

EMBL etc.



Origins

Synapse Nibbling on brain cells

Nucleus Ocean origins

Cultures Seven new scientists

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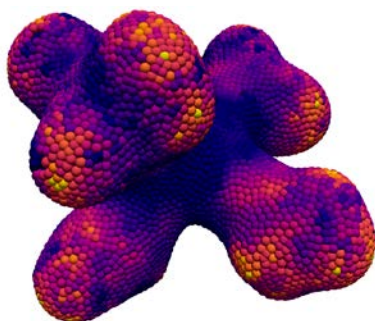
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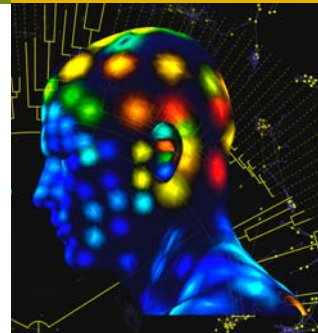
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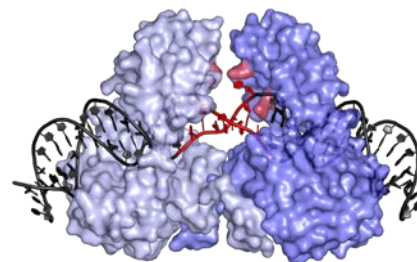
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Editorial

Some of the most fascinating questions in science are about origins. For biologists, perhaps the biggest question is: how did life begin? But the history of life is also full of smaller origin stories – moments of biological innovation that each contribute to the complexity of the living world.

In this issue, we follow an EMBL alumna's rediscovery of an elusive species in the Indian Ocean, which is providing key insights into the origin of animals with backbones (p. 18), and we explore how the study of co-evolution had its origins in Darwin's observations of orchids and insects (p. 22).

EMBL is a place where many ideas and technologies have their origin or are further developed. We talk to our scientists about how GPU computing is revolutionising their research (p. 24), and report on a method for mapping molecules on surfaces (p. 28).

We delve into the scientific origins and current research of EMBL's next Director General, Edith Heard (p. 36), and EMBL group leader Jan Korbel (p. 38).

Finally, we celebrate new beginnings: whether it's Slovakia joining us as a member state (p. 9), the company co-founded by EMBL-EBI PhD student Daniel Elías Martín Herranz (p. 39), or the seven new scientists who will head groups or facilities at EMBL (p. 32). We look forward to the new ideas and innovations that will follow.

Edward Dadswell

Editor

Word to remember Microglia

Noun, pronunciation:
/ˌmɪkrəˈɡliə/

Microglia are immune system cells that keep the brain and spinal cord healthy by 'eating up' pathogens, dead and dying neurons, and other cellular debris. Microglia also nibble on synapses to strengthen connections between neurons (p. 15).

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Belgian PhD student decodes DNA and wins a bitcoin

PhD student Sander Wuyts won the DNA Storage Bitcoin Challenge issued by EMBL-EBI's Nick Goldman in 2015

BY MARY TODD BERGMAN

The challenge

On 21 January 2015 at the World Economic Forum's annual meeting in Davos, Switzerland, Nick Goldman from EMBL-EBI described a new method for storing digital information in DNA. At the end of his talk, he issued a challenge.

"Bitcoin is a form of money that now only exists on computers, and with cryptography, that's something we can easily store in DNA," explained Goldman. "We've bought a bitcoin for €200 and encoded its information into DNA." Goldman

distributed DNA samples in test tubes. The first person to decode the DNA and find the 'private key' would win the bitcoin.

Good timing

One week before the deadline, Sander Wuyts, a PhD student at the University of Antwerp and Vrije Universiteit Brussel, in Belgium, was the first to master the method and decode the private key, taking possession of the bitcoin.

Its value on 19 January 2018: around €9500.

The contender

Now completing his PhD in microbiology – exploring the universe of bacteria through DNA – Wuyts has the right balance of passion, coding skills and great colleagues to tackle complex puzzles like Goldman's DNA Storage Bitcoin Challenge.

Wuyts saw Goldman issue the challenge on YouTube back in 2015, but it was a tweet about the deadline in December 2017 – plus the skills he had acquired in the meantime – that made him swing into action.

Once he started, Wuyts became aware that decoding the bitcoin wouldn't be quite as simple as

following a recipe. After one failed attempt and an essential pause over Christmas, he worked tirelessly to put the data from sequencing into the right order and decode the files.


"I was extremely surprised and excited when the decoded files appeared, perfectly readable. There were the instructions on how to claim the bitcoin, a drawing of James Joyce and some other things."

He revealed his uncertainty about whether his efforts would actually pay off: "Before participating in this challenge, I had my doubts about the feasibility of such a DNA technology – but now I don't."

Wuyts intends to sell his bitcoin and use the proceeds to invest in science projects, thank the people who helped him, and celebrate earning his PhD in style.

Goldman, N *et al.* *Nature*, 23 January 2013. DOI: 10.1038/nature11875

 FULL VERSION ONLINE:
BIT.LY/embl-91-01

 READ SANDER'S BLOG POST
ABOUT HOW HE DID IT:
BIT.LY/embl-91-01b



SANDER WUYTS

Sample of DNA in which one bitcoin (and some other files) were encoded, as posted to Sander Wuyts.

Commonly used drugs affect our gut bacteria

One in four drugs with human targets inhibit the growth of bacteria in the human gut

BY IRIS KRUIJEN

The human gut contains a large number of bacterial species, collectively referred to as the gut microbiome. In the past decade, it has become clear that the composition of the gut microbiome affects human health. It is also well known that antibiotics have a large impact on this microbiome, for

example by causing gastrointestinal side effects.

A few commonly used non-antibiotic drugs have recently been shown to cause changes in the composition of the gut microbiome, but the full extent of this phenomenon was unknown until now. EMBL researchers led by Peer Bork, Kiran Patil, Nassos Typas and Georg Zeller screened over 1000 marketed drugs against 40 representative bacteria from the human gut, and found that more than a quarter of the non-antibiotics affected the

growth of at least one species in the microbiome. These drugs cause antibiotic-like side effects and may promote antibiotic resistance. Since many drug-microbe interactions are likely to be specific to each person, these findings also open paths to personalised drug therapies aimed at the individual gut microbiome.

Maier, L, Pruteanu, M, Kuhn, M *et al.* *Nature*, 19 March 2018. DOI: 10.1038/nature25979

 FULL VERSION ONLINE:
[BIT.LY/embl-91-03](https://bit.ly/embl-91-03)

JULIA CARTASIOVA/EMBL

New target could stop spread of drug resistance

EMBL scientists unravel the molecular basis of a major mechanism of antibiotic resistance transfer

BY IRIS KRUIJEN

Bacteria have developed resistance to most of the drug compounds we use today. One of the major drivers of resistance spreading between

bacteria is transposons, or jumping DNA: genetic elements that can switch locations in the genome autonomously. When transferred between bacteria, transposons can carry antibiotic resistance genes within them.

In a study published in *Cell*, Orsolya Barabas and her group provided the first crystal structure of a protein-DNA machine that inserts transposons into recipient bacteria.

The research team discovered that the workhorse of the transposon insertion machine, the transposase protein, has an unusual shape. This



enables it to restructure the DNA, allowing it to insert its cargo – such as antibiotic resistance genes – into an extremely diverse range of bacteria.

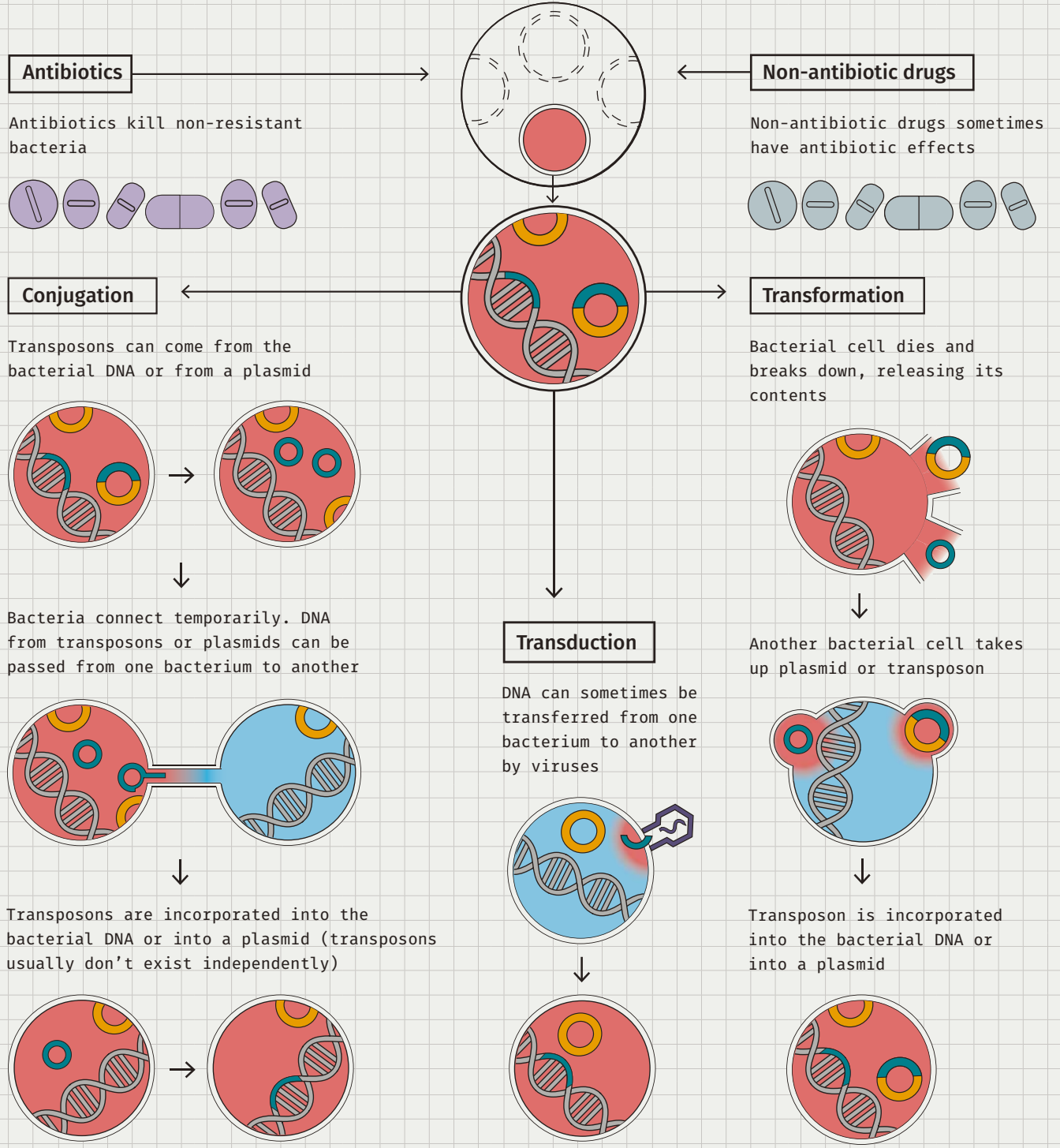
Rubio-Cosials, A *et al.* *Cell*, 15 March 2018. DOI: 10.1016/j.cell.2018.02.032

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ALEXSANDRA KROLIK/EMBL

How antibiotic resistance spreads

- Resistant bacterium
- Non-resistant bacterium
- Plasmid - Loop of DNA
- Virus
- Transposon - Small piece of DNA that can change its position within a genome, or move from one DNA molecule to another



Molecular cuisine for gut bacteria

EMBL scientists show how to grow a wide range of gut bacteria in the lab

BY IRIS KRUIJEN

The bacteria living in the gut have a big impact on our health. But researchers still don't know what kind of food most of our gut bacteria like to live on, or precisely how they metabolise nutrients.

A recent *Nature Microbiology* article reports on the growth characteristics of the main human gut bacteria in 19 different growth media, with well-defined recipes. Peer Bork, Kiran Patil and Nassos Typas, all group leaders at EMBL Heidelberg, led the work.

This resource provides scientists with tools to experimentally investigate gut microbiome ecology, helping them go beyond correlations to identify causes and effects.

Tramontano, M, Andrejev, S *et al.* *Nature Microbiology*, 19 March 2018. DOI: 10.1038/s41564-018-0123-9

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[BIT.LY/embl-91-05](https://bit.ly/embl-91-05)



ALEXSANDRA KROLIK/EMBL

Synchronised waves control embryonic patterning

EMBL scientists show the importance of precise timing in developing embryos

BY IRIS KRUIJEN

During an embryo's journey from a single cell to a complex organism, countless patterning processes make sure that the right cells develop in exactly the right location and at the right time. Cells activate specific genes in a rhythmic manner during this early development, resulting in waves of activation sweeping through the embryo.

In mouse embryos, two signalling pathways that are key to the

formation of new segments are called Wnt and Notch. Both show periodic pulses of activity, which occur at the same pace as the formation of the segments. Scientists from the Aulehla and Merten groups at EMBL have shown that the timing between the two pathways' waves is responsible for segmentation. At a specific time point, the Wnt and Notch waves synchronise and overlap, coinciding with the formation of a new segment.

To test what happened when the two waves were not in sync, the research team developed a new experimental strategy to control the rhythm of Wnt and Notch pulses. Katharina Sonnen, an EMBL postdoctoral researcher working in both the Aulehla and Merten labs,

developed a system that enabled her to synchronise the waves to an external rhythm. Strikingly, a new segment was made only when the Wnt and Notch waves synchronised. Changing their relative timing prevented segment formation.

Sonnen, K *et al.* *Cell*, 22 February 2018. DOI: 10.1016/j.cell.2018.01.026

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[BIT.LY/embl-91-06](https://bit.ly/embl-91-06)



ALEXSANDRA KROLIK/EMBL

Wet-lab e-learning courses go live

EMBL launches its first wet-lab e-learning courses: introductions to optogenetics and CLEM

BY BERTA CARREÑO

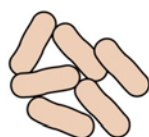
EMBL has launched its first online courses focusing on research from laboratories at EMBL Heidelberg: An Introduction to Optogenetics and An Introduction to On-section CLEM (Correlative Light and Electron Microscopy). The courses combine different e-learning materials, ranging from how-to videos to interactive elements and exercises. More courses will become available in the coming months, covering other areas of EMBL expertise.

EMBL's free online courses are aimed at a range of audiences, from molecular biologists wanting to learn a particular technique to non-scientists interested in the latest discoveries and advances. They feature some of the cutting-edge research and new technologies used at the different EMBL sites, and build on the success of EMBL-EBI's bioinformatics online training platform.

If there's a topic you'd like to see covered in a new e-learning course, or you have expertise to contribute, get in touch with the e-learning team at: support.e-learning@embl.de.



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Bacteria



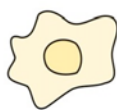
Nematode
worm



Yeast



Fruit fly



Cell culture



Mouse

Optogenetics, which has been successfully used in a diverse range of organisms, is introduced in one of the new e-learning courses.



Slovakia becomes EMBL member state

BY BERTA CARREÑO

EMBL welcomed the Slovak Republic as its latest member state on 29 January 2018. The accession of Slovakia to EMBL membership emphasises the organisation's commitment to promoting European science and collaboration among researchers.

As a member state, Slovakia gains access to all of EMBL's services and facilities. Its new status also allows Slovakia to vote in EMBL's Council, the governing body that makes important decisions about the organisation. Up to two Slovakian delegates will join the Council, helping to shape EMBL's future programmes.

Since Slovakia became an EMBL prospect member state in 2014, the ties between the two parties have become stronger: EMBL and Slovakia have applied for joint grants and contributed to joint publications. To stimulate collaboration with the Slovak research community, EMBL held a workshop at Comenius University's Science Park in Bratislava, Slovakia, in 2017.



READ ONLINE:
BIT.LY/embl-91-08

Axon guidance and bundling are linked

Rob Meijers' group at EMBL Hamburg has found that axon guidance is more complicated than was previously thought. During spinal cord development, neurons have to project axons across the midline to coordinate movements between the left and right sides of the body. Meijers' group discovered how a molecule that guides axons towards the midline (Netrin-1) works together with another molecule that drives axons to gather into bundles (Draxin).

Liu, Y *et al.* *Neuron*, 1 March 2018. DOI: 10.1016/j.neuron.2018.02.010

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[BIT.LY/embl-91-09](https://bit.ly/embl-91-09)

From blood vessels to blood stem cells

Cells develop from stem cells. However, blood stem cells develop from vascular cells, which line the walls of our blood vessels. Christophe Lancri's group at EMBL Rome studies the transcriptional regulation involved in this critical biological process during embryonic development. Using advanced bioinformatics analysis, Lancri and collaborators recently predicted that some of the transcription factors involved had opposing activities. Essentially, two cell fates are competing with each other in one cell.

Bergiers, I *et al.* *eLife*, 20 March 2018. DOI: 10.7554/eLife.29312

 FULL VERSION ONLINE:
[BIT.LY/embl-91-10](https://bit.ly/embl-91-10)

Women in Science Day: school event

Neus Martinez and Xavi Diego, members of the Sharpe group at EMBL Barcelona, visited the Eulàlia Bota Primary School in the city to talk about women, science and curiosity with 6-year-old children. The objective of the event was to awaken future Albert Einsteins and Marie Curies in the audience and to share the idea that anyone can be a scientist as long as they are curious!

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School visit to mark the 2018 International Day of Women and Girls in Science.

CARLA MANZANAS/EMBL



How drugs affect the life and death of proteins

Proteins are responsible for countless activities in the cell. When reacting to external stimuli, stress or drug treatment, cells adjust their protein levels. Scientists at EMBL and Cellzome have developed a new technology, called multiplexed proteome dynamics profiling (mPDP), to monitor the effects of drug treatments on protein degradation and synthesis. The tool allows scientists to investigate protein degradation mechanisms, their role in disease, and their modulation by drug treatment.

Savitski, MM, Zinn, N, Faelth-Savitski, M *et al. Cell*, 15 March 2018. DOI: 10.1016/j.cell.2018.02.030

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[BIT.LY/embl-91-13](https://bit.ly/embl-91-13)

Information (arrows) emanating from chromatin to give rise to different cell types.

Chromatin usage reveals developmental trajectories

Both cell type and developmental stage can be deduced from measurements of chromatin accessibility in thousands of single cells. Researchers at EMBL and the University of Washington, USA, used this approach to uncover how cells in developing embryos regulate their identity as they decide what kind of cell to become. This new and more systematic approach

allows researchers to analyse all the different cell types in an embryo at the same time and, importantly, at single-cell resolution.

Cusanovich, DA, Reddington, JP, Garfield, DA *et al. Nature*, 14 March 2018. DOI: 10.1038/nature25981

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[BIT.LY/embl-91-12](https://bit.ly/embl-91-12)

Jacques Dubochet donates Nobel medal to EMBL

Jacques Dubochet, who was awarded the 2017 Nobel Prize in Chemistry, donated an official replica of his Nobel medal to EMBL. The replica will be displayed when the EMBL Archive is inaugurated this summer. In the accompanying note, Dubochet states: "I am pleased to offer this copy of my Nobel medal to EMBL in testimony of my great thankfulness to an institution that, in my view, would deserve to be the laureate of the Prize."



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Jacques Dubochet holding his Nobel medal during Nobel week.

ALEXANDER MAHMOUD ©NOBEL MEDIA AB 2017

The genetic risk factors for depression

Researchers at EMBL-EBI and collaborators have found that the genetic contribution to depression may differ between people who have experienced serious adversities in life and those who haven't. Results from this genome-wide association study show that by removing people who have experienced major adversities from a cohort, researchers can get a clearer view of the molecular mechanisms associated with depression.

Peterson, RE, Cai, N *et al.* *American Journal of Psychiatry*, 2 March 2018. DOI: 10.1176/appi.ajp.2017.17060621



FULL VERSION ONLINE:
[BIT.LY/embl-91-15](https://bit.ly/embl-91-15)

New cryo-EM service at EMBL Heidelberg

Scientists who want to obtain detailed structures of biological molecules now have a new facility to turn to: the cryo-electron microscopy (cryo-EM) service platform at EMBL Heidelberg. The platform enables scientists from other institutions to access state-of-the-art microscopes for high-resolution data collection. Experts Wim Hagen and Felix Weis are on hand to support researchers with everything from handling the microscopes to acquiring data at the highest possible resolution.



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[BIT.LY/embl-91-16](https://bit.ly/embl-91-16)

ERC Scientific Council meets in Heidelberg

From 28 February to 2 March, EMBL and EMBO hosted the European Research Council (ERC) Scientific Council in Heidelberg. More than 20 ERC Council members joined ERC President Jean-Pierre Bourguignon to discuss topics of strategic importance for the funding body. An open workshop stimulated exchange between ERC representatives and the local life-science community on the opportunities and challenges of applying for and obtaining an ERC grant in the life sciences.



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[BIT.LY/embl-91-17](https://bit.ly/embl-91-17)

New corporate partner for EMBL

California-based company 10x Genomics, Inc., whose innovative Chromium™ System was listed as one of the top 10 innovations of 2017 by *The Scientist*, has joined the EMBL Advanced Training Centre Corporate Partnership Programme. Under the programme's auspices, 10x Genomics and EMBL will serve a global community of investigators, providing advanced training in single-cell genomics and transcriptomics at the Advanced Training Centre in Heidelberg.



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[BIT.LY/embl-91-18](https://bit.ly/embl-91-18)



EMBL-EBI Training used robot avatars to help two new mothers learn about genomics.

JEFF DOWLING/EMBL

Using robot avatars in bioinformatics training

For the first time, EMBL-EBI Training has enabled two students to complete a course in genomics using robot avatars. The students are healthcare professionals who have recently had babies. From the comfort of their home, each student controlled a 40 cm tall robot avatar located in class, which can transmit video, speak and even whisper to colleagues.

The technology, initially developed to help children with long-term illness attend school, allowed the new mothers to actively take part in wet lab and bioinformatics modules just two weeks after giving birth.



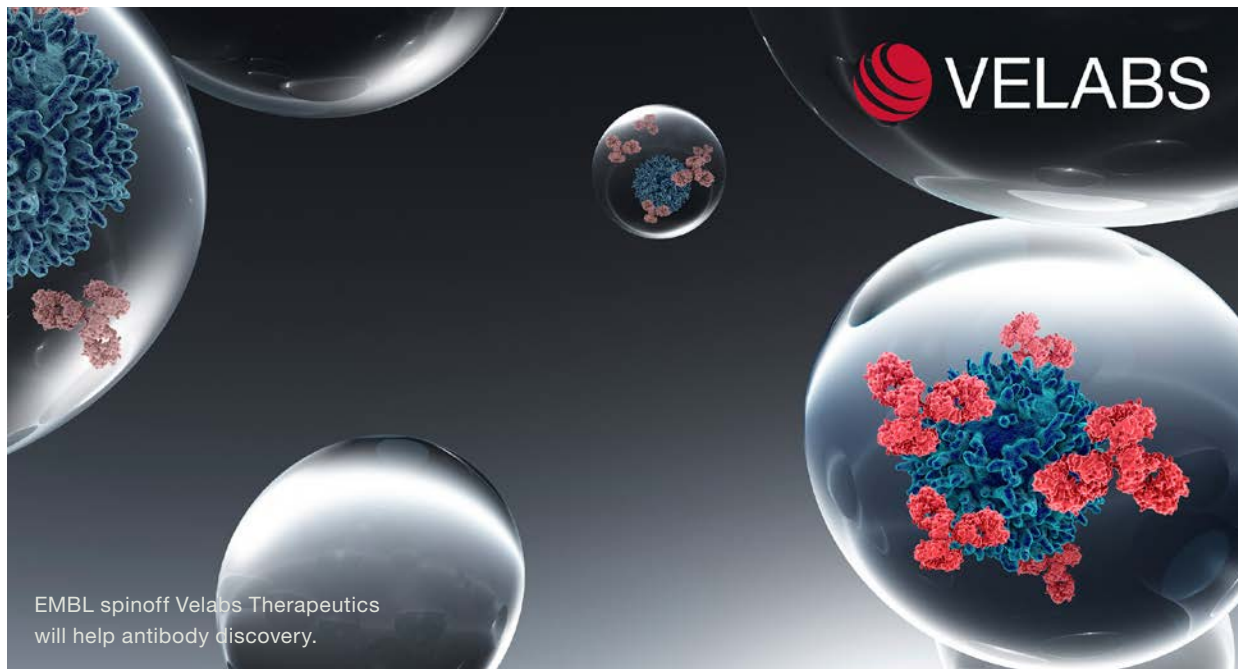
FULL VERSION ONLINE:
[BIT.LY/embl-91-19](https://bit.ly/embl-91-19)

EMBL spinoff to help antibody discovery

Microfluidics technology developed at EMBL enables the rapid screening of antibodies, which can help in the development of new therapies. Through its technology transfer arm, EMBLEM, and with the support of private investors, EMBL has launched spinoff

company Velabs Therapeutics to make a new microfluidics platform – based on the EMBL technology – available to the global antibody research community.

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[BIT.LY/embl-91-20](https://bit.ly/embl-91-20)



EMBL spinoff Velabs Therapeutics will help antibody discovery.

Loops, loops and loops: how DNA gets organised

Scientists have puzzled for decades over how cells package more than two metres of DNA into tiny chromosomes while preparing for cell division. EMBL researchers and collaborators have finally managed to isolate and film the process, and have witnessed – in real time – how a single protein complex called condensin reels in DNA to extrude a loop. By extruding many such loops in long strands of DNA, the cell packs its genome so it can be distributed evenly between its two daughter cells.

Ganji, M *et al.* *Science*, 22 February 2018. DOI: 10.1126/science.aar7831

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[BIT.LY/embl-91-21](https://bit.ly/embl-91-21)

One-way crossing across the midline

Andrew McCarthy's group at EMBL Grenoble has solved a decades-long debate on a key process in brain and embryo development. Using X-ray crystallography and electron microscopy, the scientists describe the structural changes resulting from the binding of the neural receptor Robo with the Slit protein in humans. Their findings demonstrate that correct guidance of the axons across the midline of the brain is triggered by a conformational change of the Robo receptor.

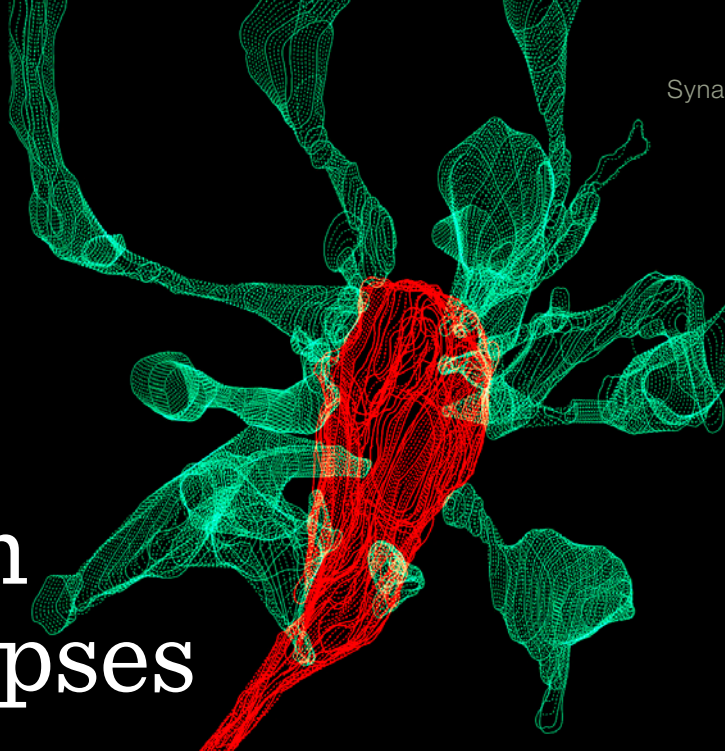
Aleksandrova, N *et al.* *Structure*, 4 January 2018. DOI: 10.1016/j.str.2017.12.003

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[BIT.LY/embl-91-22](https://bit.ly/embl-91-22)



Captured: microglia nibbling on brain synapses

LAETITIA WEINHARD/EMBL



Massive imaging study finds that microglia strengthen synapses

BY IRIS KRUIJEN

Around one-tenth of the cells in your brain are immune system cells called microglia. Researchers have proposed that microglia pluck off and eat synapses – connections between brain cells – as an essential step in the pruning of connections during early circuit refinement. But, until now, no one had seen them do it.

Stronger synapses

That is why Laetitia Weinhard, from the Gross group at EMBL Rome, set out on a massive imaging study to see this process in action in the mouse brain, in collaboration with the Schwab team at EMBL Heidelberg. “Our findings suggest that microglia are nibbling synapses as a way to make them stronger, rather than weaker,” says Cornelius Gross, who led the work.

Warm welcome

The team saw that in around half the cases where microglia contact a synapse, the synapse head sends out thin projections, or ‘filopodia’, to greet them. In one particularly dramatic case, 15 synapse heads extended filopodia toward a single microglia as it picked on a synapse.

It turns out that microglia might underlie the formation of double synapses, where the terminal end of a neuron releases neurotransmitters onto two neighbouring partners instead of one. This process can support

Multiple synapse heads send out filopodia (green), which converge on one microglia (red), as seen by focused ion beam scanning electron microscopy.

effective connectivity between neurons. As Weinhard explained: “This shows that microglia are broadly involved in structural plasticity and might induce the rearrangement of synapses, a mechanism underlying learning and memory.”

Perseverance

The team recently published the results of this work – their first attempt to visualise this process in the brain – which was the culmination of five years of technological development. Ultimately, by combining correlative light and electron microscopy (CLEM) and light-sheet fluorescence microscopy – a technique developed at EMBL – the researchers were able to make the first movie of microglia eating synapses.

“This is what neuroscientists fantasised about for years, but nobody had ever seen before,” says Gross. “These findings allow us to propose a mechanism for the role of microglia in the remodelling and evolution of brain circuits during development.”

Weinhard, L *et al.* *Nature Communications*, 26 March 2018.
DOI: 10.1038/s41467-018-03566-5



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[BIT.LY/embl-91-23](https://bit.ly/embl-91-23)

Cambridge selected for Health Data Research UK site

Jointly run by EMBL-EBI, the new site will unleash the potential of data and technologies for medical research

BY OANA STROE

Health Data Research UK (HDR UK) has awarded £30 million to six sites across the UK to apply advanced data science to challenging issues in healthcare. The Cambridge site of HDR UK will be jointly run by the Wellcome Sanger Institute, the University of Cambridge and EMBL-EBI. The initiative hopes to unleash the potential for data and technologies to drive breakthroughs in medical research. The ultimate goal is to improve how we prevent, detect and diagnose diseases like cancer, heart disease and asthma.

Building on experience

“EMBL-EBI believes data sharing is essential for improving our understanding of human health and disease,” explains Ewan Birney, Director of EMBL-EBI. “Contributing our expertise in data management and big data analysis to HDR UK is just one way we are supporting the development of biomedical informatics institutes across Europe and beyond. This is an exciting opportunity for science and public health, and we are pleased to be a part of it. Our experience with HDR UK will help us build the foundations for interactions with similar partners in other countries.”

Harnessing data science

“The volume of health data is already vast, and we have every reason to expect it will continue to grow quickly. We must find effective, efficient ways to harness this data for both clinical research and practising medicine,” says Helen Parkinson, Head of Molecular Archival Resources at EMBL-EBI and Associate Director of the Cambridge HDR UK site. “We need a very broad range of collaborations to ensure the data being collected and analysed is robust, precise and translatable. With a rich, connected ecosystem of healthcare data, we can support discovery by future generations of scientists and change healthcare for the better.”



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 **HDRUK**
Health Data Research UK



Diverse origins

Delve into stories about the evolution of animals and plants, technologies and methods



Ocean origins

ISTOCK

EMBL alumna Èlia Benito-Gutiérrez on how her research and career evolved after searching the seas

The calm waters of an atoll, surrounded by the Indian Ocean.

BY EMMA STEER

For Archimedes, the eureka moment came as he took a bath. For EMBL alumna Èlia Benito-Gutiérrez, the bath was a little bigger: she was on a boat in the Indian Ocean. Under the burning midday sun, Benito-Gutiérrez focused her portable microscope on the bizarre-looking creature again. From the asymmetrical egg pouch, the striped spine-like structure running like a stack of coins along its length, and the ever-intriguing mouth tentacles, it seemed that she had discovered the mythical *Epigonichthys*. Lost for more than 100 years, this elusive animal has still not been formally described. Yet its rediscovery is proving vital for evolutionary biology research and has

made a major impact on Benito-Gutiérrez's academic career.

Back in time

Benito-Gutiérrez's journey began while working at EMBL Heidelberg as a postdoctoral fellow in the Arendt group. During this time, she discovered a manuscript from 1893 that pinpointed the last known location of a species in the Indian Ocean called *Epigonichthys* – an elusive sea creature with an aptitude for hiding.

Epigonichthys belongs to a group of organisms known as cephalochordates – small marine animals that burrow in the sand under the sea.



SILVIA ROHR

At first glance, they look like a cross between a fish and a worm and, in a sense, they are. They don't have a backbone, so can't be classed as vertebrates, yet their notochord – a structure made of a substance similar to cartilage, which runs the length of their thin bodies – distinctly separates them from invertebrates. This notochord can be described as a primitive backbone. In cephalochordates, it acts like a spine, sending out simple nerve signals and supporting the body's structure. It also transiently exists in human embryos, acting to organise and develop our skull, spine and parts of the brain, but is broken down shortly before birth.

The notochord provides an important evolutionary link between cephalochordates and humans. It represents the transitional period in evolutionary biology during which vertebrates and non-vertebrates split into separate groups. Because cephalochordates have changed very little in millions of years, they're an excellent model system to study – not only for this physical characteristic, but also for their genome.

Although *Epigonichthys* was discovered more than 100 years ago, it has never been described in detail. To confuse matters further, the name *Epigonichthys* has often

been used interchangeably with another name, *Asymmetron*, making it unclear if the literature is always referring to the same animal. "One of our aims, when we first went to the Maldives, was to find uncharacterised cephalochordates such as *Epigonichthys* and describe their physical characteristics, as well as explore the information that their genomes were hiding," says Benito-Gutiérrez. With the advancement of different sequencing techniques, these genomic secrets can finally come to light. They have the potential to unlock some of the mysteries surrounding human origins and evolution.

Searching the sand

With this in mind, it's easier to appreciate why Benito-Gutiérrez travelled thousands of miles and braved searing temperatures to search for the cephalochordates. "Each day we sailed for three hours in a traditional Maldivian boat >>

Benito-Gutiérrez searching for cephalochordates.

"There were distinct differences that made me realise this was something new. It was incredibly exciting"



SILVIA ROHR

Benito-Gutiérrez inspecting sand samples from the sea bed.

>> called a ‘dhoni’ to reach the quiet atolls,” she explains. These secluded lagoons, enclosed by coral banks and surrounded by miles of choppy ocean, require great skill to navigate. The local sailors, however, were happy to help. “They’re amazing people,” says Benito-Gutiérrez. “They were completely fascinated to hear that they were so close to these living fossils. I learned afterwards that they were having so much fun searching with us, that they ended up doing a kind of lottery each day to decide who would sail us out!”

Indeed, Benito-Gutiérrez went out on the boats many times, both during the day and at night. Upon arrival at their chosen locations, she

and the crew used handheld grabbing tools to reach into the water and carefully collect sand from the sea bed. They then sieved it in search of their live treasure. “In the beginning, we couldn’t find anything,” says Benito-Gutiérrez. “It was very frustrating.” In fact, they sailed to 22 different GPS points before discovering *Epigonichthys*. “When I first saw it, I thought that, yes, this looks like a cephalochordate,” she explains, “but there were distinct differences that made me realise this was something new. It was incredibly exciting.” Yet considering how difficult it was to find these creatures, their journey back to Heidelberg was relatively smooth. The Tara Oceans team scheduled a stop to collect the samples and bring them back to EMBL, alive and well.

Tree of life

It wasn’t until Benito-Gutiérrez had the creatures in the lab that she began to realise how much potential this project had. “I set up the lab at EMBL and looked after the animals myself,” she says. “We started sequencing the *Epigonichthys* genome there, but after a while the project just became too much for one person to manage.” Subsequently, in 2015,

“If we understand the origin of our genome, we can better understand how our current genome works”



SILVIA ROHR



SILVIA ROHR



ELIA BENITO-GUTIÉRREZ

Benito-Gutiérrez's career itself evolved as she made the move from postdoctoral fellow to group leader at the University of Cambridge. "It's been an intense time these last couple of years! But this exciting research is one of the reasons I wanted to set up my own lab."

Now Benito-Gutiérrez's lab houses a giant living ecosystem, which she and a dedicated team care for. "We can study and compare the genomes of three types of cephalochordates, which is something not many other groups can claim," she explains. "We're quite sure that they share a close common ancestor. What we're currently unsure about is which cephalochordate is most 'basal' – the one that has remained most similar to the common ancestor." With the research carried out by Benito-Gutiérrez and her team, it might be time for a complete reconstruction of the way cephalochordates are classified.

Unravelling the genome

This research might even provide insights into our own DNA, as it is likely that our genome has evolved from that of ancestral cephalochordates. "By sequencing the human

genome, we're only seeing the end product," explains Benito-Gutiérrez. "If we understand the origin of our genome, we can better understand how our current genome works." For example, duplicate versions of our genes have arisen during evolution and taken up different locations within our genome. Similar duplications and gene rearrangements can occur in cancer, indicating that parallel mechanisms could be at play.

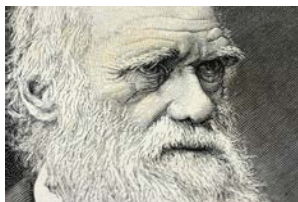
The current plan for Benito-Gutiérrez is to continue researching this unusual creature and its hugely informative genome. As well as discovering more about the origins of the human genome and how it can go wrong, she hopes that confusions about the classification of cephalochordates, which have arisen over the past century, can also be unpicked. "There's so much still to find out," says Benito-Gutiérrez. "I don't think the mystery surrounding *Epigonichthys* is solved just yet."

Benito-Gutiérrez on the dhoni boat (above left) and in the lab at EMBL (above, top). Cephalochordate specimens (above).



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On the orchids of Darwin



ISTOCK

How Darwin's work revealed the intimate relationship between orchids and insects

BY ANDREA CERASE

Darwin's studies of orchids firmly established the idea that many types of flowers are pollinated by insects.

Many people know about Charles Darwin's voyage on the *Beagle* and his detailed examination of the finches on the Galapagos Islands, which gave him crucial insights for developing his theory of evolution. It is less well known that Darwin spent a considerable amount of time studying orchids, too. *Fertilisation of Orchids* was, in fact, the next book he published after his famous *On the Origin of Species*.

Darwin's studies of orchids began in England, not far from his home in Kent. He was amazed and fascinated by the huge variety of colours and shapes in this family of plants. From painstaking observations, meticulous dissections of local and exotic species, and field experiments, Darwin concluded that orchids, unlike self-pollinating or wind-pollinated plants, relied on insects for pollination. He suggested that cross-fertilisation – in which one plant is fertilised by pollen from another – would increase a plant's genetic fitness and provide the diversity needed for natural selection, leading to evolution and the development of new species. He hypothesised that the mesmerising combinations of forms and colours in orchids

all served the same purpose: to attract insects to achieve this cross-fertilisation. As he wrote in the closing chapter of *Fertilisation of Orchids*: “In my examination of Orchids, hardly any fact has so much struck me as the endless diversity of structure,—the prodigality of resources,—for gaining the very same end, namely, the fertilisation of one flower by the pollen of another.”

Tools of attraction

Orchids, unlike most flowers, have asymmetrical petals. In particular, the modified lower petal, or labellum – Latin for ‘lip’ – in orchids has evolved in a myriad of shapes and colours. Darwin hypothesised that such variety was needed to attract different kinds of pollinating insects. He also suggested that some orchids have evolved special one-to-one relationships with their respective pollinators, rewarding them with nectar in exchange for their help with pollination.

We now know that only some orchids produce nectar, but all of them have found a way to attract insects to spread their pollen. Some orchid flowers attract insects with special colours or patterns, while others use trickery, releasing sexual pheromones to ‘seduce’



ISTOCK

The bee orchid, *Ophrys apifera*, has a lower petal that resembles the body of a female bee, and its flower produces a scent to match.

insects. Some species have a labellum that is modified to such an extent that it looks like the back of a female insect, encouraging males to try to mate with it.

Mysterious moth

When *Fertilisation of Orchids* was first published in 1862, it was relatively well received by botanists and academics, but strongly criticised by proponents of natural theology such as George Campbell, Eighth Duke of Argyll, who ridiculed Darwin's theories in his 1867 book, *The Reign of Law*. In particular, Argyll severely criticised one of Darwin's predictions about the existence of an extreme one-to-one orchid-insect partnership. After carefully examining an orchid from Madagascar, Darwin had concluded that it was most likely fertilised by a moth with

a proboscis nearly 30 cm long – something Argyll described as “nothing but the vaguest and most unsatisfactory conjecture”.

Such a moth was eventually found in Madagascar, but unfortunately not until 21 years after Darwin's death. While Darwin himself did not see this or many of his other theories confirmed, his book on orchids represents an important part of his legacy. It laid the foundations for another branch of evolutionary studies, co-evolution, which examines the way two or more species can have mutual effects on one another's evolution. This remains a fascinating area of study for scientists around the world.



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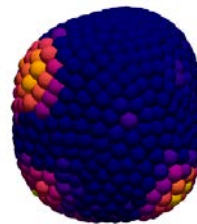
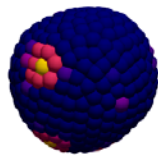
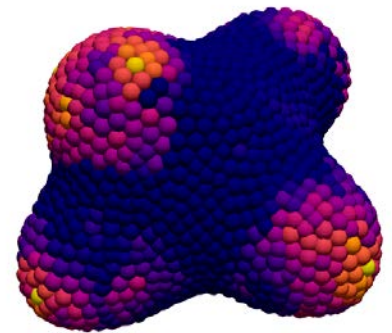


Examination of a Madagascan orchid persuaded Darwin that its nectar must be drunk by a moth with a proboscis 30 cm long. Such a moth, *Xanthopan morgani*, was found living in Madagascar in 1903.

ESCU/LAPIO (CC BY-SA 3.0)

The rise of GPU computing in science

Discover how EMBL scientists are using GPU computing to push biology forward



BY BERTA CARREÑO AND LAURA HOWES

A couple of years ago, researchers at EMBL Barcelona did something quite radical. They threw away their carefully crafted software and started again from scratch. The reason, indirectly, was computer gaming.

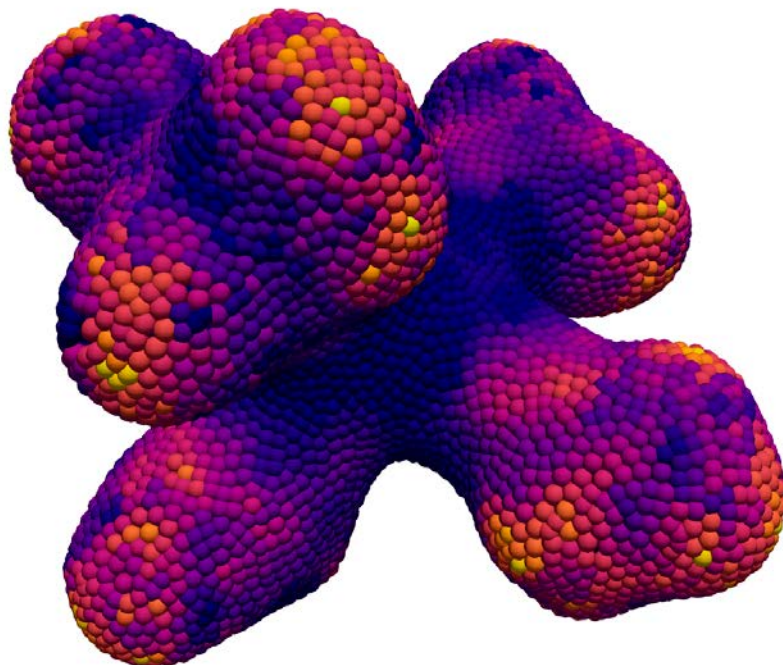
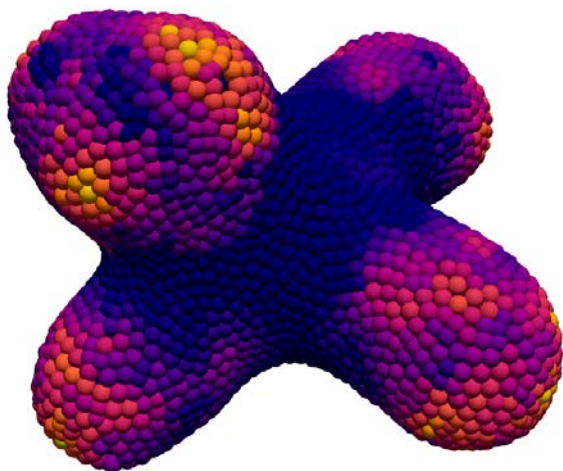
“I had discussed it with my team on and off over the past five years,” says James Sharpe, head of EMBL Barcelona. “But there is a lot of effort involved in rewriting or writing a new simulation from scratch.”

It took the right person to come along before the Sharpe group could take the plunge. When Philipp Germann joined the group as a postdoc, he played with the existing software for a couple of months before deciding to completely rewrite a multicellular dynamics simulation, this time designed to

run on graphics processing units (GPUs). The resulting new software can run simulations with hundreds of thousands of cells in a matter of seconds on a single graphics card. The previous software would take minutes, hours or even days to run. In the words of Sharpe, “It ended up fantastically well.”

Graphical computation

Open up any personal computer and you will find it packed with chips and components. They include the central processing unit (CPU), which does a lot of the heavy lifting and complicated processing, and the GPU which quickly creates the images you see on your screen – such as the ad in your Facebook feed or the computer game you play at the end of the day to relax. GPUs contain hundreds or thousands of very specialised processors called cores. These cores are small and simple,



and although they're not as flexible as CPU cores, they can do one particular thing very, very fast: work out what your screen should display.

In computer games, every little region of the screen is the result of an independent mathematical calculation that works out what that little bit of the screen should look like. You can do those calculations one by one, or you can divide the screen into lots of little bits, and do all the calculations in parallel. That's exactly what the GPU is good at: doing lots and lots of identical calculations simultaneously, with each one independent of the others. As computer game graphics became more complex – from *Spacewar* to *Call of Duty* – so did GPUs. The problem of how to render the image from a computer game is split into hundreds of thousands of little parallel calculations all done in a fraction of a second.

“For us,” explains Sharpe, “it turns out that the kind of calculation required for computer games is similar to the kind of calculation we want to do. We try to simulate tissues and organs, how they grow, how their development works. And similarly, if we have a tissue with a hundred thousand cells, we can divide that cell population into little groups of cells, and

each GPU can do the calculation for that little group.” Just as the image on a screen can be divided up, so too can the model tissue. “Every cell has the same genome and every cell has to make the same calculations, that's why it fits so well into GPUs.”

GPU software requires programming languages with extra features that deal with the parallelisation of the problem, such as CUDA, but “programming and writing simulation software is similarly complicated whether you are running it on CPUs or GPUs,” adds Sharpe. It can be challenging to find a programmer who can understand the biological questions and then write the code, he notes. Sharpe says that there's one major benefit of this shift to GPU computing, though: cost. A full-size CPU cluster costs a lot of money and resources to run, he explains. “We have switched over to being able to run everything in our own lab on our own computers' graphics cards. We will probably start using GPU clusters [racks of dedicated GPUs] in the future. But, still, it's saving a huge amount of time and money in this work.”

Clusters of computation

In EMBL Heidelberg, the server room hums and flashes with computing power. Inside, >>

The Sharpe group at EMBL Barcelona is using GPUs to build agent-based models for morphogenesis, like this branching sequence.



Animation shows how a deep-learning model learns to recognise sequence patterns that underlie cancer mutations.

>> the High Performance Computing (HPC) cluster serves scientists across EMBL's sites and packages up their different problems to be solved by a mix of CPUs and GPUs.

“When I came here, there were no GPUs installed,” explains Jurij Pečar, the engineer who looks after the HPC cluster. “So I went around interviewing scientists to learn what they’d need. One of the main requests was that they had software coming up able to use GPUs, so we invested in our first machine. As people started using GPUs, they realised how it speeds up their work and then, of course, we had to buy more.”

That is hardly a surprise when you realise that the microscopy image analysis that used to take about 30 days to run on 250 CPUs now takes just 30 hours on a single GPU. And some of the largest users of the GPUs at EMBL Heidelberg are the microscopy facilities. “Only six years ago, we were still shooting film and we had to develop the film in the darkroom manually,” recalls Wim Hagen of the Electron Microscopy facility. “Develop, fix, wash, dry, then scan the negatives and hope you didn’t make a mistake. Good people could do three boxes a day. Nowadays, it’s fully automated. We get 2000 to 3000 images a day and that pushes things.”

What is GPU computing?

The central processing unit (CPU) is the ‘brain’ of a computer. Its function is to carry out calculations that enable the computer to run software. The CPU is split into processing units, called cores, that receive instructions, perform calculations, and take actions on these instructions. The key power of the CPU is its flexibility to multitask with many different types of jobs. It can perform tasks quickly but, like our conscious brain, can focus on only a few ‘threads’ at a time.

The graphics processing unit (GPU) is a specialised component that was designed to handle graphics. Whereas CPUs have from four to eight cores, GPUs consist of thousands of small cores that can handle many threads simultaneously.

GPU computing is the application of GPUs to accelerate the CPU’s computing by transferring compute-intensive portions of the code to the GPU, where many threads can be handled in parallel. For suitable tasks, this

makes calculations much faster to perform and offers cost and power efficiencies.

GPU computing was initially developed for graphics-intensive computational problems such as 3D rendering and gaming, but is now being applied to a variety of domains including complex modelling, simulation and cutting-edge research – such as the Sharpe group’s computer simulations of mammalian limb development.



Balancing the users

Just as microscopy technology has improved, so everything has scaled, requiring more and more computing power. But while it might seem intuitive that processing microscopy images, or modelling cells as if they were areas on a screen, could be suited to GPU computing, other teams have other uses for the HPC cluster – for example, using deep learning to process huge sets of data from cancer patients.

“Deep learning is a big buzzword and I’m also into it,” explains Esa Pitkänen, a postdoctoral fellow in the Korbek group at EMBL Heidelberg. “Graphics processing runs on linear algebra and while linear algebra is very straightforward mathematics, you need to do a lot of it. GPUs parallelise this computation on a massive scale, and that happens to be exactly the same mathematics that you use to train deep neural networks. It’s very simple: it’s a perfect fit.”

Pitkänen’s data is based on several thousand tumour samples, and the data he has is multi-layered. “We have sequencing data, methylation data, transcriptomics data, and then auxiliary and clinical data to top it off.” Pitkänen is trying to get his program to recognise patterns by letting the software learn how to recreate the data. In a sense, being able to recreate the data from a simple code indicates that the code – a few numbers, for example – captures the essential patterns in the data. It could be considered a more refined version of the suggested purchases we all get when we go internet shopping: people who have this mutation here, and this attribute here, also share similar tumour characteristics. To do that on CPUs, says Pitkänen, would take tens to hundreds of times as long. Instead, he trained his model in two days. “The whole process of training the deep neural networks is inherently massively parallel. And the way GPUs work is really well suited to train those models,” Pitkänen explains.

Back at the HPC cluster, Pečar’s main challenge, he says, is working with the users so that the big jobs from the microscopes can run at the same time as other programmes like Pitkänen’s. According to Pečar, GPU users need to work out how to move data from the



EMBL

main memory to the GPU memory efficiently. This means that developing the algorithms for the GPU is getting more technical, which in turn is now driving innovation. “I think programming for games is more exciting in the short term,” he admits. “But I’d rather work on something that has at least the hope of making the world a better place some time in the future.”

EMBL Heidelberg server room.

Growing graphically

Although computer games first drove the development of GPUs, chip manufacturers are now optimising their GPUs for other applications, like Sharpe’s modelling or Pitkänen’s deep-learning applications. It seems GPU-based computing is growing in the life sciences, and in the EMBL IT department.

“There are parts of biology that are not so suited to GPU computing, like some tasks in sequence-based informatics where you’re first uploading a huge dataset, and then slowly chugging your way through it,” concludes Sharpe. “But I believe in a certain version of systems biology – the approach in which you build computer simulations of a biological process as a way of understanding the dynamical mechanisms of the system. Using computers in this way – simulating dynamics [rather than analysing data] – is still quite rare, but I expect and hope it will grow and become a part of all biological projects.”



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Mapping molecules on people, fields and ATMs

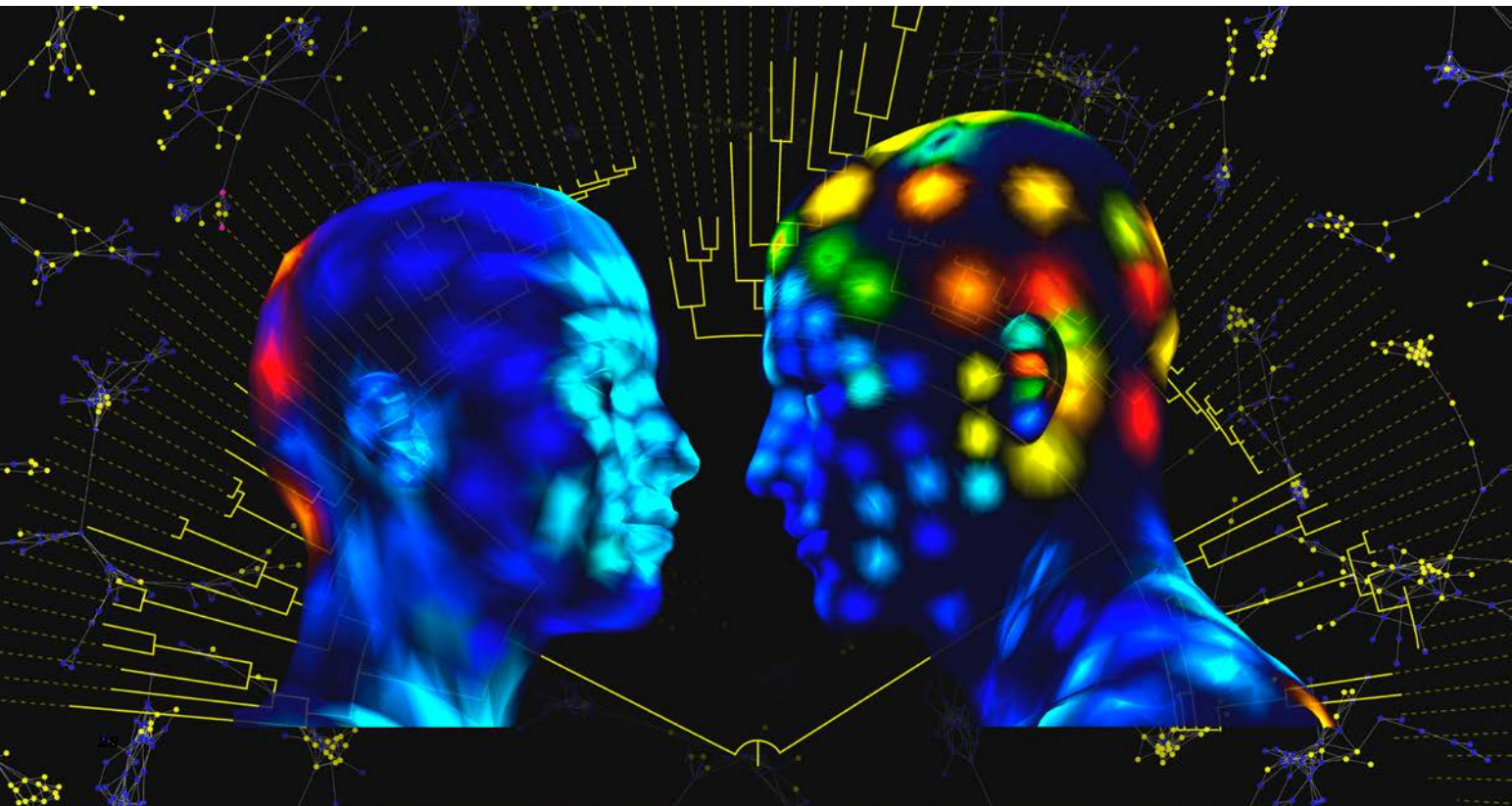
A free, standardised method is raising interest in forensics, agriculture and microbiome studies

BY IRIS KRUIJEN

These glowing avatars are maps of molecules. Every day, every inch of skin on your body comes into contact with thousands of molecules – from skin cream, sweat, and even the microbes that call your skin home. Now, scientists can create interactive 3D maps that show where each molecule lingers on our bodies, thanks to a new method developed by Theodore Alexandrov's team at EMBL and collaborators at the University of California, San Diego (UCSD), and

made available in *Nature Protocols*. When the scientists first used this approach to map the molecules on the skin of two volunteers, they found traces of sun cream and other hygiene products – three days after they'd last been used.

Having been approached by colleagues from fields as diverse as forensics, cosmetics, ecology and agriculture, the team has now converted the method into a step-by-step technique and intuitive software.



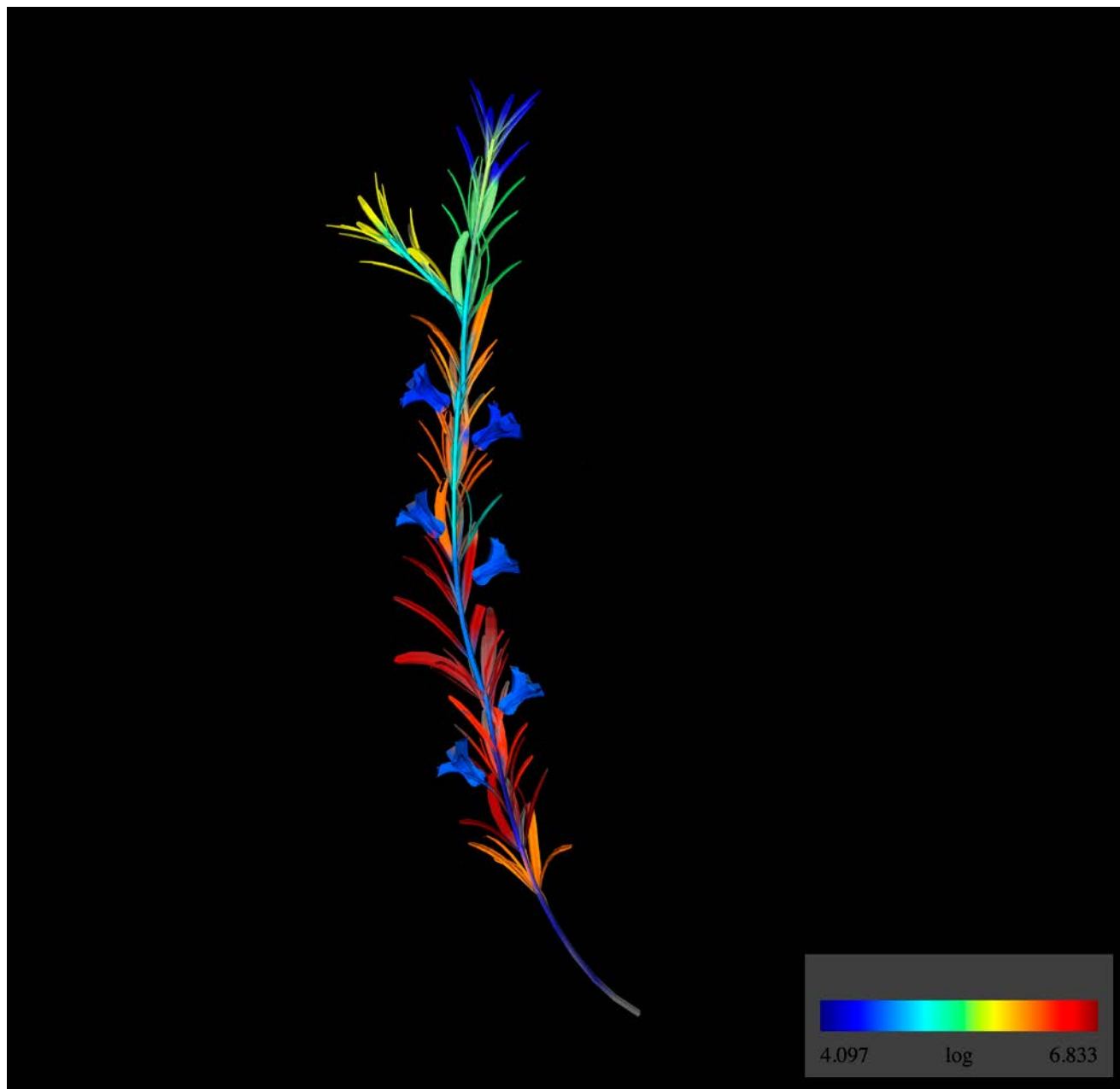


ALEXANDROV / TEAM/EMBL

Can you guess which four digits a volunteer typed into this ATM?

If you guessed 1, 0, 7 and 8, you are right. The colour of the dots represents the amount of a molecule that was transferred from the person's finger to the keypad. "There are much easier ways of stealing someone's PIN," says Alexandrov. "We first had to clean the ATM with methanol, then swab it and perform mass

spectrometry, so it's unlikely someone would steal your PIN this way. But it does show nicely that we transfer molecules from our skin to the objects we interact with – and that we can measure and map that. This has raised lots of interest from forensics experts." In previous work, for instance, the scientists were able to make predictions about people's lifestyles based on the molecules found on their mobile phones. >>



ALEXANDROV TEAM/EMBL AND DORRENSTEIN TEAM/UCSD

>> The researchers used a sprig of rosemary collected on campus at UCSD to demonstrate that the method can be applied to agriculture. Researchers could use the method to see if pesticides or other products sprayed on a field spread to neighbouring fields, and if they could identify patterns in that spread. In this image, you can see that the old leaves at the bottom of the rosemary sprig have much higher levels of the flavonoid cirsimaritin than the newer leaves at the top. Using maps like

this, scientists can study how plants transport molecules from old leaves to young ones, and how they react to stress.

Protsyuk, I, Melnik, AV, Nothias, LF *et al.* *Nature Protocols*, 21 December 2017. DOI: 10.1038/nprot.2017.122

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ADOBE STOCK AND EMBL

Welcome to EMBL

Seven scientists start their labs at EMBL

BY BERTA CARREÑO, SARAH B. PUSCHMANN, EMMA STEER AND OANA STROE

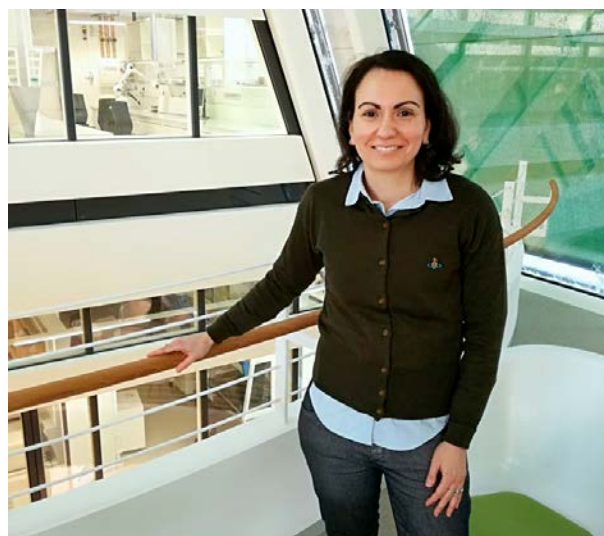
The past few months have seen EMBL welcome seven new group or facility heads. From sequences to sea anemones, their work spans a broad range of topics. We find out what keeps them inspired, motivated and dedicated.

Maria Garcia Alai

Sample Preparation and Characterisation Facility,
EMBL Hamburg

My team and I provide high-throughput crystallisation experiments to help users determine the biophysical characterisation of proteins. I've learnt that I really like the interaction with users, helping them design and set up experiments.

Some of the users that come to the facility in Hamburg are not structural biologists, so we provide them with support and supervision. At the end of the day, you feel like you have done something useful and have helped out – that's something I enjoy. Some scientists prefer to have a big question and answer that. I like to see what the puzzle looks like in the end too, but the truth is, I have so much fun with the methodology and applying the technology. When designing these experiments, it's important to focus on the problem that you want to solve. Keep it clear and simple, and it will be beautiful.



JOANNA PIEPRZYK/EMBL



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MARIETTA SCHUPP/EMBL

Aissam Ikmi

EMBL Heidelberg

We study the starlet sea anemone, *Nematostella vectensis*, to understand how developing multicellular organisms respond to changes in their environment while simultaneously executing their genetic program.

Growing up in Morocco, I was addicted to science documentaries and fascinated by the way life was visualised at varying scales: from the level of individual cells up to whole organisms. When I went to France to do my undergraduate studies, I knew I loved biology. But it was not until I opened a developmental biology textbook and saw a picture of a normal-looking fly alongside a mutant fly that had four wings instead of two that I knew I would become a biologist. I was hooked, eager to understand how animals are built and how genes and other factors control their development and the genetic programs that give rise to the huge range of shapes that we see in nature.



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Sara Cuylen-Häring

EMBL Heidelberg

My lab is interested in the biophysical properties of chromosomes and other cellular assemblies that lack membranes – for example, the nucleolus.

I'm looking for people who are excited about the research we're doing in my group. Specific technical skills or in-depth knowledge of chromosome biology are less important for me – these are attributes that can be learned. But you cannot teach traits like passion for research, curiosity or motivation. I like to work with young scientists who are eager to learn and are not afraid of exploring completely novel techniques or research directions. Cutting-edge science is never predictable, and I like unconventional experiments. My philosophy is that any innovative idea is worth a try – even if it seems crazy or unlikely to work.



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MARIETTA SCHUPP/EMBL

Arnaud Krebs

EMBL Heidelberg

My group will be developing new approaches to further understand transcription factors, which bind to DNA ‘switches’ to regulate which genes get activated or repressed.

I see this transition to group leader as an exciting opportunity to explore new scientific ideas and share the thrill of science. It’s going to be very enriching to develop projects with people in my lab: to plant a seed and see how it evolves. I think scientific ideas often need to mature in order to reach their full potential, and discussing with lab colleagues is, in my opinion, the fastest way to get there. It’s something that has had a very strong impact on my career. I would advise young scientists not to run to the next obvious thing; go for something that really excites you. It’s certainly riskier – but totally worth it!

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MARILETTA SCHUPP/EMBL




MARILETTA SCHUPP/EMBL

Eva Kowalinski

EMBL Grenoble

My team researches RNA editing, a processing step that diversifies RNA sequences by deleting, adding or modifying parts of the RNA.

EMBL Grenoble is a lively European science hub. The site’s relatively small size encourages you to get out of your bubble, seek collaborations, invite external speakers and look beyond the horizon. There’s definitely a special spirit about EMBL. The environment is open and collaborative, and everyone gives stimulating input to everyone else’s research. I want the people in my lab to be passionate about science and to love what they do. I learnt from my own experience that there are times when everything goes well and the experiments are successful. But there are also periods when progress feels slow-moving, and that’s when you need to be resilient – it takes willpower and passion. There are ups and downs, so you have to love what you do and really want it.

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Matthieu Boulard

EMBL Rome

My lab focuses on epigenetics and tries to understand why the genetic code can be interpreted differently by different cells or individuals.

I hope to collaborate with other research groups here, including labs interested in completely disparate questions. I try to be creative and encourage imaginative initiatives in my lab. As is the case for musicians and painters, if you want to move your field in a new direction, you have to propose something new to your peers. Whether or not they accept it is a different question! The reality is that it's difficult to achieve something without experiencing failure. But in the real world, we have to succeed at some point. One of the important and difficult challenges I face is to judge the amount of failure that is acceptable before I switch my focus or change my approach.



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PASCAL BEUDIN/EMBL



DANIEL SAGE/EPFL

Virginie Uhlmann

EMBL-EBI

My group will help biologists get precise information from their images by developing analysis tools that blend mathematical models and computer vision algorithms.

It's important to keep sight of the bigger picture. We're all working on very specific research projects but should remember how they fit into the wider world of science. The way I see it, all scientists are working together to help understand our world. I'm hoping to find enthusiastic PhD students and postdoctoral fellows that are as excited as I am about working at the intersection of biology, computer science and mathematics. This type of interdisciplinary work isn't an easy career path, so ambition and a strong motivation are key!



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The scientific origins of Edith Heard

EMBL's next Director General reflects on the questions that drive her research

BY SARAH B. PUSCHMANN
AND EDWARD DADSWELL

When Edith Heard was a child of about seven or eight, her father sat her down at the kitchen table in their London home to teach her some basic arithmetic. It wasn't long before she began asking questions: why do we count? How did the numbers we use get chosen? Where did they come from? No one around her knew the answers. "My poor father, just trying to teach me how to add – I think he was at his wits' end," she says, smiling. She recalls lying awake at night, questions about the origins of numbers churning in her mind long after her parents had gone to sleep.

The questions that Heard has been unable to let go of in her adult life concern epigenetics: the study of changes in gene expression that are stable, heritable, and reversible – without affecting the DNA sequence. A self-declared late convert to biology – Heard had her first introduction to the field while studying Natural Sciences at Cambridge, having



Edith Heard will take up her role as EMBL Director General in January 2019.

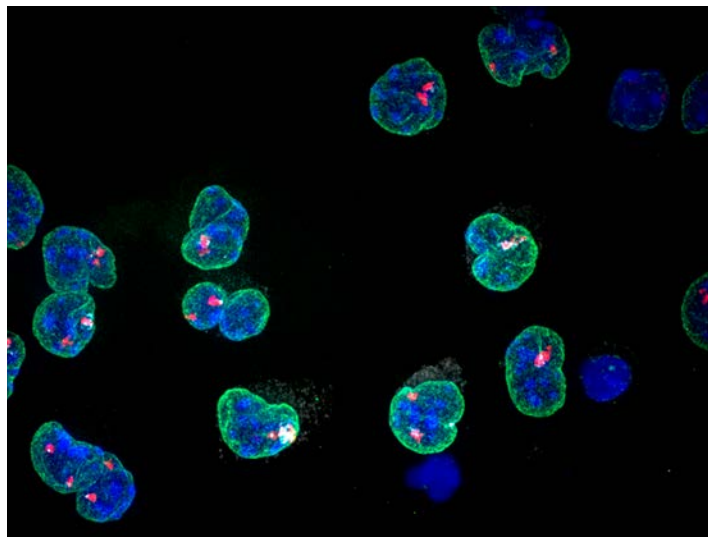
originally intended to pursue a career in physics – she left university with a passion for genetics.

Fathoming silence

The key epigenetic mystery that continues to fascinate Heard is the silencing of a chromosome that occurs in most female mammals. Usually, if a fertilised egg inherits an X chromosome from its mother and a Y chromosome from its father, it develops into a male. If it inherits an X chromosome from each parent, it develops into a female. But there's a catch: having two functioning X chromosomes in the same cell can be fatal.

Cells in females solve this problem in a seemingly simple way: they switch one X chromosome off – a process called X inactivation. But, as Heard has discovered through her investigations, nothing about the way X inactivation works is simple. During her postdoctoral work at the Pasteur Institute, Heard helped to narrow down the region of the X chromosome that acts as the master control centre for X inactivation. This X-inactivation centre produces a key player in the inactivation process: a large RNA molecule called Xist (X-inactive specific transcript), which can associate with the X chromosome it is transcribed from, triggering chromosome-wide silencing.

Heard's work led to the unexpected discovery that production of Xist requires regulatory DNA sequences – sequences that control the gene's expression – which must be located at large distances away from it on the X chromosome. Later, the hunt for these missing sequences by the Heard Lab, in collaboration with Job Dekker at the University of Massachusetts, led to the discovery of large, self-interacting regions of the genome that they called topologically associating domains (TADs).¹ This discovery opened up an exciting new area of research, as TADs are regions of DNA that often bring regulatory elements located on different parts of a chromosome into close contact. Disrupting TADs can lead to



MIKAEL ATTIA AND EDITH HEARD/INSTITUT CURIE

disease because changing the 3D organisation of the chromosome can disrupt normal gene regulation.

Space for curiosity

Currently Director of the Genetics and Developmental Biology Department at the Curie Institute in Paris, Heard will take up the role of EMBL Director General in January 2019. She will go on tackling questions about epigenetics and gene regulation, since she plans to continue running her lab while working as EMBL Director General. Looking ahead to that role, she emphasises the importance of supporting both applied research – having clear applications in fields such as medicine and industry – and research that is more fundamental. “It's important to make space for curiosity-driven research, even when a tangible purpose isn't immediately apparent,” says Heard. “We have learned again and again that basic research, when nurtured over time, leads to profound applications.”

In this image of developing cells, fluorescent molecules reveal DNA (blue), part of the X chromosomes (red), and the Xist RNA (white). The green colour shows a region of the cells' nuclei called the nuclear lamina.

¹ Nora, EP *et al.* *Nature*, 11 April 2012. DOI: 10.1038/nature11049



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MARIETTA SCHUPP/EMBL

Exploring genetic variation

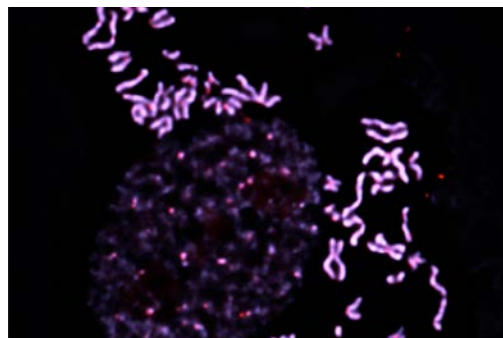
EMBL group leader Jan Korbelt reflects on his scientific origins and current research

BY EDWARD DADSWELL

Growing up, the books Jan Korbelt liked to read were standard childhood fodder: astronomy, dinosaurs and archaeology caught his imagination. It was only in his final years at school, when he started learning about genetics, that an interest in biology really took hold.

As an undergraduate, Korbelt spent a few months as an intern at the Roslin Institute in Edinburgh, UK, at the same time that Dolly the sheep was in residence. “The experimental research I pursued there inspired me,” he says. “Later, this led me to study computational biology with a molecular biology angle. It was a fascinating and helpful time.” Both computational and more traditional lab research now happen side by side in Korbelt’s lab at EMBL. “I was lucky because I got the

As a cell prepares to divide, its chromosomes (shown here in pink) condense, becoming more tightly coiled and easier to observe under the microscope. The faint structure in the centre is a cell nucleus in which the chromosomes are in their usual decondensed state.



KORBELT GROUP/EMBL

right people in my lab,” says Korbelt. “It now feels very natural for us to combine the two approaches.”

Shattering chromosomes

Korbelt’s research focuses on structural variation in the human genome: that is, how our DNA rearranges – a process that has implications for ageing and diseases including cancer. One area of study is a process the Korbelt group co-discovered, known as chromothripsis, or ‘chromosome shattering’. In this process, a chromosome undergoes multiple structural rearrangements in a single catastrophic event. Korbelt and his lab have been working to uncover the molecular processes by which chromothripsis occurs.

Korbelt is now one of the leaders of the Pan-Cancer Analysis of Whole Genomes project, which aims to identify common patterns of cancer mutations. At the European Association for Cancer Research (EACR) Congress in July, he will receive the Pezcoller Foundation-EACR Cancer Researcher Award (p. 44). “It’s a huge honour for me, because it recognises the work of my group that started here at EMBL,” says Korbelt. “It’s a very strong motivation for us to continue pursuing this vital area of research.”

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[BIT.LY/embl-91-37](https://bit.ly/embl-91-37)

PhD goals: why not start a company?

Daniel Elías Martín Herranz is in the third year of his PhD in Janet Thornton's group at EMBL-EBI, but unlike other PhD students, he is also starting a company

BY OANA STROE

Tell us about your start-up.

It all started with a conversation I had with co-founder Thomas Stubbs, who was doing his PhD in Wolf Reik's group at the Babraham Institute. We had been working on the epigenetics of ageing and wanted to explore how we can use epigenetic data to predict certain things people care about – effects of diet, exercise, stress, air pollution and so on. One day, someone from RebelBio, the world's first life sciences accelerator, contacted me on LinkedIn. RebelBio offers seed funding, lab space, mentorship and other helpful support for starting your own business. We joined forces with the other co-founders, fellow scientist Toby Call, and Charles Ball – an expert in marketing and sales – and that's how our company, Chronomics, was born.

What kind of service will you offer?

We want to use epigenetic data to monitor the well-being and health of individuals over time and help to improve them. We send people a saliva collection kit, sequence the sample, process the information and give them access to their results through our secure online platform.

How has your work at EMBL-EBI supported you in making this leap?

In my PhD, I am trying to understand the

biological mechanisms behind the epigenetic clock, a predictor of biological ageing. I've been exposed to an amazing community of researchers here, both on the computational side at EMBL-EBI and on the wet lab side at the Babraham. I'm incredibly thankful to my supervisor, Janet Thornton, for her support.

Would you recommend this experience to others?

Absolutely! If you have ideas you want to explore as an entrepreneur, you should definitely try it. You can do great science and be an entrepreneur at the same time. Entrepreneurship gives you more freedom in how you push things forward and teaches you things that are also useful in academia.

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EMBL

Humans of EMBL: Past lives

Discover the journeys that brought people to EMBL

BY EMMA STEER

 FULL VERSION ONLINE:
[BIT.LY/embl-91-39](https://bit.ly/embl-91-39)

Iran in particular was a fascinating country

This was something my parents wanted to do with me as a kid, in the 1970s. The idea was to drive to India, following the Silk Road. That was the tail end of people driving through Iran, Afghanistan and India. Then there was the Iranian Revolution. With American passports, we couldn't go any more.

This summer, with my wife and kids, we took the classic Silk Route and went through eleven countries. The first day we entered a new country, everybody was anxious, but fundamentally, I wasn't that afraid. I was curious. Iran in particular was a fascinating country. I met an older man in the street there. His eyes were very... in Italian you'd say 'sveglio'; he was very awake. He was the only person I met who gave me some insights into the inner workings of Iran. He had seen how things had changed with the current regime.

Cornelius Gross

Deputy Head of Unit and Senior Scientist,
EMBL Rome



CORNELIUS GROSS

MARIETTA SCHUPP/EMBL



I also play the flute and bass guitar, but piano was always my favourite instrument

I'm a classically trained pianist. I enjoy most musical genres, but my favourites are the Romantic composers like Liszt, Mendelssohn, Chopin and Tchaikovsky. I also play the flute and bass guitar, but piano was always my favourite instrument. I started teaching piano when I was 17, mainly one-on-one, but when I came to Germany I also taught at the music school in Heidelberg. I'm still in contact with one of my first students here. She started learning to play piano when she was 55. She taught me that it's never too late to start something, and our lessons were always full of laughter. Now she has become an honorary grandma to my two children. She was the first person at the hospital when my son was born and she came and visited us all when my daughter was born too, so she's really known them from the beginning!

Nicki Vegiopoulos
Marketing Manager, EMBL Heidelberg

I've reinvented myself over the past ten years

I tell people I've had four or five careers so far! Over the past ten years, I've reinvented myself a number of times. As an employment counsellor, one of the biggest things was helping students to find summer jobs, so helping with CVs, cover letters, application forms, interviews, etc. I think the most rewarding thing about that was helping students find their first job and knowing that you've really helped someone with a skill that they're going to use throughout their life. In fact, about five years ago, someone re-connected with me on Facebook after they got their first job. It was a very gratifying moment to know that you can have that kind of impact on someone's life.

Andrew Hercules
User Experience Designer, EMBL-EBI

RODICA PETRUSEN/SCH/EMBL



There was an amazing feeling of solidarity and unity

When I lived in the Netherlands, I loved sports and organising sporting events. Then, when I moved to France, several French friends mentioned the Dutch Foundation Alpe d'HuZes. It's this incredible event that raises money to fight cancer. Each June, up to 5000 people cycle, run or just walk up the Alpe d'Huez in France, up to six times in one day. That explains the name Alpe d'HuZes: 'zes' means six in Dutch.

As a volunteer, my main job was to liaise with local administrations and translate, but we also had a lot of help from the local people. All sorts of people go up the mountain, including people who have cancer and those who have lost family or friends to the disease. I thought they were never going to make it, but with the help of the others, they did. There was an amazing feeling of solidarity and unity.

Elise Bralet

Liaison Officer, EMBL Grenoble



If you find something you're passionate about, life changes completely

I never loved training to be a chef, but I simply didn't question it. I didn't love school, but everybody told me you have to go to school, right? It's not optional. No one ever said you have to be passionate about what you're doing all day long. Now, I've come to enjoy cooking and I still cook a lot, but it's different if you cook for yourself or for friends, compared to cooking in a restaurant. In a restaurant, you're just cleaning and peeling potatoes. Then slowly you learn to cook. It's a bit of an assembly line where you just pump it out.

It would have been the path of least resistance for me to just continue and not be happy. The job makes you unhappy, but it's just background noise. If you can overcome that and find something you're passionate about, life changes completely.

Jonas Hartmann

PhD Student, EMBL Heidelberg

I've always built, sold and played didgeridoos

I played didgeridoo for the first time at a birthday party when I was 18, and that very same week I was like, "I have to have one!" Since then I've always built, sold and played didgeridoos.

The trick is the circular breathing, where you're pushing air out of your mouth and breathing in at the same time so you have a continuous tone. The longest I've been able to do it in one go was for an hour and a half. I was playing with a pianist at a party in South Africa and we were just playing and playing and playing. After a certain amount of time, you don't know what you're playing or even if you're playing. It's only when you stop that you realise your lips are full of blisters.

Justin Graham-Parker
Kindergarten Assistant, EMBL Heidelberg



MARIETTA SCHUPPEMBL

It was absolutely fantastic, such a magical moment

I was the head of a musical theatre academy in South Africa for twelve years. We were called Stagedoor Academy, like the artists' entrance to the theatre. Our students had decided musical theatre was the career they wanted to pursue.

It was a very vibrant, creative and innovative environment to work in, full of unexpected moments. One colleague of mine, who was the opera singer and opera trainer, loved Japan and her experiences there. She was telling us about her trip to Japan when she suddenly burst into song, singing this Japanese folk song which she had learnt there. As it wasn't an opera song, I got to hear her normal singing voice, the one we seldom hear from opera singers. It was absolutely fantastic, such a magical moment and so different from anything we had heard before. It was beautiful.

Roné Pawson
Training and Development Officer, EMBL Heidelberg



MARIETTA SCHUPPEMBL



Awards & honours

Theodore Alexandrov (centre) receiving the Chica und Heinz Schaller Research Award.

EMBL Director General-elect **Edith Heard** was awarded the 2017 Inserm Grand Prix for her work in epigenetics. The annual prize honours a scientist working in the French research community whose work has led to remarkable progress in understanding in the field of human health. Heard received the award at a ceremony on 30 November 2017 in Paris, France.

In December 2017, the Australian National University awarded **Matthias Hentze** an honorary PhD “for his exceptional contributions to science” at a graduation ceremony in Canberra, Australia. Hentze received the traditional hood and certificate before entertaining the attendees with a speech on his career to date.

In February 2018, **Theodore Alexandrov** was awarded the Chica and Heinz Schaller Research Award for achievements in the biomedical sciences at a ceremony at Heidelberg University for his pioneering work on the metabolome (see p. 28 of this issue to read more about his work). Alexandrov also received an ERC consolidator grant for the METACELL project this year, while **Julia Mahamid**, who joined the Structural and Computational Biology Unit in 2017, received an ERC starting grant that began in 2018.

Lars Velten, a postdoctoral researcher in Lars Steinmetz’s group, won the Otto-Schmeil-Preis for young researchers from the Heidelberg Academy of Sciences and Humanities in Germany. Velten was awarded the prize together with Simon Haas, a collaborator at the German Cancer Research Centre.

EMBL-EBI Director **Ewan Birney** has been appointed as a new member of the UKRI-BBSRC Council and will take up his appointment in April 2019. The Council is responsible for advising and making decisions on scientific, research and innovation matters, as delegated to it by the UK Research and Innovation Board.

In April 2018, EMBL Director General **Iain Mattaj** signed the National Academy of Sciences’ registry of membership during the academy’s annual meeting in Washington, DC, USA. This follows Mattaj’s election as a foreign associate last year.

In June, **Jan Korbel** will receive the Pezcoller Foundation-European Association for Cancer Research (EACR) Cancer Researcher Award for excellence and achievements in cancer research at the EACR25 Congress in Amsterdam, Netherlands.

Alumni

EMBL



The EMBL launch pad

This edition highlights the paths that our alumni have taken from their EMBL origins. Alumni from the IT team reflect on how their experiences at EMBL have helped them take on leading roles within other multinational organisations (p. 46). We showcase this year's talented winners of the John Kendrew and Lennart Philipson Awards (p. 48), and report that Nobel Prize winner and EMBL alumnus Jacques Dubochet has donated his Nobel medal to EMBL (p. 12). We also share how an EMBL alumna's discovery in the Maldives led to her becoming a group leader at the University of Cambridge (p. 18). Finally, as Mark Green begins his retirement, he reflects on his 20 years of service, as well as his biggest achievements, as Head of Administration at EMBL-EBI (p. 50).

To learn more about how EMBL shapes people's paths, check this issue's back cover for the next EMBL alumni event near you.

Mehrnoosh Rayner

Head of Alumni Relations

Harnessing alumni expertise

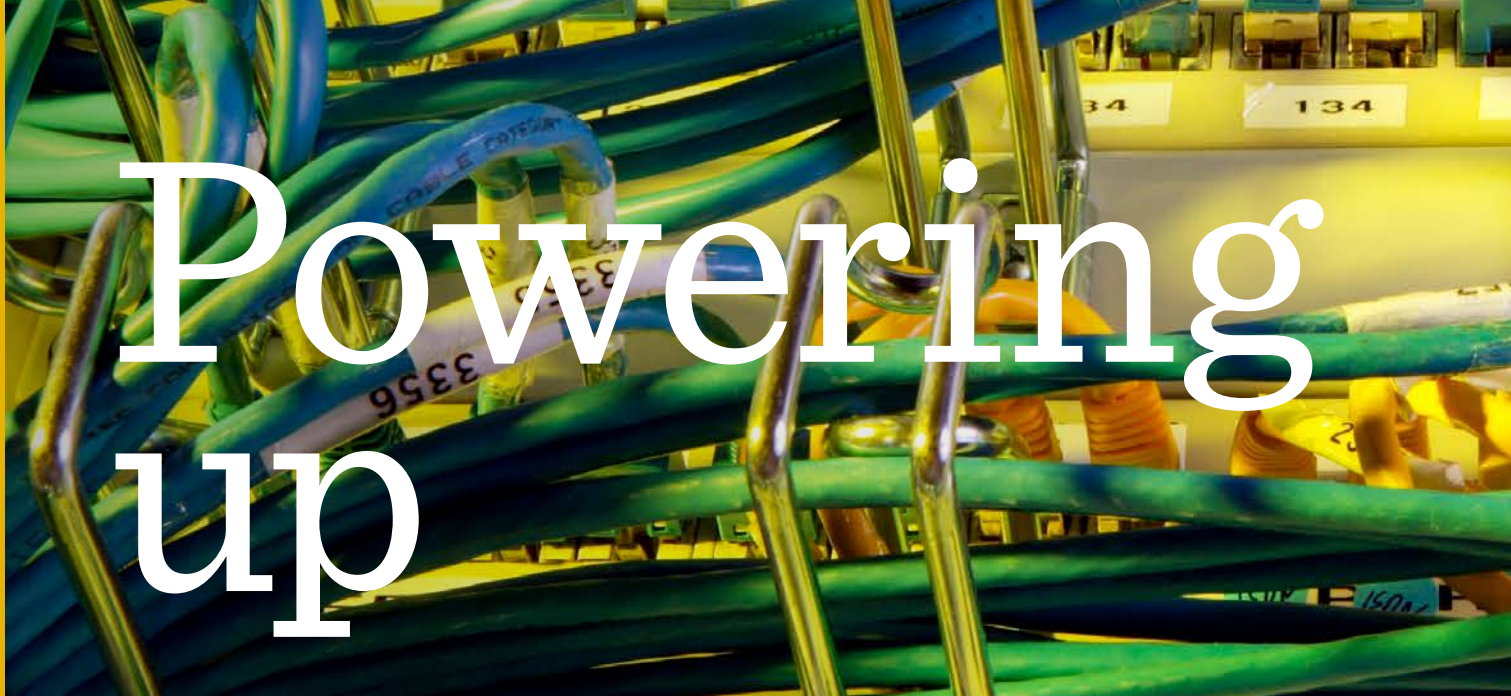
EMBL has always relied on the support of volunteers, such as Scientific Advisory Committee members, council delegates, advisors, ambassadors, event organisers, speakers, fundraisers and Alumni Association board members. To formalise, communicate and strategically expand the support that alumni voluntarily bring to EMBL, the Alumni Volunteer Programme was set up, and Peter Papagiannis joined EMBL as Alumni Volunteer Officer in September 2017.

"Our volunteers are the cornerstone of our strong alumni community. They bring ideas and expertise, expand networks and raise awareness around the world, making our programmes both meaningful and relevant," Papagiannis says. "When the IT team asked us to help communicate the opportunities they can provide to IT professionals, it didn't take long to find the perfect ambassadors." (p. 46)

The Alumni Volunteer Programme is also working with the

Human Resources and Finance departments. The alumni network is helping with recruitment and collecting best practices for specific grant administration projects.

The Alumni Relations team are identifying alumni with relevant experience for specific projects and campaigns and may be contacting you soon. If you'd like to learn more, please contact Peter Papagiannis (alumni@embl.org).



Powering up

Alumni share how joining EMBL's IT team was a career upgrade

BY PETER PAPAGIANNIS

Francisco Lozano Alemany
Head of IT Services

International Agency for Research on Cancer,
World Health Organization



KATIE LOZANO

What did you enjoy most about your role in IT at EMBL?

It was great that I could be involved in many different projects and in a broad range of technologies. Managing the IT for an organisation like EMBL poses huge technical challenges, so it required our team to collaborate efficiently and to strongly support each other, which allowed me to learn a lot about topics for which I was not directly responsible. I also enjoyed being in contact with the scientists and asking them about their research, as I spent a lot of time in their labs.

Francisco Lozano Alemany was at EMBL from 1996 to 2005.

What made working in IT at EMBL unique?

The exposure to cutting-edge IT technologies: top research relies on top IT solutions. EMBL has a very good IT infrastructure as well as regular training. The international environment also offers the chance for personal growth – that was one of the first things I missed when I left.

How did working at EMBL help your career path?

EMBL helped me in three different ways: I learnt how a world-leading research centre functions from an IT perspective, I gained an incredible network of contacts, and I enriched my CV for my next career step.



Mervi Lampinen Director IT, One IT Country Lead Germany MSD Sharp & Dohme GmbH

What did you enjoy most about your role in IT at EMBL?

IT is an integral part of daily life at EMBL. Every newcomer – short-term or long-term – has to visit IT for a user account, email address, computer and general IT support. Meeting this diverse group of people from all over the world – and having to use all my linguistic and technical skills to provide the best service we could – made it very interesting.

Also, due to the international make-up of EMBL, you have the opportunity to learn a lot from other countries and institutes by interacting with staff – this helps you work in any country in the world afterwards. I mostly enjoyed the quick pace, the opportunity to learn and develop, and the very informal yet structured way of working.

What made working in IT at EMBL unique?

EMBL supports many different

IT platforms. This is a challenge, but a great learning opportunity. Also, the technical environment is very varied, which gave me the best opportunity to learn the latest technologies, before they were even commercialised. Developments surrounding the cloud, big data and other tools in this area are always first adopted and used at institutes like EMBL.

How did working at EMBL help your career path?

EMBL offers learning and development opportunities that help you work both in industry and in academia. They helped me learn my strengths and my passion for IT management. They also helped me understand what kind of business transformation is required to go from offline brick and mortar to online. Working in an international environment like EMBL made me choose large multinational and international companies after leaving.



Mervi Lampinen was at EMBL from 1994 to 1998.

What did you learn at EMBL?

One should embrace EMBL's short-term contracts as an investment in one's career. It is an opportunity to help you get to the next stage in your career. Many thanks, EMBL, for the wildest time of my life, in both my professional and private life. It was the greatest learning experience ever!



LEARN MORE ABOUT EMBL'S IT SERVICES TEAM:
[EMBL.DE/itservices](https://embl.de/itservices)

Alumni award

EMBL recognises the outstanding work of alumni with the John Kendrew and Lennart Philipson Awards

BY BERTA CARREÑO

HARVARD MEDICAL SCHOOL



Nils Gehlenborg, who received the John Kendrew Award, was a PhD student at EMBL-EBI from 2006 to 2010.

Big data to find new questions

For centuries, data visualisation has helped humanity identify patterns and gain new insights. When London suffered a cholera outbreak in 1854, the English physician John Snow used a map to trace the source of the infection to the water pump in Broad Street, Soho. Now – in the era of big data – visualisation is more important than ever.

EMBL alumnus Nils Gehlenborg is advancing the visualisation of complex genomic and

clinical data sets with highly innovative contributions. “I use computer science to build tools and visual interfaces that enable researchers to efficiently interact with biomedical data,” he explains.

As a PhD student in the Brazma group at EMBL-EBI, Gehlenborg worked on making large collections of gene expression data visually accessible so that biologists could discover patterns more easily. He is now Assistant Professor of Biomedical Informatics at Harvard Medical School, where he develops tools to visualise various types of data from large-scale cancer genomics studies such as the Cancer Genome Atlas. Gehlenborg also tackles visualisation problems across scales as co-investigator of the 4D Nucleome Data Coordination and Integration Center, funded by the US National Institutes of Health. With his team, he has created tools that allow scientists to see patterns at the chromosome level, and then to zoom down to find patterns at the level of DNA bases – the individual letters of the genetic sequence.

Gehlenborg’s lab is also exploring clinical applications of data visualisation using information from electronic health records. “My long-term vision is that all the data generated by clinical analysis, sensors and smartphones will be integrated,” he explains. “Rightly visualised, this will help doctors diagnose and treat patients and will also help individuals understand how their health might be influenced by their behaviour.”

winners

“I wanted to find the virus’s Achilles heel and hit it with antiviral agents”

A medical revolution

Raffaele De Francesco’s work on the hepatitis C virus (HCV) has led to a medical revolution. Previously, certain chronic viral infections were kept under control using drugs, but it was never possible to cure them completely by removing the virus from the body. De

Francesco’s work allowed hepatitis C to become the first case in the history of medicine in which a chronic viral infection was cured with direct antiviral agents.

Although the genome of HCV had been isolated and sequenced, finding a cure for hepatitis C still presented a challenge. Liver cells are difficult to grow in cell culture, and the virus didn’t function as well in cultured cells as it does in the human body. It took more than a decade to find the right conditions to grow the virus in the laboratory. It was then necessary to develop biochemical tools and assays that would help researchers find ways of interfering with HCV enzymes – preventing the virus from functioning.

In his lab at the Institute for Research in Molecular Biology (IRBM) in Pomezia, Italy, De Francesco identified, purified and developed in vitro assays for two key viral proteins, NS3/4A protease and NS5B polymerase. His discoveries allowed the scientific community to start screening for agents to inhibit the two viral enzymes, eventually leading to a cure for hepatitis C.

De Francesco explained that the huge medical need pushed him to work with all the molecular biology and biochemistry tools available, to understand what each part of the HCV genome does. “I wanted to find the virus’s Achilles heel and hit it with antiviral agents.”



FULL VERSION ONLINE:
[BIT.LY/embl-91-40](https://bit.ly/embl-91-40)

Raffaele De Francesco, who received the Lennart Philipson Award, was a postdoctoral researcher at EMBL Heidelberg from 1988 to 1990.



Twenty years of building teams and sites

Mark Green, EMBL-EBI's Head of Administration, reflects on his time at the Institute

BY EMMA STEER

After beginning his career at EMBL Heidelberg as the Internal Auditor, Mark Green went on to become the first Head of Administration at EMBL-EBI. As he retires to enjoy the next phase of his life, we catch a glimpse of the personal highlights that defined Mark's 20-year journey at EMBL.

How did you first start at EMBL?

I started at EMBL Heidelberg as an internal auditor in 1997. It was a time of great turmoil for me because I had just begun a relationship with my wife-to-be a few days before being offered the job. For almost three years, we had a long-distance relationship: she was in the UK, I was in Germany. That kind of thing was much more difficult back in the day before free roaming and all this social media malarkey. When the opportunity of a shared role between Heidelberg and Hinxton came up, I pretty much leapt at it. The travelling between sites continued until about 2003, when I finally became full time at EMBL-EBI.

What have been your greatest achievements?

We built the EMBL-EBI East Wing and the South Building, and we completely refurbished the Main Building. We transformed the place and it took huge amounts of effort by a large number of people. But I think the biggest achievement has been building teams, not buildings. EMBL-EBI is a

“I think the biggest achievement has been building teams, not buildings”

home for bright ideas and the people who can make them happen. Lots of campuses have shiny new buildings, but few have people who are as driven and collaborative as the ones you find at EMBL-EBI.

What are you going to miss?

The people and the intellectual energy in this place. If you look at the arc established by Michael Ashburner and Graham Cameron, carried on very much by Janet Thornton and followed through by Rolf Apweiler and Ewan Birney, the idea is to create an environment where people work together. EMBL-EBI is a community. It's full of a cracking intensity of interest and curiosity that brings out the best in people.

Based on an interview conducted with Mark Green by Lindsey Crosswell, Head of External Relations, EMBL-EBI.



FULL VERSION ONLINE:
BIT.LY/embl-91-41

ROBERT SLOWLEY/EMBL

Guess who!

All these babies have grown up to become EMBL group leaders. Test how well you know the EMBL community by guessing who they are!



1. Christian Löw
2. Gerard Klewegt
3. Nick Goldman
4. Matthias Hentze
5. Maria Leptin
6. Marco Marcia
7. Alba Diz-Munoz
8. Iain Mattaj
9. Evangelia Petsalaki
10. Wolfgang Huber
11. Vladimír Benes

Events

September
3-7

EMBL-EBI
EMBL Course:
Structural Bioinformatics



Upcoming meetings
Alumni

1 July
Summer party, EMBL-EBI

19 July
**Inauguration of the EMBL
Archive, EMBL Heidelberg**

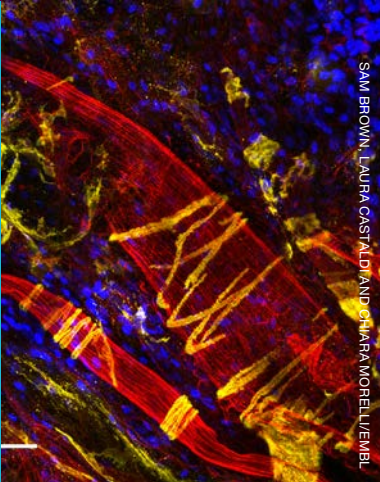
21 July
**Summer party,
EMBL Heidelberg**

5 October
**EMBL in Finland,
Biomedicum, Helsinki**

8 October
**EMBL in Spain, CBMSO,
Madrid**

September
10-18

EMBL Hamburg
EMBO Practical Course:
Membrane Protein
Expression, Purification and
Characterisation



September
29

EMBL Heidelberg
EMBO Workshop:
Chemical Biology 2018

October
2-5

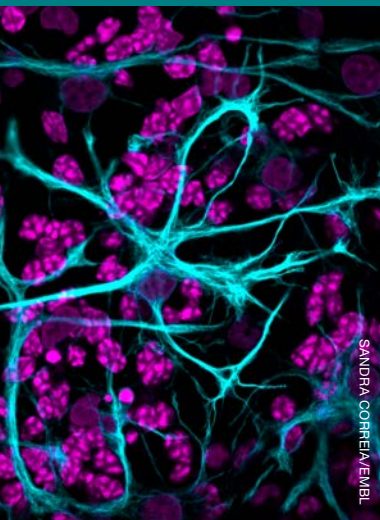
EMBL-EBI
EMBL Course:
Introduction to Next
Generation Sequencing

October
15

EMBL Barcelona
Inauguration Symposium

November
15-16

EMBL Heidelberg
EMBL Science and
Society Conference:
Infectious diseases: Past,
Present, and Future



November
22-24

EMBL Heidelberg
20th EMBL PhD Symposium:
Game Changers: Taking Life
Sciences to the Next Level



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