In July 2010, a team of Italian researchers departed Trieste and set off on the Silk Road collecting DNA samples and sensory testing information from more than 1000 people along the way. Led by Paolo Gasperini, professor of medical genetics at the University of Trieste, their goal was to understand more about how our genes, environment and lifestyle contribute to taste, food preferences and diet. "Our results are a first step towards understanding the genes that underlie the liking of common foods," he said.

K is for kudos

90% of cells in our body are bacteria: genomically and organically, our bodies are only 10% human – one of the many astonishing microbe-related facts discussed by Simon Carding.

L is for leaves

Despite all our complexity and differences, Michael Müller, professor of molecular nutrition at the University of East Anglia, ended his talk with some simple dietary advice, quoting American journalist Michael Pollan: "Eat food, not too much and mostly plants."

M is for milk

A drink of milk was off the menu for most Europeans until just a few thousand years ago. Mark Thomas, explored how fields such as genetics, archaeology, anthropology, and physiology are combining to tackle multiple questions about the rapid spread of our ability to stomach the white stuff. "Natural selection has probably worked harder on lactose persistence than any other biological characteristics of Europeans in the last 10 000 years," he said.

PHOTO: ISTOCK

N is for nutrigenomics

"How do you go about getting the type of evidence-based data where we can inform the public on what to eat?" asked Jim Kaput, head of the Systems Nutrition and Health Unit at the Nestle Institute of Health Sciences. He said getting to this "next-level" of food science requires a better understanding of the relationship between human genomes, nutrition and health – a key goal of the emerging field of nutrigenomics.

O is for 'omics

The integration of 'omic technologies will be crucial in enhancing our knowledge of how diet influences health and disease, but only if the right people are engaged in the process, explained José Ordovás, a professor of nutrition science at Tufts University. "Health professionals need to engage with the new technologies: if people learn to better understand and appreciate scientific information focused on them, they will pay more attention to health recommendations."

P is for participants

"Food is a rich field of study and areas such as security and nutrition are particularly relevant in Asia, where I am from," said Hongwei Liu, a master's student from the Czech University of Life Sciences Prague who was a participant at the conference. "I learned a lot of useful information about nutrition in the context of genes and the environment, and hope to connect my expertise with this field in the future," added Jocelyn Dunstan, a PhD student from the University of Cambridge.

EMBL PHOTOLAB/MARIETTA SCHUPP

Q is for quality
Nutritional research could be dramatically enhanced through researchers paying more attention to extreme cases in statistical studies, argued Hannelore Daniel, professor of physiology at Munich Technical University. "Too often the outliers are ignored," she said. "If you look at them, you learn more."

R is for restaurant
Enthusiasm for food and restaurants some two centuries ago in France and the 'food talk' this enthusiasm inspired in people, places and institutions, led to what Priscilla Parkhurst Ferguson described as "the triumph of French cuisine". "To appreciate what we do with food, to realise how the benefits, customs, and traditions anchor food practice, is to understand not only how food worlds are composed but also, and more importantly, how they function," she said.

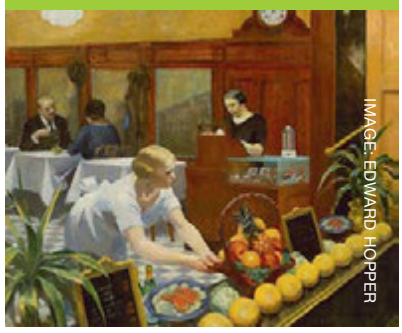


IMAGE: EDWARD HOPPER

S is for stigma
Powerful, persuasive and destructive: the stigma around obesity, both inside and outside the medical community, is greater than that from drug addiction, argued Jason Halford.

T is for (take your) time
Surprisingly, countries whose people spend the highest average time a day eating have the lowest national rates of obesity, explained Claude Fischler, a director of research at CNRS. "This raises the question: could social pressure be applied to regulate eating behaviour?" he said.

U is for USA vs France
In 1937, French author Paul Morand described New Yorkers quickly gulping down their lunch, standing in a row "like in a stable". In 1956 American sociologist Daniel Lerner countered, writing that he found French eating habits to be "rigid", as if they were in a "zoo". Fischler used this historic clash of cultures as a launch pad to explore varying views of food, body and health across western societies today, which he said could have important implications for health and nutrition.

V is for voltage
Next time you go on a date, up on stage, or take part in a race, spare a thought for why you are feeling 'butterflies' in your stomach. Simon Carding nicknames our gut our "second brain": and a deeper understanding of the often overlooked mass of neural tissue, packed with 500 million neurons and abundant neural transmitters, could shed light on connections between the lesions in the gut's nervous system and health and disease, he explained.

W is for wine
"Even before we put food into our mouths our brains make judgments about it," explained Charles Spence. "People buy a wine that tasted great while on holiday in the sun, open it on a cold winter's night and it tastes distinctly different – everyone is familiar with this experience."

X is for 'X marks the spot'
The importance of initiatives to draw up comprehensive maps of human metabolism was emphasised by Michael Müller. "This would build on substantial insights made in recent years into how genes are regulated by nutrients and food and how this in turn affects our health," he said.

Y is for yuck!
Simon Carding assessed the use of faecal transplants in treating some diseases, with trials now investigating their use in inflammatory bowel disease, type-2 diabetes, and initial studies showing promise even for treating diseases such as autism. "They work," he said "but the challenge is finding out how."

Z is for ZzZzZzZ...
Jet lag, late night shifts or simply partying too hard may disorientate the microbes that inhabit your intestinal tract, according to José Ordovás. "Do not upset your rhythms," he warned, or in other words: get a good night's sleep.

PHOTO: DANIEL FORSTER

Cultures

IMAGE: ESA/ATG MEDIALAB

PHOTO: EMBL PHOTOLAB/MARIETTA SCHUPP

IMAGE: NELLY VAN DER JAGT

Four decades at EMBL

During the past 40 years, Nelly van der Jagt has watched the Laboratory grow from scratch. In December, employee number 47 retired, leaving behind a legacy that intricately linked her life with EMBL.

BY ISABELLE KLING

"My attention was caught by a tiny advert in the local newspaper saying that EMBL was looking for an office clerk – I didn't know what EMBL was, but I was intrigued and sent in an application," explains van der Jagt, who retired from her role as Unit Administrator for the Structural and Computational Biology (SCB) Unit at EMBL Heidelberg. Thanks to that letter, she became one of just a handful of founding staff members, witnessing 40 years' worth of EMBL evolution, with a front row seat to several milestones that made the Laboratory what it is today.

Until 1982, Nelly was preparing the many documents necessary for council and finance meetings in three languages, equipped only with her trusty typewriter and copy machine – however, as robust as they may be, typewriters do not have spell checks and require Tipp-Ex to delete mistakes. "I was the first person in EMBL's administration to have a computer, around 1984," she recalls. "It was the first Macintosh – small and very expensive – and it made a massive difference to the work I was doing, but as time went on letters became a thing of the past, fax-machines disappeared, and emails kicked in."

In 1983, Nelly began working for the EMBL Director General's office and soon found herself juggling four roles: personal assistant to the DG and the Administrative Director, as well as organising practical courses for scientists and the fledgling EMBL International PhD Programme (together with John Tooze, then Executive Secretary of EMBO), before the growth of the Laboratory saw her move to a role in the SCB Unit.

"There is no such thing as "normal" when the norm can differ so much between the huge range of nationalities and cultures one finds at EMBL – it is stimulating, challenging and can quickly become a way of life," says van der Jagt, who is Dutch, has a Spanish husband, and lives in Germany. "Our daughters grew up speaking three languages at home and learning another three along the way. The advantages of being integrated into such an international environment are enormous: it shaped their entire lives in a very positive way."

Now, with the world at her feet and time on her hands, we wish her retirement will be every bit as fulfilling as her time at EMBL.

FULL STORY ONLINE:
NEWS.EMBL.DE/?p=2832

PHOTOS: EMBL PHOTOLAB/HUGO NEVES

Light the candles

Just over 40 years ago, Ken Holmes, then director of the Max Planck Institute for Biophysics in Heidelberg, brought to light the stunning potential of X-rays emitted by synchrotrons for use in structural biology experiments. On 27–28 November, staff, alumni, collaborators, and friends came together to reflect on four decades of vision, pioneering research and beamline services since EMBL Hamburg was set in motion on the Deutsches Elektronen-Synchrotron (DESY) campus soon afterwards.

For more on EMBL Hamburg's 40th anniversary, see pages 11 & 50

FULL REPORT ONLINE:
NEWS.EMBL.DE/?p=2896

Participants in Hamburg's famous town hall

Ken Holmes giving a pre-dinner speech

Renewing the DESY-EMBL partnership agreement

EMBL PHOTOLAB/MARIETTA SCHUPP

Meet the Dean

Helke Hillebrand (second from the left), together with her team (from left to right): EMBL International PhD Programme senior administrator Matija Grgurinovic, administrator Meriam Bezohra, and Postdoctoral Programme administrator Brenda Stride

Graduation ceremonies feel like the bright light at the end of a long and challenging journey – the culmination of an incredible rollercoaster of research, teamwork, and personal development.

BY ADAM GRISTWOOD

But each time a celebration takes place at EMBL, behind the scenes the hard work is continuing apace – Helke Hillebrand and her team are laying out the bricks and mortar of the internal training programme – home to more than 500 PhD students, postdocs, undergraduates, and interns across EMBL's five sites.

"Fellows are a crucial part of the academic community at EMBL, and have a tremendous impact on research, innovation, and campus life," says Hillebrand, who is EMBL's Academic Coordinator and Dean of Graduate Studies. "Our job is to provide a framework for that success, so that they can develop, collaborate and succeed. This includes screening and recruitment, advice and mentorship, and building connections with some of the best universities in Europe."

The ferns that line the windowsill of Hillebrand's office hint towards her research background, plant science, where before joining EMBL almost seven years ago she worked in research coordination, technology management and financial communication, focussing on scientific innovation. These experiences, she says, mirror the internal training programme's emphasis not only on academic success, but communication,

teamwork and innovation. “One of the most challenging aspects of a scientific management role is the need to wear a plethora of hats in parallel – all of a sudden you are required to be a teacher, fundraiser, supervisor, spokesperson, mentor and sometimes all of these at once,” she explains. “Whether in academia, industry, or other, these are important skills to develop, and can be continuously improved.”

No day the same

One day the team might be facilitating training courses, strengthening ties with other academic institutions, supporting fellows in their independent planning of symposia or retreats, or organising events such as EMBL’s Career Day. The next could involve spreading word of the programme at career fairs, negotiating contract extensions, writing grants, consulting with group leaders on academic or administrative topics, working with faculty towards defining the strategies for the future of the programmes, or providing individual support to fellows.

“Fellows are highly motivated, inquisitive, intelligent and are ambassadors of their cultures and countries,” she explains, pointing to a list of alumni destinations that reads like an encyclopaedia of scientific careers. “One challenge is to adapt and respond as science evolves and to continue to provide an environment best suited for preparing fellows for their next move. But the defining identity of the internal training programme will always remain: small group sizes, close mentorship, academic freedom, collaboration and collegiality, as well as a good dose of social activities, which make EMBL a unique place in which to learn and develop. Our offices are always open, and it is a privilege to contribute to the rich academic experience on our campuses, working with talented and inspiring young people from all over the world.”

Dick Costolo (CEO of Twitter), Emmanuelle Charpentier, Jennifer Doudna, and actress Cameron Diaz

PHOTO: KIMBERLY WHITE/BREAKTHROUGH PRIZE

Awards & Honours

Emmanuelle Charpentier – group leader at the Laboratory for Molecular Infection Medicine Sweden (MIMS), in the Nordic EMBL Partnership for Molecular Medicine – shared the Breakthrough Prize in Life Sciences for her discoveries on the bacterial CRISPR-Cas9, a powerful technology for editing genomes. The award recognises “excellence in research aimed at finding cures for intractable diseases and extending human life”. Charpentier received $3 million, and was honoured together with Berkeley’s Jennifer Doudna.

This has been a rewarding year for Joint Head of Unit **Peer Bork**. He is the fourth EMBL scientist to be elected to the German Academy of Sciences Leopoldina, to which he will be officially inaugurated in a ceremony in 2015. For his contribution to research development in the field of microbiology, the Japan Bifidus Foundation has honoured him with the Dr Tissier’s medal. He also received an honorary professorship at the University of Würzburg – becoming only the second individual to be so recognised by the University’s Faculty of Biology.

EMBL Director **Matthias Hentze** gave the 2014 Cesar Milstein Lecture – named after the Argentinian 1984 Nobel Laureate – in October, at the Leloir Institute in Buenos Aires. The following month, at Uppsala University in Sweden, he gave the third annual Lennart Philipson Memorial Lecture, honouring EMBL’s second Director General. In March 2015, he will receive the Feodor Lynen Medal at the spring meeting of the German Society for Chemistry and Molecular Biology, which recognises outstanding contributions in the subject area of the Symposium, in this case “Metals in Biology: Cellular functions and diseases”.

Pathways & Branches

Out of the darkness

Alumna Karin Ranero worked on the project for DLR on behalf of EJR-Quartz BV, together with technical project manager for the Philae Lander, Koen Geurts, and a team from the Crossmedia Department at DLR Corporate Communications

ESA/ATG MEDIALAB

The Rosetta Mission's comet landing leads to amazing and unexpected destinations in the field of science communication.

BY JULIA ROBERTI

It was one of those rare moments that made headlines worldwide, summed up in 140 characters:

The fingers hurriedly tapping on the keys, and tweeting the message in 10 languages, are those of EMBL alumna Karin Ranero, who is now editor for the German Aerospace Center (DLR) web portal. She was part of a team tasked with running the Twitter account for one of the global stars of the year – not a footballer, an actor, or a singer, but a tiny robotic probe named Philae, that went where nobody and nothing had gone before: the surface of a comet.

In November, people around the world held their breath as a live web stream showed the pinnacle of the European Space Agency's (ESA) Rosetta Mission as it carried the Philae lander to its final destination – Comet 67P – after a ten year journey across the Solar System. Five hundred million kilometers away from Earth, orbiter and lander communicated with each other and to researchers here on Earth, too. But unlike the first Moon landing, which crackled onto black and white television screens, many stayed tuned in via a very modern channel.

Ranero is one of the people in the team that gives Philae his voice and soul. "My job combines a bit of everything I have learned", explains Karin, who was an intern for the EMBL-based journal for science teachers *Science in School*. "I studied Astrophysics, but I realised that communicating science was what I enjoyed the most. I wanted to learn how to better connect with people, so I also pursued further studies in psychology and museum studies, as well as taking on communication internships. If you explain something and people can relate to it, that draws their attention and makes them want to know more – with Philae, it helped that we were able to tell this story in a fun way."

And that is exactly why @Philae2014 exploded on Twitter, reaching nearly 400,000 followers, gathering retweets from the White House and providing a source of narrative for headline stories around the world.

The story was enriched by interactions with the Rosetta spacecraft's own Twitter account, run by a team at ESA. Ranero explains that tweets between Philae and Rosetta resemble friends chatting on a great adventure – not pieces of metal in cold outer space, but beings full of emotion. "We have a great time working with the Rosetta team and the scientists at the DLR Lander Control Center. We try to think of conversations beforehand, but that can change in a minute."

Indeed, being Philae gives Ranero a direct line to DLR's Lander Control Centre. "In such moments of tension, it is important to wait for word from the experts that first have to figure out what is happening," she says. When Philae's harpoon system failed to anchor the lander on the comet, for example, Philae bounced and landed in a rugged region a few kilometers away from his target, something she points out was good luck guised as bad luck. Philae imaged structures and examined an area that might never have been seen otherwise.

Before exhausting his batteries, Philae sent a bounty of data to keep researchers here on Earth busy – and there could even be another twist in the tale. "Philae's landing site will protect him from excessive radiation," Ranero adds. "Scientists are hopeful that when Comet 67P gets closer to the Sun, Philae will have enough energy to wake up – and we will be waiting for him. I will never forget the atmosphere in the Control Center during the landing. It was a spectacular, once-in-a-lifetime event that will be written about in history books, and it was a privilege to be part of it." And thanks to her and her team, thousands of people feel the same way. Mission accomplished.

Q&A

What if EMBL scientists were machines?

As part of our '40 Questions, Answered' initiative, Aidan Budd asked: If scientists are machines that turn coffee into papers, how many coffees, how many papers*, in the last 40 years? After some smart investigations from senior librarian Tobias Sack and Head of Canteen and Cafeteria Michael Hansen, Isabelle Kling sheds some light on the matter.

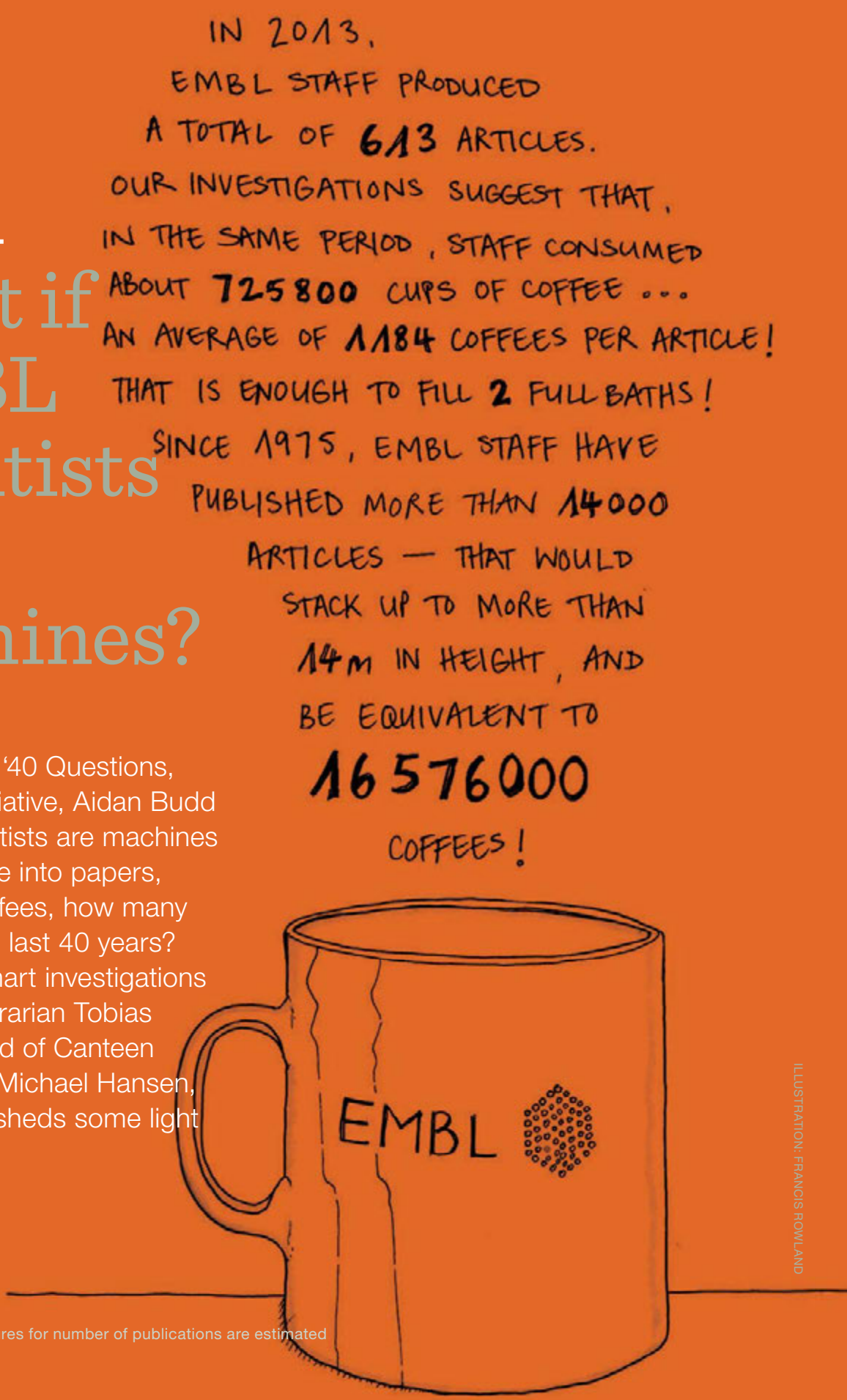


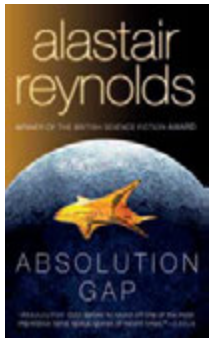
ILLUSTRATION: FRANCIS ROWLAND

MORE ONLINE AT
S.EMBL.ORG/40A

*As for coffee cups, figures for number of publications are estimated

Reviews

Which stories have illuminated something important to you? Staff from the Lab provide their favourite…



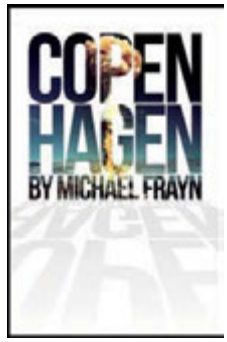


IMAGE BY STEFANIE OKUDA

The Inhibitor Trilogy, **Alistair Reynolds**

Seemingly unrelated events in distant places converging into an epic finale – how many stories like that have you read before...? Not this time. Riding "lighthuggers" for no-faster-than-light travel, creating digital sub-personas of yourself, and fighting the "nano-mould plague", you become less than a reader and more of an explorer of a dystopic future – which the reader is led to believe is the most probable one. And you may not like it one bit. Alastair Reynolds, a former European Space Agency astrophysicist, created a genuine chronicle of human kind in a science fiction trilogy – *Revelation Space, Redemption Ark, and Absolution Gap* (pictured) – starting with the archaeology of extant star-faring species and ending up with walking cathedrals. Highly recommended for techno addicts, but forbidden for bedtime readers. RASTISLAV HOROS, POSTDOC, EMBL HEIDELBERG

Copenhagen (1998), **Michael Frayn**

Why did he come to Copenhagen? The question echoes through this award winning play, which transcends history. "He" is theoretical physicist Werner Heisenberg, and the answer lurks in his visit to Niels Bohr in 1941, during the height of WWII and the race to develop the atomic bomb. Heisenberg and Bohr passed away long ago, but playwright Michael Frayn brilliantly summons their spirits in a rehearsal loop and re-imagines what happened. Human behaviour becomes as uncertain as physics principles, and as we dive into the science and history behind quantum mechanics, we witness a debate about taking moral responsibility for one's actions, and the inevitable break-up of a friendship. Interested? Watch the movie starring Daniel Craig (2002), or listen to the radio recording with *Sherlock* actor Benedict Cumberbatch (2013). JULIA ROBERTI, POSTDOC, EMBL HEIDELBERG

The Truth About Climate Change (2006), **Sir David Attenborough**

Climate change is a very hot topic at the moment and the media narrative in the past has focussed on differing opinions about the reasons underlying the increase in global temperatures recorded during the past 40 years. In 2006, David Attenborough wanted to provide an answer to this very important question. In this groundbreaking documentary, he assessed the weight of evidence as to whether this increase in temperature was due to natural causes – such as sun activity or volcano eruptions – or greenhouse gases – created by human activities. He presented compelling evidence that the latter is the main contributor to climate change, and I remember being inspired by his suggestions for five ways we can reduce it – which range from scaling up renewable energy, to population growth control. ANDREA CERESI, POSTDOC, EMBL MONTEROTONDO

Die Zeit, die Zeit (2012), **Martin Suter**

Time, just like any other measurable factor, follows a strict rule: 60 minutes = 1 hour, 24 hours = 1 day, 365 days = 1 year. *Die Zeit, die Zeit*, a novel by Swiss author Martin Suter, places this stringent definition in another light. Suter tells the story of "time nihilist" Alfred Knup, who denies the very existence of time. Alfred's thesis sounds rather simple: since time measures 'change', one should be able to stop time from passing, by avoiding changes – a mission Alfred dedicates his life to. The book has influenced how I personally perceive time; instead of accepting it as a stress-provoking constraint, I now try to look at it in a more relaxed fashion – as a subjective man-made construct that does not follow any rules except itself. INA HOLLERER, PHD STUDENT, EMBL HEIDELBERG

Alumni

New year, new ideas

PHOTO: EMBL PHOTOLAB

Last year marked EMBL's 40th anniversary, and celebrations continue apace in 2015 as we reveal our John Kendrew Award and Lennart Philipson Award winners (below), and speak to alumnus and new Nobel Laureate Stefan Hell (page 20). We also check out an alumnus-led initiative that uses breathtaking animations to explore and explain data (page 49), and catch up with Ken Holmes, one of the founding fathers of EMBL and EMBL Hamburg (pages 11 and 50). One question we are frequently asked by alumni is "how can I help?" – soon we will launch a survey to measure the ambassadorial impact of alumni after leaving EMBL, and completing this would be a really great place to start – thank you!

Mehrnoosh Rayner
Head of Alumni Relations

"Outstanding, fearless, remarkable..."

Selected for outstanding achievements – including fearless and novel scientific approaches, remarkable examples of collaboration, and active engagement in science communication –, alumna **Melina Schuh** has been awarded the 2015 John Kendrew Young Scientist Award. Melina, who was a PhD student in the Genome Biology Unit (2004–8), went on to become group leader at the Medical Research Council Laboratory of Molecular Biology, in the UK. Her group has made several major findings in the field of fertilisable eggs in mammals, providing important insights into fundamental cellular mechanisms. Melina is also engaged in an initiative called "Meeting of Minds", which brings together practitioners from the fields of science and art, to communicate science to a wider audience – work currently touring Europe as part of the "Lens on Life" exhibition.

"A founding father of cryo-EM..."

Jacques Dubochet, former group leader in the Structural and Computational Biology Unit (1978-87), is the winner of the first ever Lennart Philipson Award. The prize, set up in honour of EMBL's second Director General, recognises outstanding contributions to translational research and technology innovation. While at EMBL, Jacques, together with colleagues, developed a method to freeze thin layers of solutions of enzymes or viruses without forming ice crystals. They then looked at these layers in the electron microscope, marking the birth of cryo-electron microscopy. Jacques also developed methods to cut vitreous sections of high-pressure frozen tissue, allowing the insides of cells to be imaged by cryo-EM. He was selected for pioneering work from the late 1970s to his retirement in 2011. Jacques is now actively involved in areas such as ethics, philosophy and citizen responsibility.

Lights, camera, action

A starchy snapshot from *The Hungry Microbiome* movie

IMAGE: CHRISTOPHER HAMMANG/CSIRO

Stunning videos zooming amongst our intestines' microbial communities and investigating molecular mistakes in individual cancers, developed by the group of EMBL alumnus Sean O'Donoghue, have been selected amongst the world's top ten science animations in the 2015 International Science & Engineering Visualisation Challenge – the data visualisation equivalent of the Academy Awards.

BY THEODOROS SOLDATOS

The films *The Hungry Microbiome* and *Cancer is Not One Disease* were produced through the VizbiPlus project, which aims to present inspiring, informative and scientifically-sound animations about recent developments in the life sciences.

"While this effort is primarily geared to help improve how science is communicated, a distinctive feature is that it is not designed only to inform, but also to educate and engage the public," explains O'Donoghue, who is group leader at the Garvan Institute of Medical Research in Sydney and the Commonwealth Scientific and Industrial Research Organisation. "It is a unique combination of science and art – scientists producing the videos spend the best part of a year to deliver two to three minutes of footage, but most of this time is spent doing science, talking to other researchers, or reading papers. We want to make sure every frame is consistent with what we know is true in science."

The videos, available on YouTube, have been viewed thousands of times by people around the world, and showcased at sold-out events and festivals. "You get insight into what is going on at a scale that is otherwise inaccessible," O'Donoghue explains. "Take our gut microbiome – we know that many plant foods benefit our health, and through animation we have illuminated in intricate detail the role that the bacteria in our intestines have in this process. It is inspiring to watch and people are captivated by a world they may know little about."

Animators in O'Donoghue's groups use tools developed by other team members, such as Aquaria – a new protein structure service that provides a concise visual summary of all related Protein Data Bank structures, simplifying the process of gaining insight into molecular function. Amongst a raft of award-winning projects, his multidisciplinary teams also work on community initiatives such as the Visualising Biological Data (VIZBI) conference series, which aims to raise the global standard of data visualisation.

"Researchers are gathering data at unprecedented rates," adds O'Donoghue, who has used data visualisation techniques throughout a career spanning both academia and industry. "Humans are driven by vision – we are very effective at looking at complex information and extracting patterns. Advancements in graphics are allowing us to create more complex visualisations – essentially developing a new visual language in which we can communicate, explain and understand science."

The next VIZBI meeting is 25-27 March at the Broad Institute, Boston US. The annual event alternates between the US and EMBL Heidelberg.

WWW.VIZBI.ORG

It all started with muscle...

Ken Holmes, one of the visionaries behind the establishment of EMBL and the EMBL Hamburg outstation, looks back to where it all began.

PHOTO: KEN HOLMES

Realising the power of the synchrotron

In the late 1960s, as Director of the Department of Biophysics at the Max Planck Institute for Medical Research in Heidelberg, I was part of a group of scientists utilising X-ray diffraction as a means of studying the physiology of muscle. In principle, X-ray diffraction from contracting muscle fibres could tell us how the component molecules were moving but, until I came across the work of the Nobel Prize Winner Julius Schwinger on the theory of synchrotron radiation, we lacked enough X-ray intensity. Our subsequent search for 'rings of electrons' led us to the Deutsches Elektronen-Synchrotron (DESY) in Hamburg. Together with Gerd Rosenbaum, who had fortunately joined me as a doctoral student, we set up equipment that enabled us to use this beam to get a diffraction pattern from a muscle specimen – achieving a ten-fold gain in intensity, high optical quality, and we are still witnessing its open-ended potential today (see page 11).

EMBL Hamburg was born

The work redefined the aims of the future EMBL. At a meeting of the steering committee in Konstanz in 1969, there was a consensus that EMBL should specialise in large projects that could not be undertaken by national labs, such as synchrotron radiation. This resulted in an EMBL outstation in Hamburg, set up by Gerd and I – we built the world's first ever X-ray beamline at DESY, before EMBL officially existed. Today, alongside recombinant DNA technology, the technique is one of the twin pillars of molecular biology.

Lots of Bessel Functions

I did my PhD on the structure of the tobacco mosaic virus (TMV) at Birkbeck College London with Rosalind Franklin. Very sadly, she died of cancer before I had finished. I completed my doctorate with Aaron Klug, with whom I spent the next decade and more working out the atomic structure of TMV. This is a fibre diffraction problem and involves lots of Bessel functions. From this work I gained the expertise that enabled me to calculate the expected intensities of synchrotron radiation from Schwinger's complex formula and later apply methods I learned to solve the structure of actin.

Heidelberg adventure

Coming to Heidelberg in 1968 was something of an adventure. From an initiative originating in part from my young department at the Max Planck Institute for Medical Research, Heidelberg was offered as a site for EMBL. Founding director John Kendrew, a personal friend and colleague at the Laboratory for Molecular Biology in Cambridge, asked my wife Mary to set up the Szilard library. I also joined Heidelberg's rowing club – probably more valuable than many years of health insurance. Now we've settled in the Mühltal in Handschuhsheim. Meanwhile, EMBL has gone beyond just large science. Most important, it offers a unique venue where young scientists from all over can come to do excellent research and meet to form friendships and collaborations that are truly pan-European.

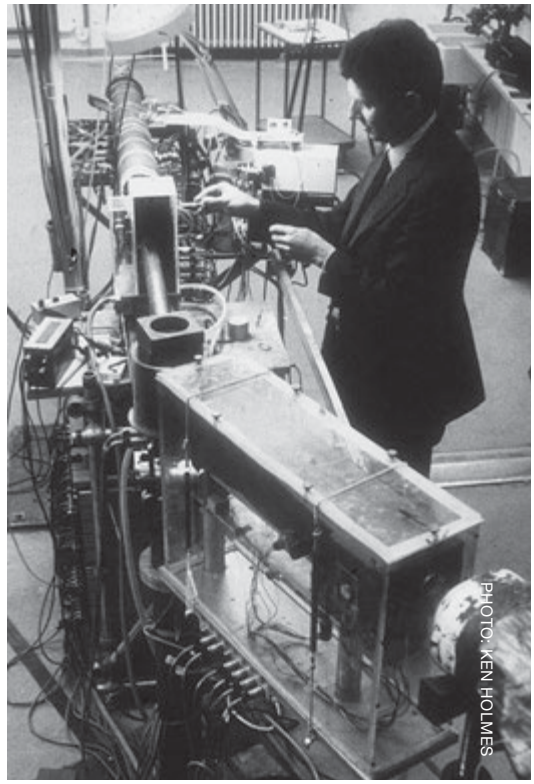


PHOTO: KEN HOLMES

Ken Holmes adjusting the first ever X-ray beamline at DESY

Locus Croatia

From sapphire waters to ancient towns, Jelena Tica, a PhD student from EMBL Heidelberg, takes us in and around her hometown of Zadar.

1 Strolling in the city, I am often impressed by modern installations, which are juxtaposed against ancient architecture – some important remains spanning thirteen centuries of Croatian history. An installation called 'Greeting to the Sun' is located in the port area of Zadar, and uses solar power to project a night-time light show.

PHOTO: MAIA SEGURA WANG

2 Travelling from region to region reveals distinct culinary traditions. One of my favourites is in Dalmatia, where alongside seafood and pasta one of the dishes of choice is 'pršut' – a home-cured ham dried out by the cold wind 'bura' and usually smoked.

3 Croatia has a rich cultural heritage – one of the most impressive is the traditional costumes and dances one finds in the different regions. One of my favourites, a traditional sword dance called the Moreška, dates back hundreds of years.

4 Croatia has a long coastline of rocky and sandy beaches. I love to travel to some of the islands, islets, rocks and reefs that line the coast – the country is rightly known as the 'land of a thousand islands'.

2

PHOTO: MAIA SEGURA WANG

3

PHOTO: INSTITUTE OF ETHNOLOGY AND FOLKLORE RESEARCH

4

PHOTO: JELENA TICA

Events

January
23

EMBL Monterotondo
Science and Society seminar: Data on a persistent problem: What's holding back female scientists? – Gerlind Wallon, Deputy Director, EMBO

February
9

EMBL Heidelberg
Distinguished Visitor Lecture – Martin Fussenegger ETH Zurich

February
9-10

EMBL Grenoble
European Learning Laboratory for the Life Sciences (ELLS) Learning Lab: Structural biology – shining light onto the fabric of life

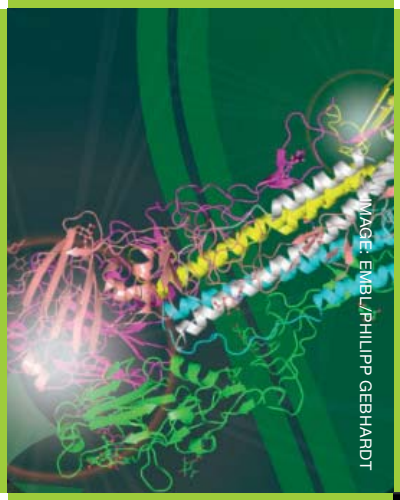


IMAGE: EMBL/PHILIPP GEBHARDT

February
18

EMBL Heidelberg
Science and Society seminar: The threat of manufactured disease: The past, present & future of biological weapons – Filippa Lentzos, King's College London

February
20

EMBL Monterotondo
Distinguished Visitor Lecture: Controlling the Cell Cycle – Sir Paul Nurse, The Royal Society, London

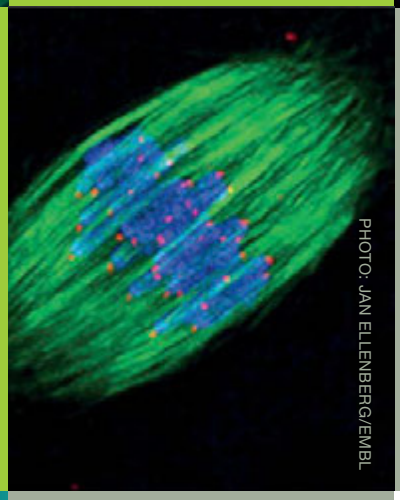


PHOTO: JAN ELLENBERG/EMBL

March
3-6

EMBL-EBI
Course: Introduction to Integrative Omics

March
9-10

EMBL-EBI
SME Bioinformatics Forum


IMAGE: EMBL-EBI/SPENCER PHILLIPS

March
29-31

EMBL Heidelberg
EMBO | EMBL Symposium: Frontiers in Stem Cells & Cancer

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