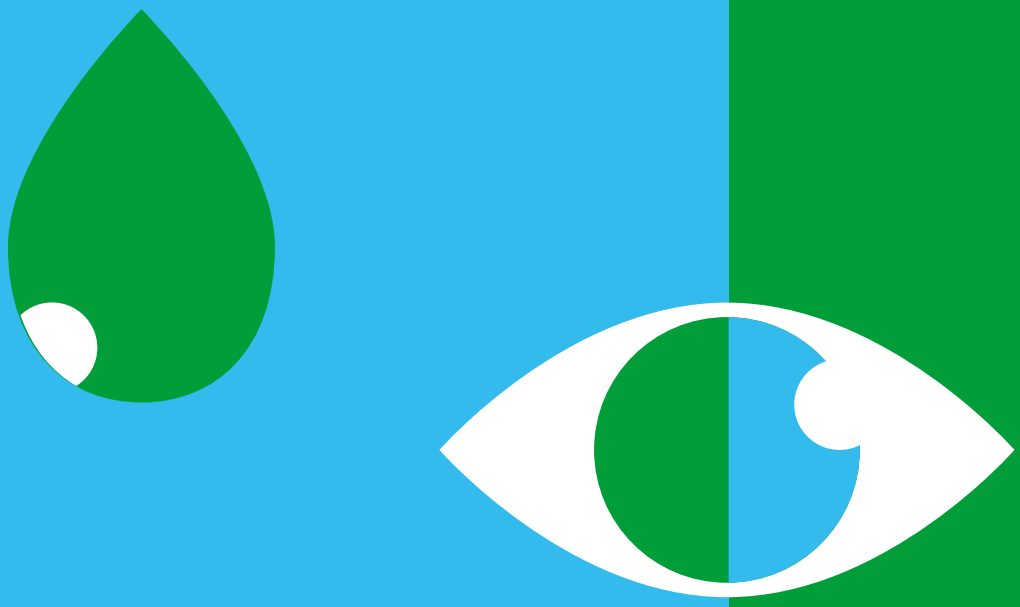
The European Molecular Biology Laboratory Magazine

Issue 92 Winter 2018/19

EMBL etc

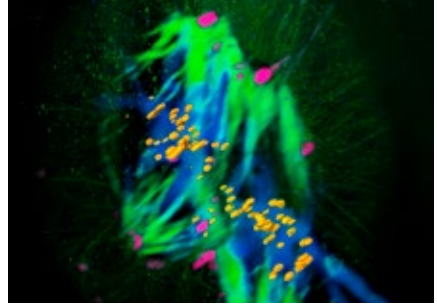


Translation

Contents

Nucleus

Feature stories



Synapse

News stories

Cultures

EMBL community stories

Alumni

MASSIMO DEL PRETE/EMBL

Editorial

At EMBL, acts of translation happen every day. Members of our international community often ask each other if a particular word or phrase has an equivalent in another language. This is translation in its most obvious form – but it's only the beginning.

No matter where they're from, biologists, mathematicians, physicists, computer scientists, and engineers need a common language when they come together to solve biological problems. This is happening at EMBL's newly inaugurated site in Barcelona (p. 46), where insights from the mathematical field of graph theory were recently used to understand pattern formation in living organisms (p. 6).

Research is often described as 'translational' when fundamental insights result in practical applications. We share examples of this process from the EMBL community (p. 24) and talk to an alumnus who translates clinical data into 3D objects that help clinicians and patients grasp what's going on beneath the skin (p. 20).

In our feature on machine learning, we investigate how EMBL scientists are using artificial neural networks to translate vast quantities of data into meaningful insights (p. 14).

Translation also happens when we take part in outreach projects (p. 36), or when we translate complex scientific concepts into engaging visual forms – whether it's in the work of EMBL's Design team (p. 42), or in the artworks made as part of an initiative to encourage school pupils to explore science in creative ways (p. 40).

Whatever your interests, we hope you'll find something here that leaves you equally inspired.

Edward Dadswell
Editor

Word to remember

Spindle

Noun, pronunciation:
/ˈspɪndəl/

A cellular structure made of microtubules that pulls the chromosomes in different directions during mitosis.

During an embryo's first cell division, chromosomes are separated by two spindles, although it was long thought that this process used only one (p. 5).

Publisher
European Molecular Biology Laboratory

Managing editor
Edward Dadswell

Editors
Mehrnoosh Rayner
Emma Steer
Oana Stroe

Design
Designyard

Printed by
ColorDruck Solutions

Contact
news@embl.de

Cover illustration
Aleksandra Krolik

NEWS.EMBL.DE

Parental chromosomes kept apart during embryo's first division

EMBL scientists show that mammalian life begins differently than we thought

BY IRIS KRUIJEN

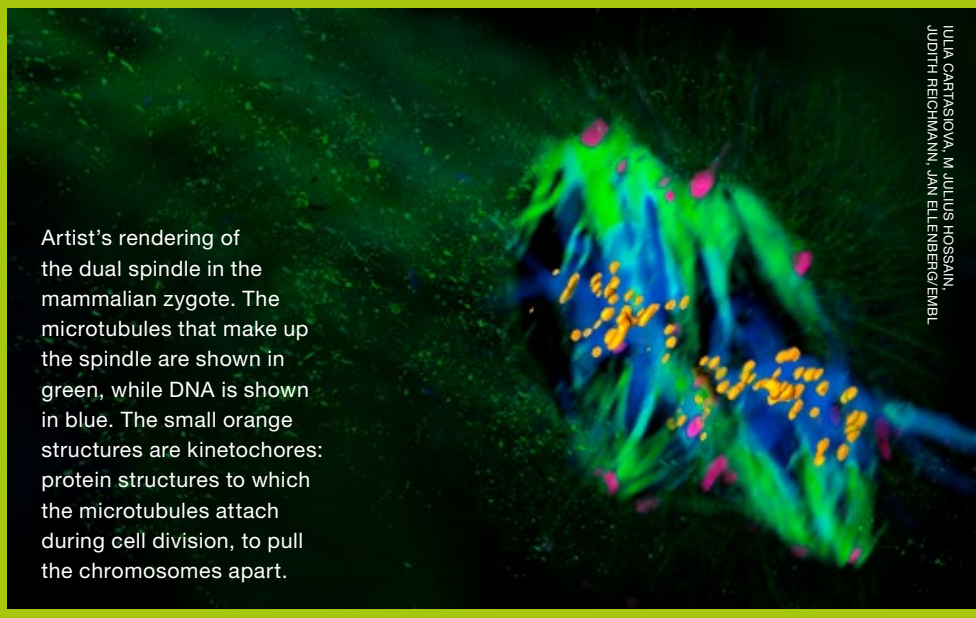
It was long thought that during an embryo's first cell division, its chromosomes are segregated into two cells by a single spindle – a structure made of microtubules that pulls the chromosomes in different directions. EMBL scientists have now shown that there are actually two spindles, one for each set of parental chromosomes. This means that the genetic information from each parent is kept apart throughout the first cell division.

This dual spindle formation might partly explain the high error rate in the early developmental stages of mammals, spanning the first few cell divisions. "The aim of this project was to find out why so many mistakes happen in those first divisions," says Jan Ellenberg, the EMBL group leader who led the project. "We already knew about dual spindle formation in simpler organisms like insects, but we never thought this would be the case in mammals like mice. This finding was a big surprise, showing that you should always be prepared for the unexpected."

The beginning of life

The new findings from this study might impact legislation. In some countries, the law states that human life begins – and is thus protected – when the maternal and paternal nuclei fuse after fertilisation. If the dual spindle process works the same in humans as it does in mice, this definition is not fully accurate, as the union in a single nucleus happens slightly later, after the first cell division.

This discovery would have been impossible without the light-sheet microscopy technology developed in the groups of Jan Ellenberg and Lars Hufnagel at EMBL, which is now available through the EMBL spin-off company *Luxendo*. This technology enables real-time and 3D imaging of the early stages of development, when embryos are very sensitive to light and would be damaged by conventional light microscopy methods. The high speed and spatial precision of light-sheet microscopy drastically reduce the amount of light that the embryo is exposed to, making possible a detailed analysis of these formerly hidden processes.



IULIA CARTASOVA, M JULIUS HOSSAIN, JUDITH REICHMANN, JAN ELLENBERG/EMBL

Artist's rendering of the dual spindle in the mammalian zygote. The microtubules that make up the spindle are shown in green, while DNA is shown in blue. The small orange structures are kinetochores: protein structures to which the microtubules attach during cell division, to pull the chromosomes apart.

Reichmann, J *et al*. *Science*, 12 July 2018. DOI: 10.1126/science.aar7462

FULL VERSION ONLINE:
BIT.LY/embl-92-01

Understanding soil through its microbiome

First global survey of soil genomics reveals a war between fungi and bacteria

BY IRIS KRUIJEN

Soil is full of life, which is essential for nutrient cycling and carbon storage. To better understand how it functions, an international research team led by EMBL and the University of Tartu, Estonia, conducted the first global study of bacteria and fungi in soil.

The team found that bacterial diversity in soil is lower if there are relatively more fungi. They also found a strong link between the number of antibiotic resistance genes in bacteria and the number of fungi, especially those with the potential for antibiotic production, such as *Penicillium*.

This information could be used to predict the spread of genes that lead to antibiotic resistance in different ecosystems – and to indicate the routes by which these genes may reach human pathogens. It could also be used to help predict and pinpoint locations with large numbers of antibiotic producers.

Bahram, M, Hildebrand, F *et al. Nature,* 1 August 2018. DOI: 10.1038/s41586-018-0386-6

FULL VERSION ONLINE:
BIT.LY/embl-92-02

Global warfare between bacteria and fungi in soil.

FALK HILDEBRAND, ALEKSANDRA KROLIK/EMBL, IN COLLABORATION WITH CAMPBELL MEDICAL ILLUSTRATION

New theory deepens understanding of Turing patterns

EMBL scientists extend Turing's theory to help understand how biological patterns are created

BY BERTA CARREÑO

Alan Turing sought to explain how patterns in nature arise with his 1952 theory of morphogenesis. The stripes of a zebra, the arrangement of our fingers and the radial whorls in the head of a sunflower, he proposed, are all determined by molecules spreading out through space and chemically interacting with each other. However, theoretical analyses seemed to show that Turing systems are intrinsically very fragile, making it unlikely that they are the real mechanism behind pattern formation in nature.

Xavier Diego, James Sharpe and colleagues from EMBL's new site in Barcelona have expanded Turing's original theory by using graph theory, a branch of mathematics that studies the properties of networks and makes it easier to work with complex, realistic systems. This work has led to the realisation that network topology is what determines many fundamental properties of a Turing system. In addition to providing a unifying view of many crucial properties of Turing systems that were previously not well understood, their new topological theory explicitly defines what is required to make a successful Turing system.

This expanded theory provides experimental research groups with a new approach to making biological cells develop in patterns in the lab. If such groups can use this approach successfully, the question of whether Turing's theory of morphogenesis applies to biological systems will finally be answered.

Diego, X *et al. Physical Review X*, 20 June 2018. DOI: 10.1103/PhysRevX.8.021071

FULL VERSION ONLINE:
BIT.LY/embl-92-03

Roots of leukaemia detectable years before diagnosis

Genetic changes in blood signal the risk of acute myeloid leukaemia years before the disease develops

BY OANA STROE

Scientists at the European Bioinformatics Institute (EMBL-EBI) and the Wellcome Sanger Institute, along with international collaborators, have discovered that it's possible to identify people at high risk of developing acute myeloid leukaemia (AML) years before they develop the disease.

The study found that blood tests looking for changes in DNA can reveal the roots of AML in healthy people. Further research could enable earlier detection and monitoring of people at risk of developing AML in the future, and increase the prospect of finding ways to reduce the likelihood of developing this cancer.

The scientists sequenced the DNA in stored blood from 124 AML patients and compared it with that from 676 people who remained free from AML or a related cancer. Remarkably, they discovered that many of the people who went on to develop AML had particular genetic changes that set them apart from those who did not. These changes could be used collectively to develop a predictive test for AML risk.

Abelson, S, Collord, G *et al. Nature*, 9 July 2018. DOI: 10.1038/s41586-018-0317-6

FULL VERSION ONLINE:
BIT.LY/embl-92-05

CRISPR: from clipping scissors to word processor

New platform transforms CRISPR gene editor into precision tool

BY IRIS KRUIJEN

Using the gene-editing tool CRISPR (see infographic, p. 31) to snip at DNA is often akin to using scissors to edit a newspaper article: you can cut out words, but it's difficult to remove individual letters or instantly know how the cuts affect the meaning of the text.

In work that will help to make the gene-editing process more precise, EMBL scientists – together with researchers at Stanford University, the Joint Initiative for Metrology in Biology, Texas A&M University and Brandeis University – have developed a new kind of CRISPR platform called MAGESTIC. By enabling an efficient 'search and replace' function for genetic material, the platform makes it possible to operate CRISPR less like a blunt cutting tool and more like a word processor.

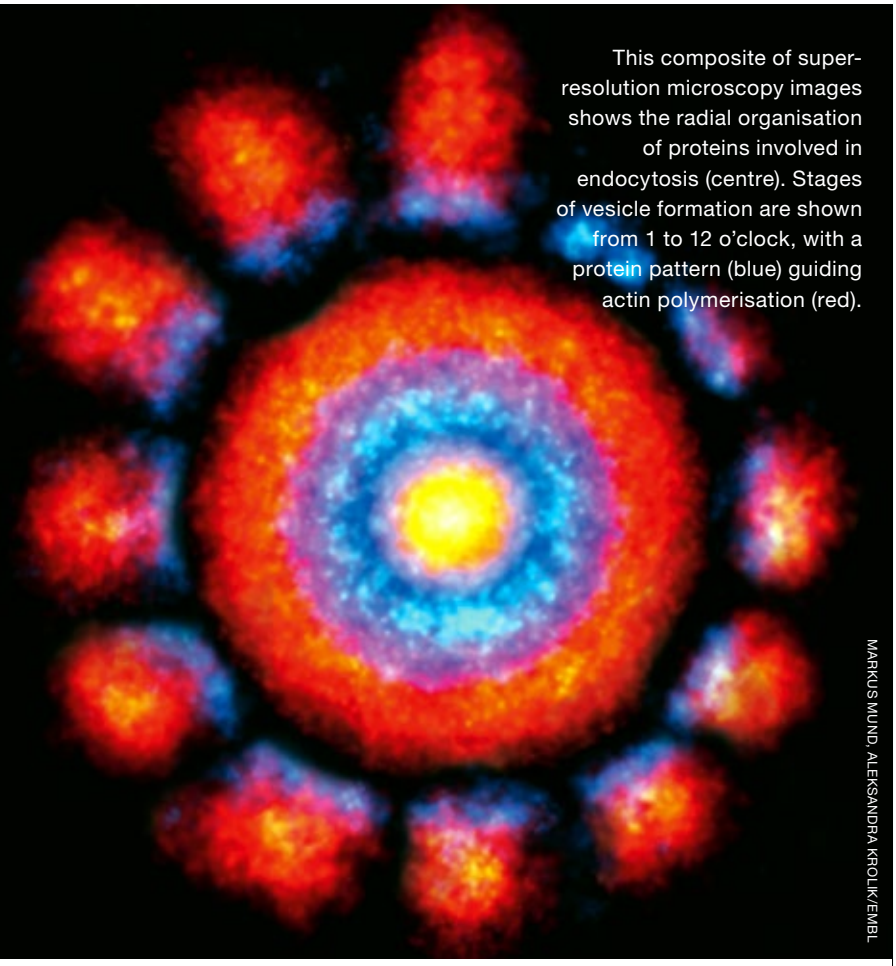
"With MAGESTIC, we can make precise and targeted changes to genotypes," says Sibylle Vonesch, one of the first authors of the paper and a postdoctoral fellow in EMBL's Steinmetz group. "For example, we can introduce small, isolated alterations into yeast genomes and investigate their effects. Eventually, we hope to be able to predict what happens in a cell based on its genetic variant."

Roy, K *et al. Nature Biotechnology*, 7 May 2018. DOI: 10.1038/nbt.4137

FULL VERSION ONLINE:
BIT.LY/embl-92-04

The MAGESTIC platform adds a new level of precision to CRISPR gene editing.

KELLY IRVINE/NIST



This composite of super-resolution microscopy images shows the radial organisation of proteins involved in endocytosis (centre). Stages of vesicle formation are shown from 1 to 12 o'clock, with a protein pattern (blue) guiding actin polymerisation (red).

MARKUS MUND, ALEKSANDRA KROLIK/EMBL

The proteins behind hungry cells

EMBL scientists have used super-resolution microscopy to see the protein machinery used by cells to 'eat' nutrients and other molecules. The research clarifies how 23 of the most important proteins involved in this task organise and assemble themselves. The researchers imaged more than 100,000 sites on yeast cell membranes, where molecules are taken into the cell in a process known as endocytosis. They discovered that different proteins gather at the membrane in a precise set of ring shapes. These shapes act as a template to recruit a protein called actin to pull the membrane inwards and surround external molecules, ready to bring them inside the cell. This information could also help researchers to understand what happens on the cell surface at the nanoscale level when cells move or divide.

Mund, M *et al. Cell*, 26 July 2018. DOI: 10.1016/j.cell.2018.06.032

FULL VERSION ONLINE:
BIT.LY/embl-92-06

New way to isolate DNA- and RNA-protein complexes

By interacting with nucleic acids (DNA and RNA), proteins create complexes that regulate cell behaviour. To understand how these complexes regulate cell function, they must be isolated from nucleic acids. Claudio Asencio, a researcher in the Hentze group, has developed a new method, called Complex Capture (2C), that simplifies the isolation of complexes by using silica-based extraction columns commonly used in labs to purify nucleic acids.

Asencio, C *et al. Life Science Alliance*, 18 June 2018. DOI: 10.26508/lsa.201800088

READ ONLINE:
BIT.LY/embl-92-07

Cohesin: a glue for DNA

Before cell division begins, a newly replicated chromosome consists of two identical threadlike strands that are joined together. Responsible for holding these sister chromatids together is a ring-shaped protein complex called cohesin. Now, researchers in Daniel Panne's group at EMBL Grenoble have published the crystal structure of a cohesin subcomplex, showing that a stretch of amino acids on the surface of cohesin effectively 'glues' it to the DNA. Further studies on cohesin and its engagement with chromatids will lead to deeper mechanistic insights into how this machinery contributes to cell division.

Li, Y *et al. eLife*, 15 August 2018. DOI: 10.7554/eLife.38356

FULL VERSION ONLINE:
BIT.LY/embl-92-08

New approach for testing cancer drug response

BY OANA STROE

Patients with seemingly similar cancers can respond differently to the same treatment. Over the past few decades, scientists have been studying the molecular signatures of tumours to predict drug sensitivity. This approach focuses primarily on understanding the molecular alterations of the tumour itself. One aspect that few studies include is the germline – or inherited – component of a patient's genome. This approach means that the relevance of germline variants for drug susceptibility is still largely unknown.

Researchers at the European Bioinformatics Institute (EMBL-EBI) have used a large collection of cancer cell lines to systematically test the relevance of germline variants for explaining differences in drug response. The analysis, which included both inherited genetic variants and variants that are caused by the tumour, was applied to 993 cell lines and 265 drugs. Surprisingly, the results show that the germline contribution to differences in drug susceptibility can be just as important as the contribution of somatic (non-germline) mutations.

Menden, MP *et al. Nature Communications*, 23 August 2018. DOI: 10.1038/s41467-018-05811-3

FULL VERSION ONLINE:
BIT.LY/embl-92-09

Personalised medicine: one data type is not enough

BY OANA STROE

EMBL researchers have designed a computational method to jointly analyse multiple types of molecular data from patients in order to identify molecular signatures that distinguish individuals. The method is called Multi-Omics Factor Analysis (MOFA), and it could be useful for understanding cancer development and suggesting new directions for personalised treatment.

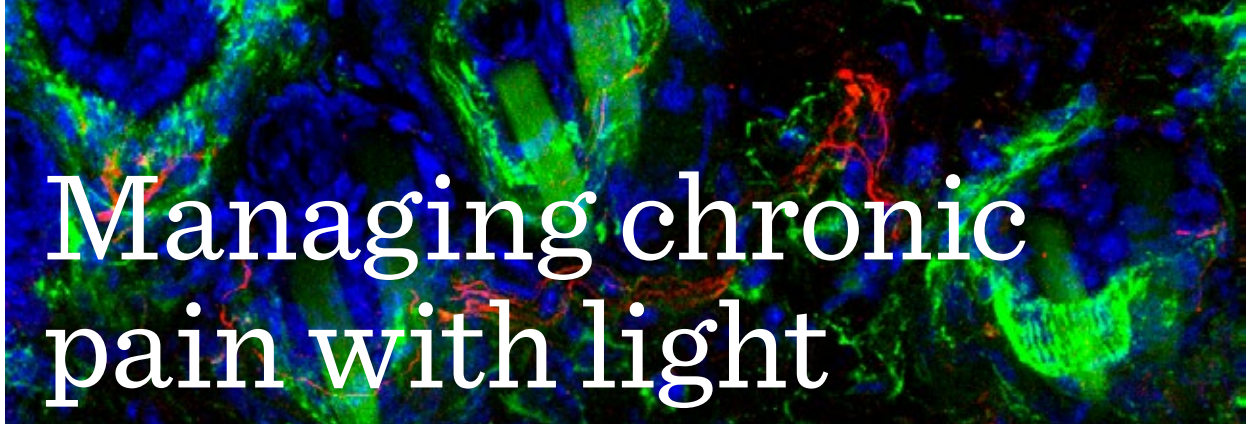
The researchers tested their new method on multi-omics data collected from 200 leukaemia patients. MOFA identified a series of factors that highlight the molecular variability between patients. This information could help researchers understand how cancer develops at an individual level. It could also help steer personalised treatment decisions.

In a second application, the researchers used MOFA to analyse multi-omics data at single-cell resolution. They're currently working on further improving the method for even larger data sets and additional experimental designs.

Argelaguet, R, Velten, B *et al. Molecular Systems Biology*, 20 June 2018. DOI: 10.15252/msb.20178124

MOFA is available as open-source software:
https://github.com/bioFAM/MOFA

FULL VERSION ONLINE:
BIT.LY/embl-92-10



Managing chronic pain with light

PAUL HEPPENSTALL/EMBL

EMBL scientists use light to manage neuropathic pain in mice

BY IRIS KRUIJEN

Imagine that the movement of a single hair on your arm causes severe pain. For patients with neuropathic pain – a chronic illness affecting 7-8% of people in Europe – this can be a daily reality.

Scientists from EMBL Rome have now identified a special population of nerve cells in the skin that are responsible for sensitivity to gentle touch. These are also the cells that cause severe pain in patients with neuropathic pain. The research team developed a light-sensitive chemical that selectively binds to this type of nerve cell. After they injected the affected skin area with the chemical and illuminated it with near-infrared light, the targeted nerve cells retracted from the skin's surface, leading to pain relief.

Clipping off the nerve endings with light ensures that neuropathic patients no longer feel the gentle touch that can cause severe pain. The effect of the therapy lasts for a few weeks, after which the nerve endings grow back. "It's like eating a strong curry, which burns the nerve endings in your mouth and desensitises them for some time," says Paul Heppenstall, the EMBL group leader who led the research team. "The nice thing about our technique is that we can specifically target the small subgroup of neurons causing neuropathic pain."

In this image of a mouse's skin, the nerve cells of interest are shown in green, surrounding the hair follicles.

Dhandapani, R *et al. Nature Communications*, 24 April 2018. DOI: 10.1038/s41467-018-04049-3

FULL VERSION ONLINE: BIT.LY/embl-92-11

Constructing new tissue shapes with light

EMBL researchers guide the shape of cells and tissues with optogenetics

BY IRIS KRUIJEN

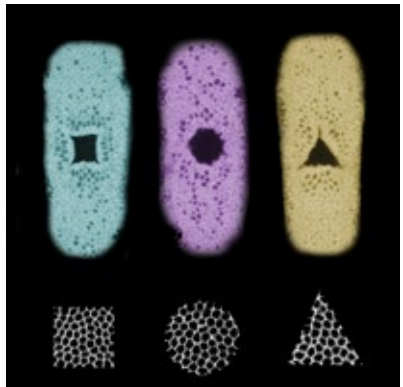
The ability to construct biological tissues in customised shapes is now one step closer. Researchers at EMBL have succeeded in guiding the folding and therefore the shape of tissues using optogenetics, a technique to control protein activity with light.

The researchers used optogenetics to reconstruct epithelial folding, a fundamental process during development in which cells move inwards and fold into the embryo, eventually giving rise to internal tissues like muscles. Remarkably, they achieved this in cells that normally do not undergo this process.

The research was carried out in developing fruit flies, but the researchers expect these methods to be applicable in other organisms and *ex vivo* stem cell cultures. Optogenetics could be an ideal technique for reconstructing and directing tissue development, which could be used to build artificial tissues in regenerative medicine.

Izquierdo, E *et al. Nature Communications*, 18 June 2018. DOI: 10.1038/s41467-018-04754-z

FULL VERSION ONLINE: BIT.LY/embl-92-12

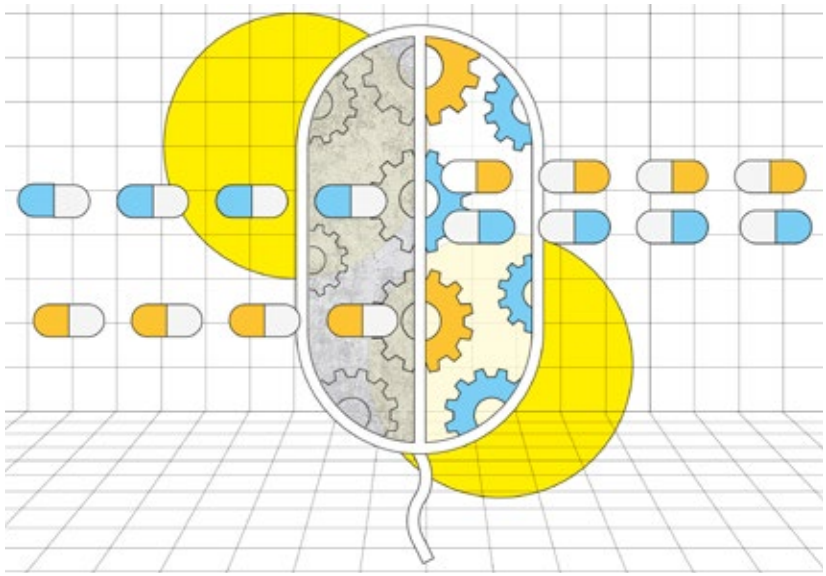


Examples of the tissue shapes the team created. The lower images (black and white) show the cells that were illuminated. The upper images are of three fruit fly embryos, demonstrating how the illuminated cells folded inwards after light activation.

EMILIANO IZQUIERDO/EMBL

Combining antibiotics changes their effectiveness

The effectiveness of antibiotics can be altered by combining them with each other, with non-antibiotic drugs, or even with food additives



ALEKSANDRA KROLIK/EMBL

EMBL researchers profiled the effects of almost 3000 drug combinations.

BY EMMA STEER

Overuse and misuse of antibiotics have led to widespread antibiotic resistance. However, specific combinations of drugs can help to fight multidrug-resistant bacterial infections. In the first large-scale screening of its kind, scientists led by EMBL group leader Nassos Typas have profiled the effects of almost 3000 drug combinations on three different disease-causing bacteria.

Curiously, food additives such as vanillin – the compound that gives vanilla its distinctive taste – could change the effectiveness of antibiotics. Vanillin helped one antibiotic, spectinomycin, to enter bacterial cells and inhibit their growth. Spectinomycin was originally developed in the early 1960s for treating gonorrhoea but is rarely used nowadays due to the development of bacterial resistance. However, in combination with vanillin it could extend the arsenal of weapons in the war against antibiotic-resistant bacteria.

Despite this success, vanillin lessened the effect of many other types of antibiotic on bacterial cells. According to Nassos Typas, combinations of drugs that *decrease* the effect of antibiotics could also be beneficial to human health. "Antibiotics can lead to collateral damage and side effects because they target beneficial bacteria as well. But the effects of these drug combinations are highly selective, and often affect only a few bacterial species. In the future, we could use drug combinations to selectively prevent the harmful effects of antibiotics on beneficial bacteria. This would also decrease the development of antibiotic resistance, as beneficial bacteria would not be put under pressure to evolve antibiotic resistance, which can later be transferred to dangerous bacteria."

The effects of specific drug combinations are largely unexplored and rarely studied in clinical settings. Investigations in mice and subsequent clinical studies are still required to test the effectiveness of particular drug combinations in humans. However, this research will help scientists to understand some of the general principles behind drug-drug interactions, and will enable more rational selection of drug pairs in the future.

Brochado, A *et al. Nature*, 4 July 2018. DOI: 10.1038/s41586-018-0278-9

FULL VERSION ONLINE:
BIT.LY/embl-92-13

First interactive model of human cell division

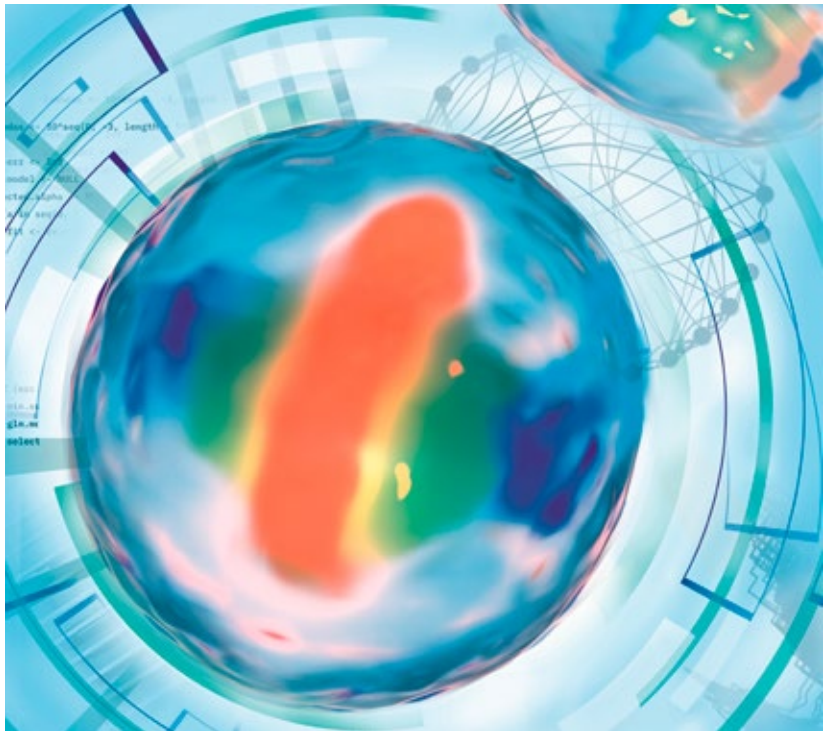
A 4D computer model allows real-time tracking of proteins during mitosis

BY IRIS KRUIJEN

Mitosis – how one cell divides and becomes two – is one of the fundamental processes of life. Researchers at EMBL have now produced the first interactive map of the proteins that make our cells divide, allowing users to track exactly where and in which groups proteins drive mitosis forward.

In 2010, a large study led by the same EMBL group identified which parts of the human genome are required for a human cell to divide, as part of the EU MitoCheck project. But it's proteins that carry out most of the work in a cell, and processes like mitosis require the tight coordination of hundreds of different proteins.

"Until now, individual labs have mostly been looking at single proteins in living cells," says Jan Ellenberg, the group leader at EMBL who led the project. "Supported by the follow-up EU project MitoSys, we are now able to take a systems approach and look at the bigger picture by studying the dynamic networks that many proteins form in living human cells."



ALEKSANDRA KROLIK/EMBL

The resulting Mitotic Cell Atlas integrates these data to produce an interactive 4D computer model. In this public resource, scientists can freely choose any combination of mitotic proteins and see in real time where and with which other proteins they work during cell division.

Sharing the tools to make more cell atlases

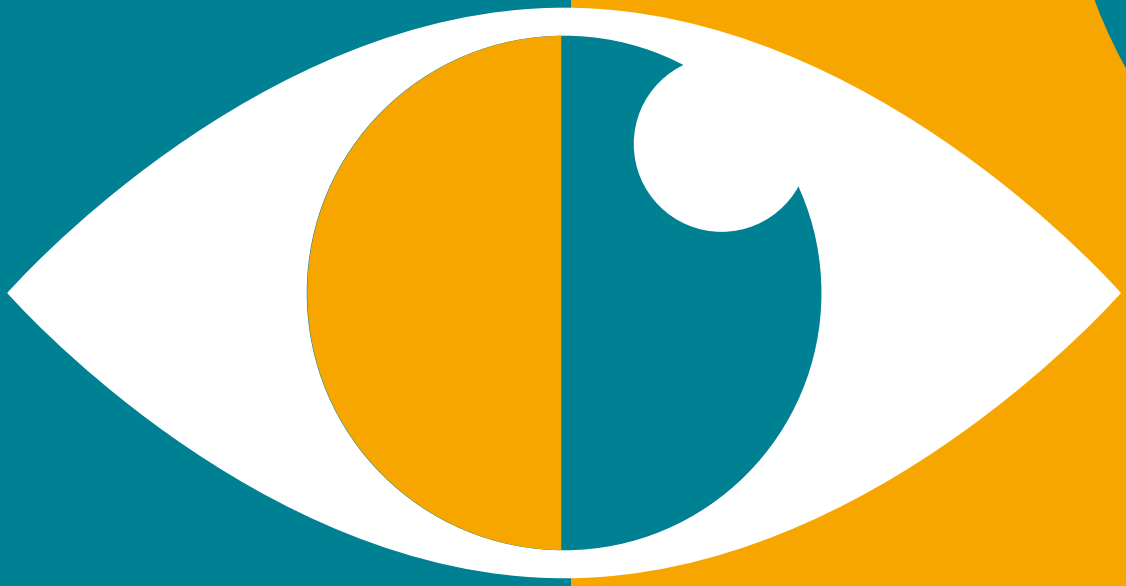
Cell division is an essential process of life. When it goes wrong, problems like infertility and cancer can occur. "The technologies developed here can be used to study proteins that drive cellular functions other than mitosis, for example cell death, cell migration or metastasis of cancer cells," explains Ellenberg. "By looking at the dynamic networks these proteins form, we can identify critical vulnerabilities, points where there's only one protein responsible for linking two tasks together without a backup."

To enable more such studies in future, the experimental methods, the quantitative microscopy platform and the code to create dynamic protein atlases are now openly available for others to use.

Cai, Y, Hossain, MJ *et al. Nature*, 10 September 2018. DOI: 10.1038/s41586-018-0518-z

FULL VERSION ONLINE:
BIT.LY/embl-92-14

ALEKSANDRA KROLIK/EMBL



Deep insights

Members of the EMBL community are translating fundamental science into far-reaching benefits

ISTOCK

An *in silico* hope for biology:

Machine learning

How EMBL scientists are using machine learning to advance biology

BY BERTA CARREÑO

"I'm excited by the problems EMBL biologists want me to help them solve using image analysis!" exclaims Anna Kreshuk with a smile. Kreshuk is one of many researchers across EMBL's sites who use machine learning to solve problems in biology. Just months after starting as a group leader at EMBL, she has a growing list of collaborators who want to use her methods to automatically extract information from microscopy images.

"I'm excited by the problems EMBL biologists want me to help them solve"

After a degree in mathematics, Kreshuk worked for three years at CERN as a scientific programmer before pursuing a PhD in machine learning. Since the completion of her PhD in 2012, the field of machine learning has exploded.

Machine-learning algorithms don't use a specific set of instructions to accomplish a particular task. Instead, the machine learns how to perform a task by using large amounts of data and learning the data's internal structure. Machine learning can work in multiple ways. The simplest way is supervised – you show the system examples of what you want, and it learns the characteristics that will help it find such examples again. These methods are widely used to classify data or make predictions. At the other end of the spectrum are unsupervised methods, where the machine finds motifs in the underlying structure of the data and uses them to cluster the data into categories.

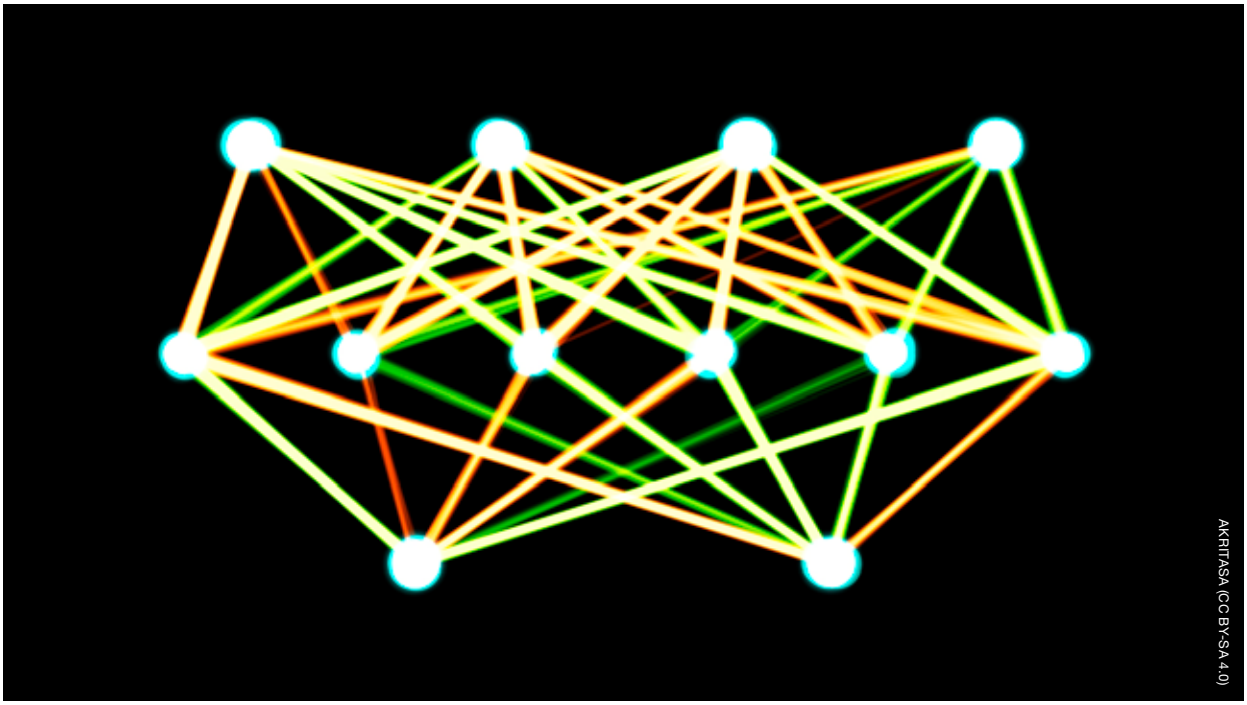
Machine learning techniques often involve the use of artificial neural networks (ANNs), which consist of a set of nodes – known as artificial neurons – with connections between them. In the image of an ANN overleaf, the white circles represent artificial neurons. The lines are connections from the output of one artificial neuron to the input of another. In this case, the network has four nodes in the input layer, six so-called hidden nodes and two nodes in the output layer.

One class of ANNs are deep neural networks (DNNs). In a DNN, instead of having one layer between the input and output layers, there are many hidden layers all interconnected. At the output end, a back-propagation algorithm goes back though the layers, adjusting the mathematical weight given to each of the connections in the network until the final result matches the output of the training data.

A specialised type of DNN is a convolutional neural network (CNN). When using a non-convolutional DNN for image analysis, each neuron in the first layer takes the whole image as its input. In a CNN, by contrast, individual neurons do not respond to the whole image, but only to a restricted region of it called the receptive field. This reduces the >>


EDWARD DADSWELL/EMBL

Anna Kreshuk.



A single-layer feed-forward artificial neural network with four input nodes, six hidden nodes, and two output nodes.

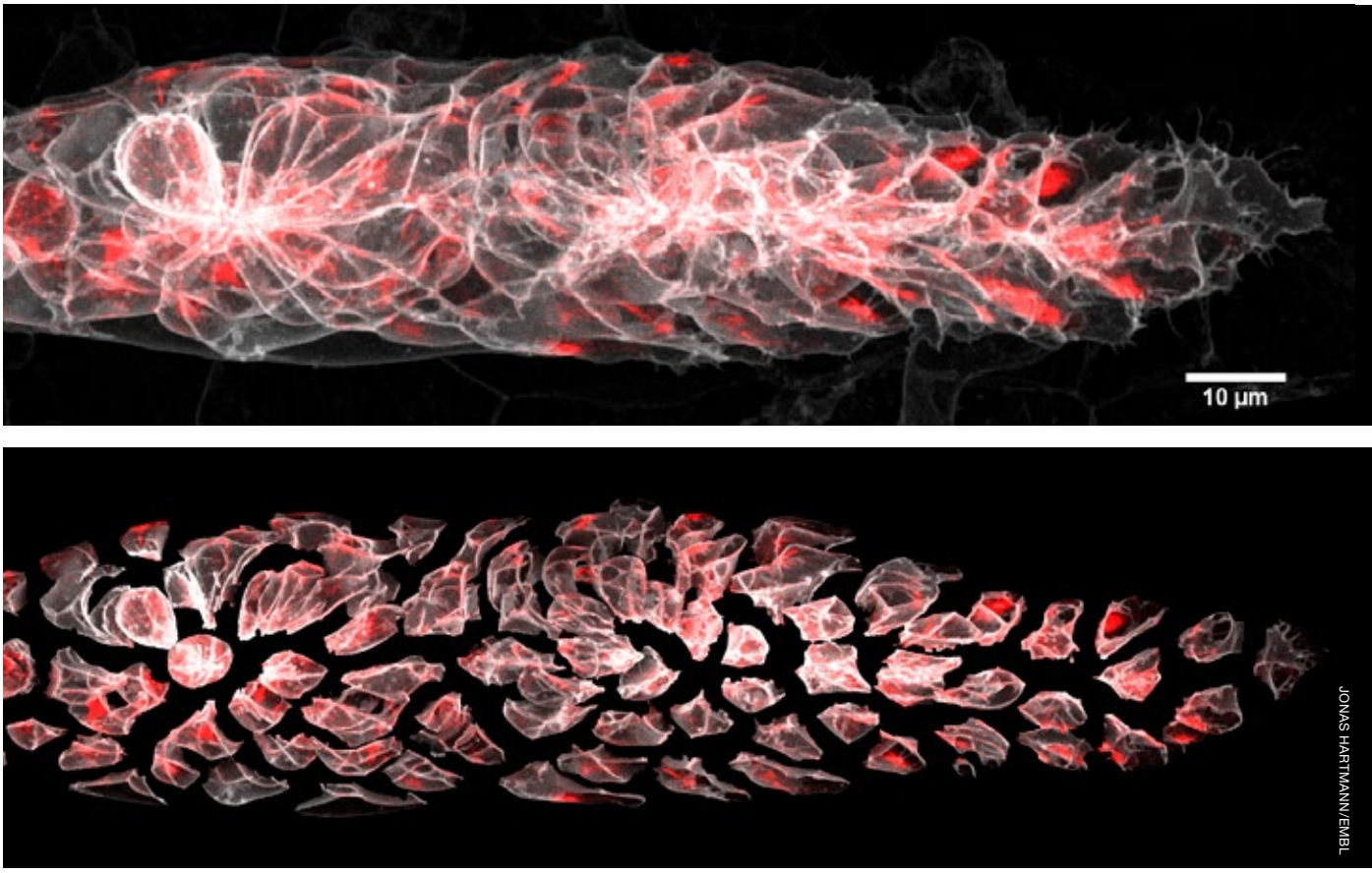
>> complexity of the neural network while still allowing it to outperform other types of neural network on image analysis tasks.

Computer vision

One of the most popular applications of machine learning is in image analysis. Jonas Hartmann, a PhD student in the Gilmour group, is interested in using image analysis to understand how the cells in a tissue interact. "I'm fascinated to observe how cells come together and create new behaviours that you couldn't easily see in a reductionist way," he explains. To understand how this works, Hartmann studies the zebrafish posterior lateral line primordium (pLLP), a group of about 100 cells in the zebrafish embryo that move collectively, differentiate, and make different shapes. Hartmann wants to learn how such processes are integrated and coordinated within a tissue. To do so, he is building an atlas.

"I'm fascinated to observe how cells come together and create new behaviours"

Jonas Hartmann.



JONAS HARTMANN/EMBL

Upper panel: The zebrafish posterior lateral line primordium (pLLP) is revealed using fluorescence microscopy. Cell membranes are shown in grey and actin filaments in red. Lower panel: The same image, but with the cells shown at smaller size and shifted apart slightly. This visualisation becomes possible once the cells have been segmented by means of an automated image analysis pipeline.

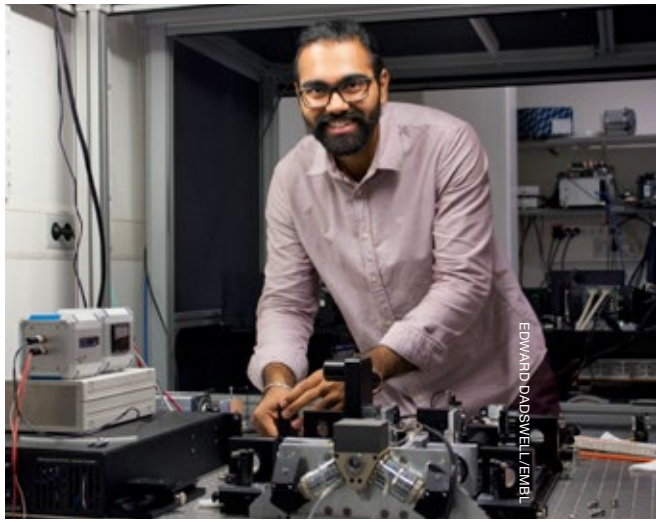
"The idea is to build a cell atlas where you have a reference measurement that you can use as a coordinate system, allowing you to superimpose other measurements. You can then map all your information together and see the relationships between the different features." To make his atlas, Hartmann used microscopy images of the pLLP with both the cell membranes (the reference measurement) and one of many other proteins of interest highlighted. An example of one such protein is actin – a filament-forming protein involved in cell movement and changes in cell shape. Hartmann applied visual filters and feature-extraction techniques to segment each of the cells in the tissue and numerically describe their shapes. Finally, he used machine learning to find the relationship between the reference measurement (the membranes) and the measurement of interest (e.g. actin) to create the atlas.

Machine-learning methods fall into the category of 'narrow artificial intelligence': given a narrowly defined task and the right training data, machines are able to learn how to perform specific tasks as well as, or in some cases better than, humans can. Also – an especially appealing feature to some – machines can work non-stop.

Following cells in real time

"In today's world, I think everybody wants to work better and faster," says Rajwinder Singh, a PhD student in the Hufnagel

>>



Rajwinder Singh.

>> group. Singh is studying the early stages of cell differentiation in mouse embryos. During the first stages of embryonic development, all the cells are the same, but when the embryo undergoes the transition from the 8- to the 16-cell stage, its cells start to differentiate. When a cell divides at this stage, the two daughter cells that form are slightly different to each other because they will belong to different kinds of tissues. When this happens, Singh extracts the two daughter cells to see how their patterns of gene expression differ. Unfortunately for him, it's impossible to predict when these cell divisions will happen, so he needs to sit at the microscope for five or six hours, waiting. He's therefore keen to teach a computer how to recognise this event.

In collaboration with Kreshuk, Singh plans to teach the machine to segment the image in real time. By providing enough images of the kind of cell divisions he's interested in – which occur radially and below the surface – the machine will be able to learn exactly what Singh is looking for. When acquiring the data in real time, it will be able to determine whether a particular cell division is an event of interest.

Black box

Machine-learning algorithms are being used around the world every day, filtering your spam emails or recognising faces on Facebook. But it's almost impossible to understand how a machine makes a particular decision or prediction – a concept known as uninterpretability.

Once the data is fed into the machine, the input nodes start abstracting it, passing the information forward and connecting it to the different nodes of the system, which

What is machine learning?

Babies start learning the moment they're born. Whether it's holding a spoon or mastering French irregular verbs, we learn by taking in new information and improve through repetition. But the ability to learn and improve at a task is not confined to humans or animals: computers can do it too.

Machine learning brings together statistics and computer science so that computers can learn to perform a specific task without being programmed to do so. For a computer to learn, it needs to have some initial data on how to do a specific task. The computer finds statistical patterns in the data that enable it to establish an algorithm by which future data will be sorted. The more useful data the machine has access to over time, the more finely tuned its algorithm will become and the more accurate its decisions will be. The ultimate goal of machine learning is for the algorithm to be able to generalise beyond the information it has seen and successfully interpret new data.

Machine learning is already widely applied: whether it's filtering spam emails, autocorrecting your texting mistakes, or suggesting what movie to watch next, you probably benefit from machine learning dozens of times a day without knowing it.

in the case of a deep network may exist in very large numbers. As Kreshuk puts it, "The calculations are happening in a multidimensional space. Even if you can soak in all the parameters and imagine what it's doing with them – because it's not doing anything complicated – there are just too many of them. It's very hard to interpret what's going on inside."

That situation might soon change, however. "For image analysis applications, uninterpretability can still be alright," continues Kreshuk. "But in clinical applications, for example, it's different. There are a lot of people working on making the black box more interpretable and understanding what drives and influences these decisions. Everyone wants to know, and I think we'll see a breakthrough in this direction in the next few years."

Genomics

Lara Urban, a PhD student in the Stegle group at EMBL-EBI, is combining the human genome and CNNs to predict splicing patterns – changes in the way genetic information is used to make proteins, which allow a single gene to code for more than one protein.

Lara Urban.

"It's very hard to interpret what's going on inside"

In her project, Urban wanted to assess which patterns in the genome are important for predicting splicing, and to see if DNA methylation – the addition of a specific chemical group to the DNA molecule – plays a role in splicing. Urban used different machine-learning methods to tackle this problem. "It depends on what you want to do," she says. "If it's about making predictions, many machine-learning models work well enough, but to find novel DNA motifs that influence splicing patterns, convolutional neural networks are the perfect tool."

Urban is an ecologist by training, and although she currently works on cancer genomics, she hopes to apply her machine-learning skills to ecology one day. "I'd like to apply machine learning to the genomes of endangered species to investigate their susceptibility to various diseases," she explains. "Or see how the genome changes as a result of evolutionary or environmental pressures."

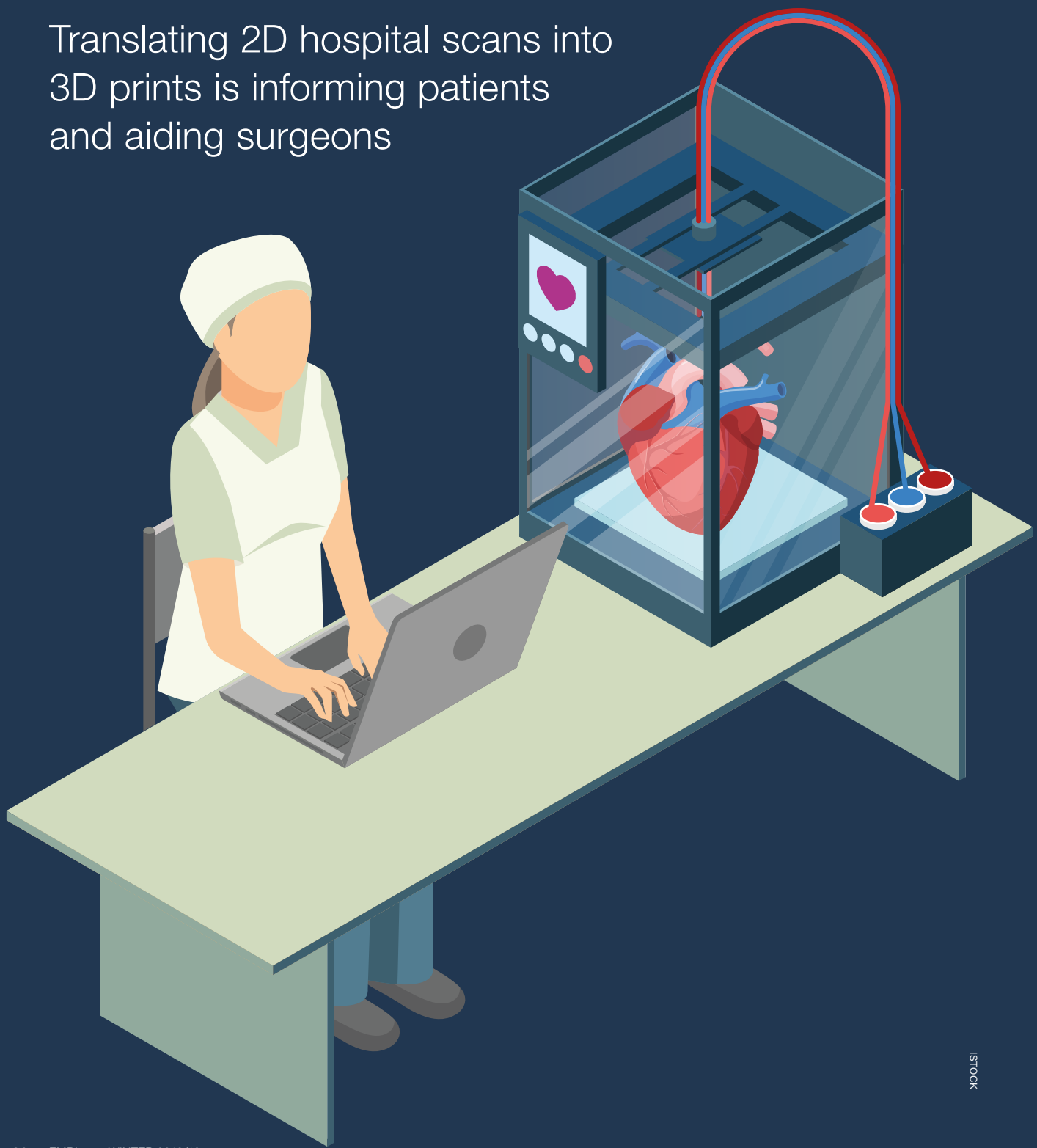
Breaking bottlenecks

Kreshuk and her group hope to put an end to one of the most time-consuming parts of biological research. "I want to remove the bottlenecks that exist in biological image analysis pipelines. I want to enable people to do more ambitious experiments, to do things that just take too long to do by hand. Things that people are not even planning because it would take too much time!" she says. "That way, they'll be able to think about more interesting things and have the freedom to be truly creative."

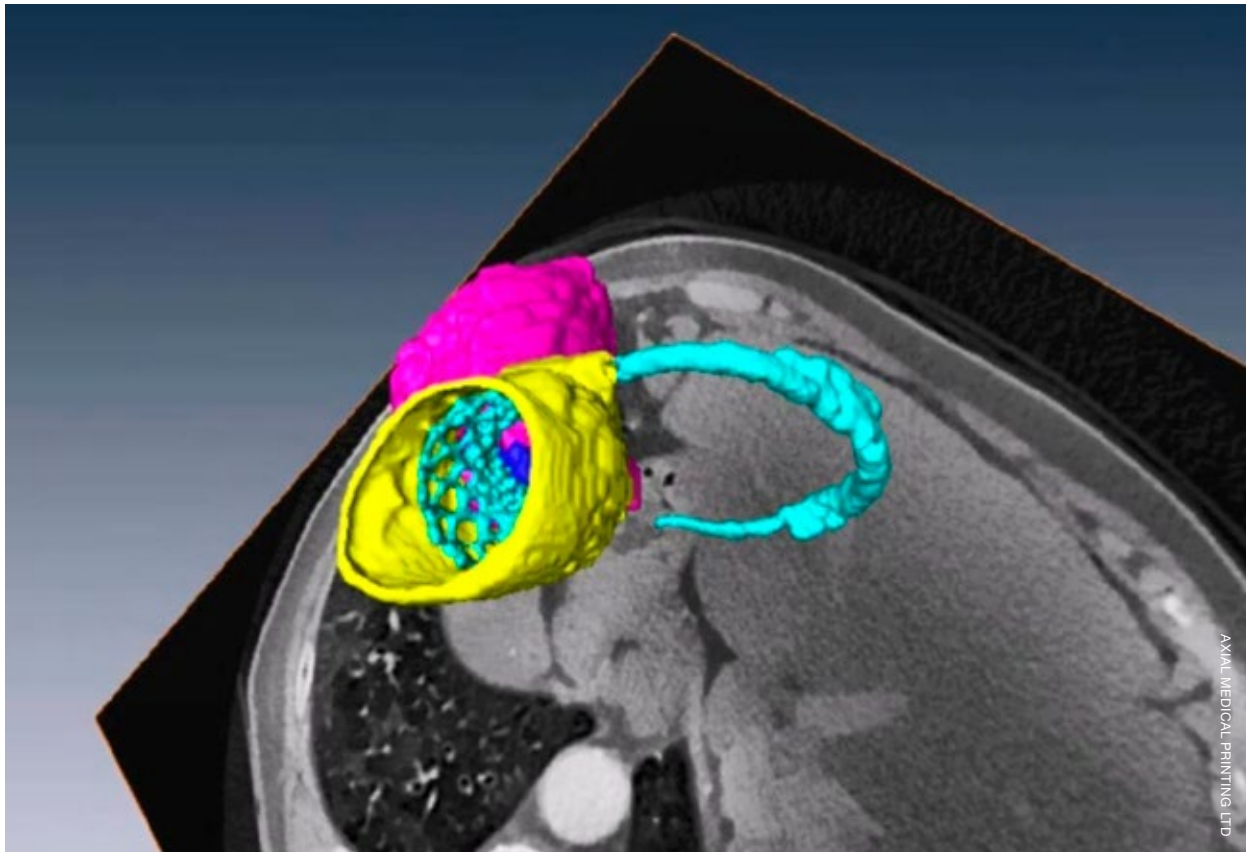
READ ONLINE:
BIT.LY/embl-92-15

In the flesh

Translating 2D hospital scans into 3D prints is informing patients and aiding surgeons



ISTOCK



A 3D digital reconstruction of a heart, formed using information from an MRI scan.

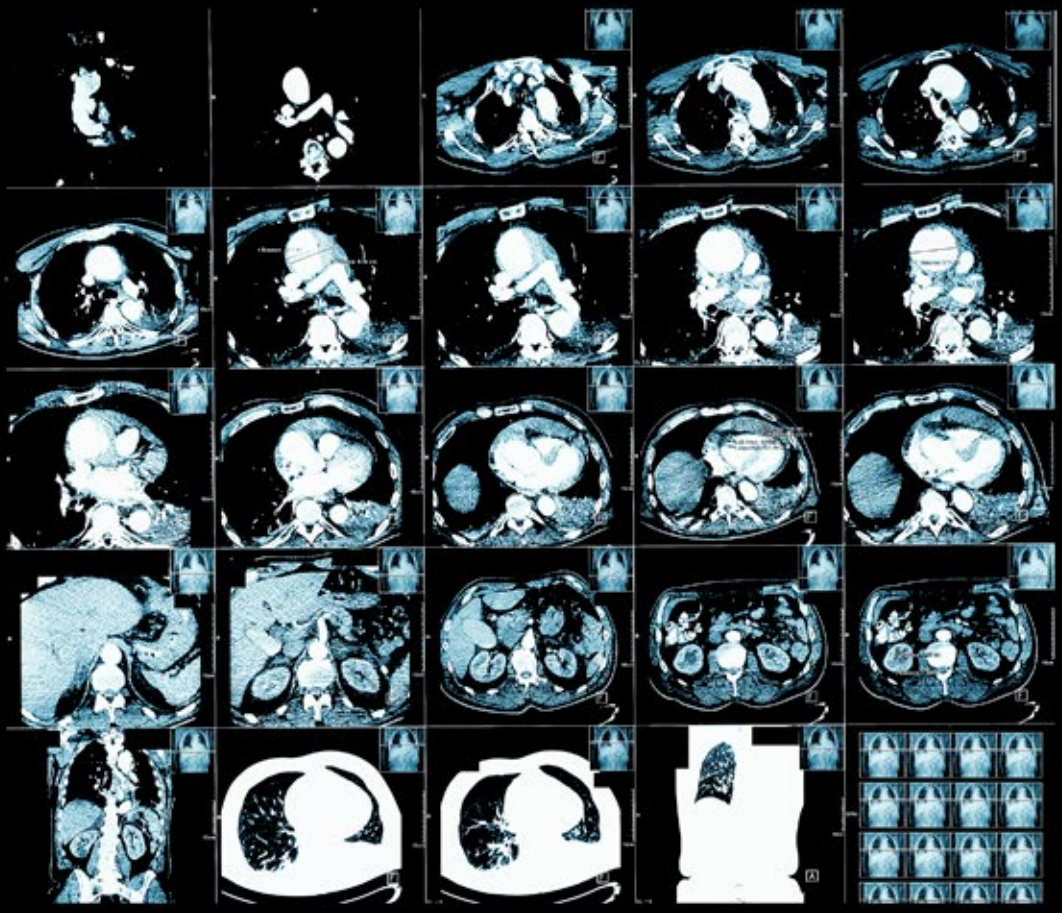
BY EMMA STEER

"The patient had been told that his knee looked like a smashed eggshell," says Niall Haslam, EMBL alumnus and Chief Technology Officer at axial3D – a medical 3D printing company. "But he was still planning to ride a downhill mountain bike race the following month." For both Haslam and the clinicians involved, it was clear that the patient hadn't fully understood the surgical situation or its implications. The hospital scans that the patient had seen had provided detailed information about the bones inside his leg. But sometimes only a physical object can help someone understand the reality of a physical problem. "Only when he held the 3D printed shards did he grasp the enormity of the situation," says Haslam.

Within reach

Since the early 2010s, the business of 3D printing has grown rapidly. The technique's versatility means that anything from innovative lab tools to educational knick-knacks can be produced relatively quickly and cheaply. Medical 3D printing is also on the rise and, at axial3D, life-size anatomical models can be produced within 48 hours. Haslam's experience at EMBL – as a former postdoc in the Gibson team – has helped axial3D to grow from a start-up into a successful business. At EMBL, Haslam learned how to usefully bring together large amounts of data onto one website so that researchers could design better antibodies. Now, at axial3D, he uses these skills to handle the digital side of printing 3D anatomical models. This gives both clinicians and patients the chance to see, hold and truly understand what is going on underneath the skin.

The production process for such a model appears simple. First, clinicians log in to axial3D's website to upload a 2D scan. Within two days, this image is translated into a 3D printed object, ready to dispatch by post. >>



A series of MRI images looking inside a patient's chest. Such images can sometimes look like an abstract painting.

ISTOCK

>> Between these steps, however, finely crafted algorithms – written by Haslam and his team – run the show.

Works of art

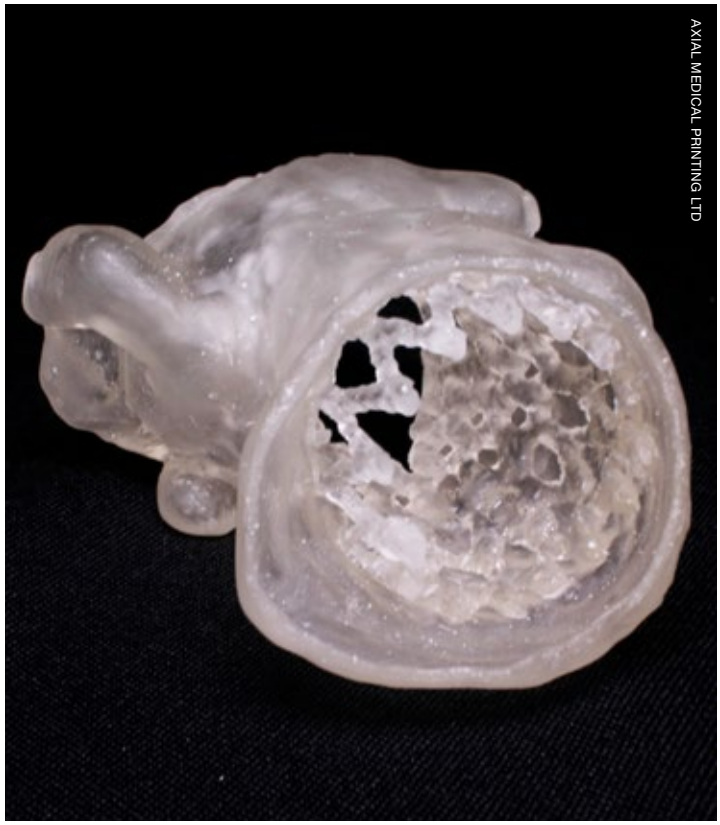
In a case like that of the patient's shattered knee, a machine-learning algorithm identifies the bone in each scan image by drawing an outline around it. The identified regions are then manually checked, and the algorithm is told where it succeeded and where it failed. This allows it to learn and make better decisions the next time. In this respect, machine-learning algorithms are similar to humans: practice makes perfect.

A 3D digital representation of the bone then needs to be created. Just as Michelangelo chiselled *David* out of a marble block, another computer program chips away at a virtual cuboid, uncovering the sections of bone that were identified within. At this point, more human interaction is needed to smooth out inconsistencies and neaten up the edges before the final, physical sculpture can be created. Instructed by the digital file, the 3D printer zips around, systematically laying down a scaffold of plastic threads until the shape of the bone becomes recognisable.

Although the underlying algorithms are complex, it was important for Haslam and his team that the online platform remain simple. "It doesn't matter if you've written the most powerful algorithm available," says Haslam. "If no one can work out how to use it, it may as well not exist."

On the same page

Making complicated information accessible is a goal that Haslam shares with the doctors who use axial3D to explain complex surgical concepts to their patients. Hospital scans can look more like an abstract painting than the neat diagrams often used to depict human anatomy inside textbooks. A soft organ, such as the heart, is particularly prone to these abstractions because it's also squeezed



A 3D anatomical model of a heart, printed by axial3D.

EMBL alumnus and Chief Technology Officer at axial3D, Niall Haslam.

between the lungs and chest muscles, which can slightly change its shape. Coupled with unexpected deformities – caused by developmental diseases in children, for example – the heart's shape might differ significantly from expectations. This is one reason why children's cardiac surgeons are using 3D printed models of the heart to explain to parents which parts of their child's heart haven't developed properly – and how surgery can help. By further informing parents, this approach ensures that both parties have a shared level of understanding and that parents can meaningfully question the surgeon performing the operation. Importantly, the risk of a parent delaying or even refusing to give consent for life-saving surgery is decreased.

Surgeons can also benefit from these models by using them to help plan surgical procedures and avoid possible complications. Important decisions about where to cut within an organ can be more easily taken before the first incision is made. Fewer complications can mean that patients need to spend less time under general anaesthetic. And, from a pragmatic point of view, avoiding unexpected increases in surgery times can also prevent cancellations later in the day or overtime for surgical staff.

By printing 3D anatomical models, axial3D is providing solutions to real-world problems. To do this, it brings together people with very different backgrounds, including patients, doctors and computer coders. Yet despite the differences in people's background knowledge and specialisms, everyone needs to be able to communicate effectively with one another. "If I say one thing but you understand another, then we can't usefully move forward together with an idea," says Haslam. "This is true whether you're a patient speaking with a surgeon or a doctor ordering a 3D print from our website. We need to be speaking the same language."

FULL VERSION ONLINE:
BIT.LY/embl-92-16

Blue skies and green forests

When fundamental research translates into clinical applications

BY EMMA STEER

In the summer of 1999, Ilaria Ferlenghi sat at a microscope, staring intently at the greyscale image swimming into and out of focus on screen. She was inside the microscopy facility at EMBL's Heidelberg site, using one of two cryo-electron microscopes. Within the blur, she was searching for a glimpse of the tick-borne encephalitis virus (TBEV) – a virus for which south-west Germany is particularly renowned. In the forest outside the laboratory, hikers were attempting to avoid TBEV. Those sensible enough covered their ankles, to protect themselves from TBEV-infected ticks lurking in the undergrowth. Anyone infected with TBEV risks fever, seizures and even death.

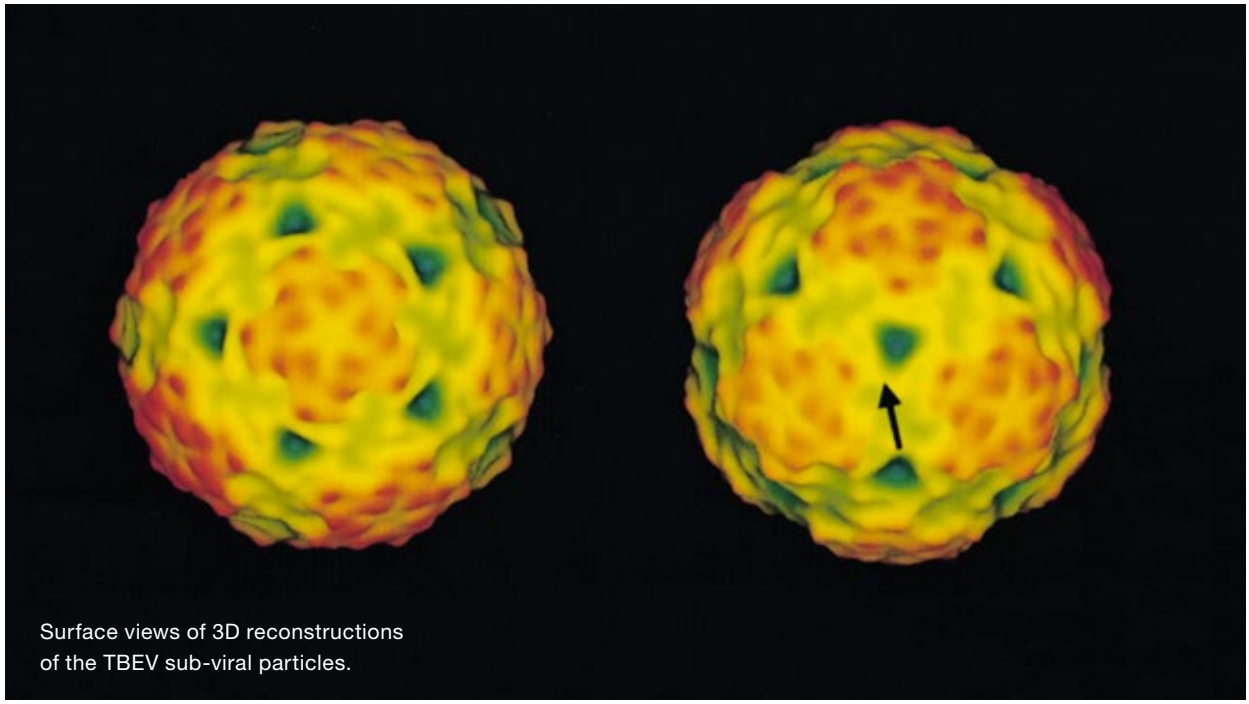
Viral gatekeepers

TBEV's symptoms in humans arise because the virus invades and disrupts the central nervous system. After a bite from an infected tick, proteins that form the outer shell of TBEV enable the virus to invade cells. Some of these proteins act to protect the virus's genetic material from harm, while others interact specifically with proteins on the surface of the host cell. Like a key in a lock, this interaction between viral and cell proteins grants the virus access to the cell. There, it can hijack the molecular machinery needed to replicate itself many times over, damaging cells and causing clinical symptoms in the process.

"We were playing with science. We didn't set out to save lives"

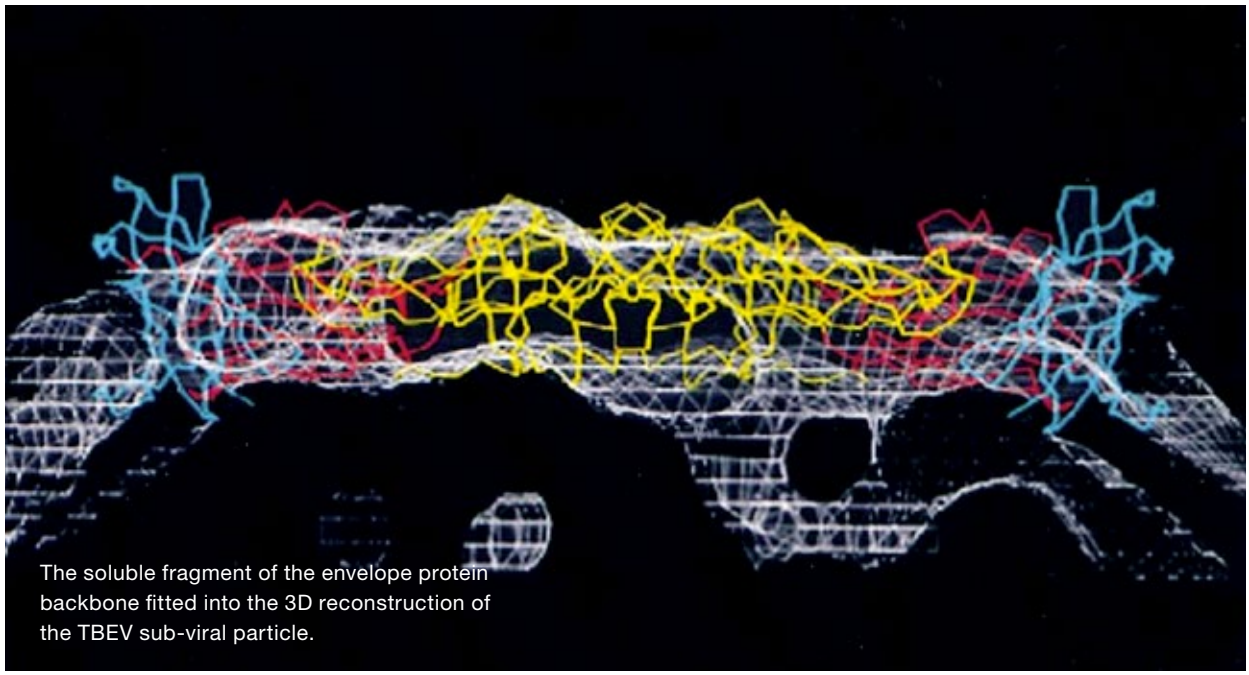
Part of Ferlenghi's research at EMBL involved imaging the whole virus as well as discovering the structure of the surrounding surface proteins, mainly using cryo-electron microscopy (cryo-EM). At the time, however, cryo-EM wasn't considered a particularly important technique for revealing protein structures. Other research groups were using X-ray crystallography instead, and in doing so could achieve much higher-resolution images.

Yet the use of just one imaging technique is never enough to be confident about a protein structure – validation via different tools is vital. This was why Ferlenghi wanted to further develop cryo-EM as a structural



Surface views of 3D reconstructions of the TBEV sub-viral particles.

ILARIA FERLENGHI/EMBL; ELSEVIER

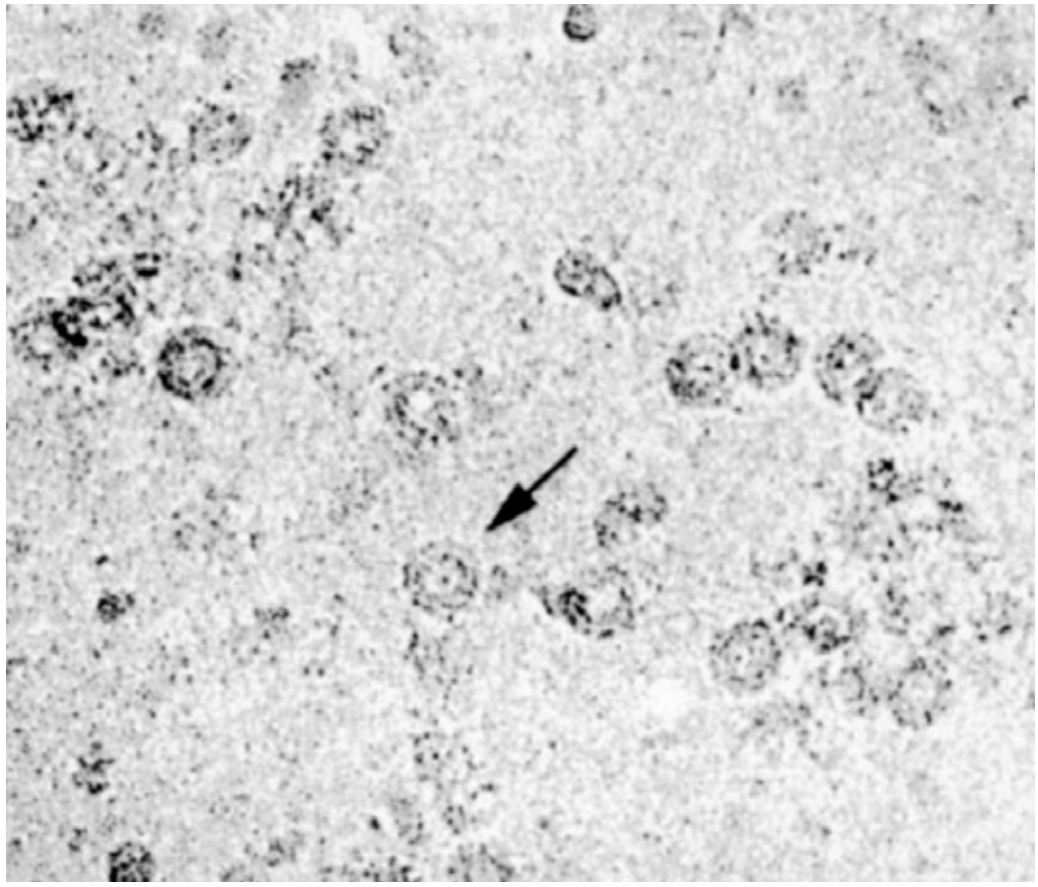


The soluble fragment of the envelope protein backbone fitted into the 3D reconstruction of the TBEV sub-viral particle.

ILARIA FERLENGHI/EMBL; ELSEVIER

biology technique by studying TBEV and other viruses. Development of this technique – led by Ferlenghi's supervisor, the late Steve Fuller – continued the influential work kickstarted by Nobel Prize winner Jacques Dubochet at EMBL in the 1980s.

While at EMBL, Ferlenghi succeeded in her aim. By imaging the structure of the TBEV proteins in both their wild-type and mutant forms, Ferlenghi gained a better understanding of how they interact with proteins on the host cell's surface. The mechanism by which they enter the cell >>



ILARIA FERLENGHI/EMBL; ELSEVIER

Cryo-EM image of the TBEV sub-viral particles.

>> became clearer too. “At the time we didn’t know if it would be important or not. We were playing with science,” recalls Ferlenghi. “We didn’t set out to save lives.”

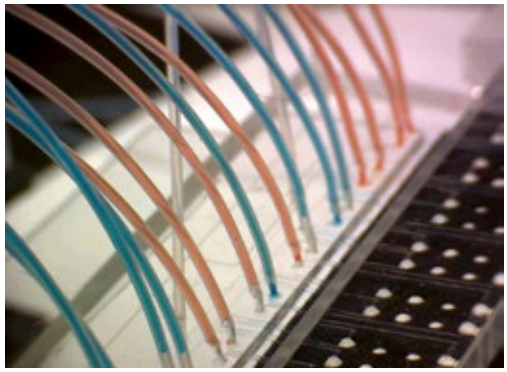
Chemotherapy combinations

Fast-forward 20 years and EMBL scientists still ‘play with science’. At EMBL, researchers have the freedom to ask fundamental scientific questions that help to further human knowledge. Often, a clinical application might not be foreseeable, but potential applications can strike at any time.

Current research in Christoph Merten’s group, for instance, focuses predominantly on the development and production of microfluidic devices. These widgets combine silicon chips, maze-like plastic tube networks and bespoke computer code to allow automated, high-throughput screening of biological samples. By Merten’s own admission, the instruments – although functional and useful – are often “ugly and not particularly user-friendly”. But, by collaborating with clinicians and other researchers, the group can use the instruments to provide a good proof of principle for clinical applications.

Merten’s latest partnership, with clinicians and researchers at Uniklinik RWTH Aachen and Heidelberg University, enables these microfluidic devices to be used to test the efficacy of chemotherapy combinations on biopsies from cancer patients. When validated in mice, the combined therapies recommended by the microfluidics data were more effective than standard care.

This kind of research is driving the advancement of personalised medicine. But Merten is quick to warn that, although everyone involved in the project is keen to see this knowledge translated into new clinical therapies, there are still many years before that can become a reality. “We would need to be exceptionally confident in our results



RAMESH UTHARALA/EMBL

Microfluidic device in the Merten lab.

MEHRNOOSH RAYNER/EMBL

EMBL alumna and Head of Structural Vaccinology at GlaxoSmithKline in Siena, Ilaria Ferlenghi.

FABIOLA GIUSTI/GSK

The travelling microscope, in its new home at GSK in Siena, Italy.

before we can recommend a treatment to a patient," says Merten. "People's lives are at stake."

Viral vaccines

It's sensible for Merten to be cautious. Clinical applications of fundamental research require a lot of investigation, investment by industry, and – importantly – time. For Ferlenghi, this combination has been a recipe for success. Almost 20 years after leaving EMBL, and with several senior research positions behind her, she is now Head of Structural Vaccinology at GlaxoSmithKline (GSK) in Siena, Italy. Alongside her team, she still uses cryo-EM – surprisingly, even the microscope is the same. "After a brief stint with Steve [Fuller] at the University of Oxford, the cryo-EM I used at EMBL is with me again," says Ferlenghi. "We use it at GSK all the time and it still works!" Now, however, it's used to look at the protein structures of potential vaccines to help inform their clinical development.

"The cryo-EM I used at EMBL is with me again"

One of the most successful candidates to date? A vaccine against TBEV.

This vaccine is given to people throughout the world – including the hikers exploring the forest outside EMBL. Ferlenghi is certain that this discovery wouldn't have been possible without the skills she learned at EMBL or the virus structures that she – and other researchers in the field – discovered. At EMBL, the overarching research aim is to advance human knowledge, but one benefit is that this can also improve human health. The question remains – who else's blue-sky thinking could translate to the clinic, and when?

READ ONLINE:
BIT.LY/embl-92-17

ALEKSANDRA KROLIK/EMBL

Identifying the unknown

EMBL's GeneCore steps up to examine what's growing inside the petri dish

MARIETTA SCHUPP/EMBL

(Left to right) EMBL GeneCore members Jonathan Landry, Vladimir Benes and Anja Telzerow in the lab.

BY EMMA STEER

Munich, the Bavarian state capital, is the quintessential German town. From lederhosen to Oktoberfest, it's filled with tradition and antiquity. It was here, however, that a curious group gathered to discuss one of the most revolutionary biological techniques of the 21st century: CRISPR-Cas, the latest tool for gene editing (see explainer: What is gene editing?). Its convenience and affordability make CRISPR-Cas particularly accessible, but who should be using it, and what for? For most attendees sitting in the sunlit seminar room, this was a topic for discussion. But at the close of that day's meeting, a Bavarian government official asked one of the organisers to hand over the CRISPR-Cas kit sitting unopened at the front of the room. No explanation was given.

In the lab

CRISPR-Cas is already being used in research labs around the world. It allows biologists to cut strands of DNA in specific places to insert or delete particular genes (see infographic: How does CRISPR-Cas work?). At EMBL, CRISPR-Cas is found almost everywhere, both in research and as an educational tool. It's used to insert genes to fluorescently label and track proteins in zebrafish, or to delete genes in lab-grown brain cells to mimic neurodegenerative diseases, allowing scientists to study these conditions. EMBL co-organised a CRISPR-Cas course in >>

>> September 2018, teaching scientists how best to use the technique, through theoretical and practical sessions. And researchers at EMBL Rome have visited a local school to introduce the concept to pupils and discuss its implications.

In Germany, CRISPR-Cas technology is strictly limited to certified labs, but people's curiosity extends much further. Those particularly interested in its application are members of the do-it-yourself biology (DIYbio) community, whose scientific backgrounds are as broad and varied as their aims. Their portrayal in the press has been mixed, with journalists alternately highlighting DIYbio's potential dangers or educational possibilities.

At the DIYbio space in Munich, one group of enthusiastic undergraduate students have set their sights on the International Genetically Engineered Machine (iGEM) science competition. Others are more interested in improving the taste of their homemade kombucha – a type of fermented tea – by creating automated monitoring systems. Whatever their interests, these groups share a common curiosity and fascination with biology.

CRISPR kitchen

Rüdiger Trojok is one such DIY biologist. Today he works alongside industry partners to translate creative biological ideas into start-up companies. Prior to this, he completed his formal biology training to master's level and for almost five years he worked in Berlin as a policy consultant for the German parliament. There, he advised on changes to the laws surrounding genetically modified organism (GMO) regulations and applications. In Berlin, Trojok set up a home laboratory and would regularly call government officials to clarify the legality of certain techniques he wished to use. "Techniques such as making green fluorescent protein in bacteria are relatively safe and have been known about for a long time," says Trojok. "But for DIY biologists, there are a lot of grey areas concerning the current GMO laws."

As new biological techniques such as CRISPR-Cas surface, Trojok believes that people's curiosity about biology will grow. In light of this, he set up the CRISPR.kitchen in 2017 – a week-long event in Munich to explain what CRISPR-Cas is and how it works. Discussions about the ethical issues and legal framework surrounding the technique were a key part of the event. To solidify the concepts, Trojok bought a DIY CRISPR-Cas kit online from a US company. "From its description I knew that it was legal to own it, but not to use it," says Trojok. "That's why I invited officials from the Bavarian government department for health and food safety [LGL] to the event – I wanted to discuss the legality surrounding the kit."

>>

What is gene editing?

Genes are sections of DNA that usually act as code for building a specific protein within a cell. Different proteins might affect how a cell looks or functions, including its susceptibility to disease.

Genes can be edited in the lab to change a cell's characteristics. A gene can be deleted so that the protein it encodes won't be made. Deleting a gene and studying how the cell or organism changes can give researchers an idea of what cell characteristics the deleted gene normally controls. Deleting a gene can also mimic a genetic disease, so that the disease and its potential treatments can be further researched. Alternatively, a gene that encodes a new protein can be inserted into the DNA, potentially altering the cell's characteristics.

How CRISPR-Cas works

CRISPR = Clustered Regularly Interspaced Short Palindromic Repeats

CRISPR-Cas is a recent technical advancement in DNA editing. It is based on a trick that bacteria use to copy and paste short sequences of viral DNA into their own DNA as part of their defence system. Scientists have harnessed this system, alongside a cell's own DNA repair machinery, to edit a cell's genome.

DNA – the genetic material in the nucleus of a cell which contains the code for making proteins

Guide RNA (gRNA) – an RNA strand, created by scientists, that matches the targeted DNA sequence

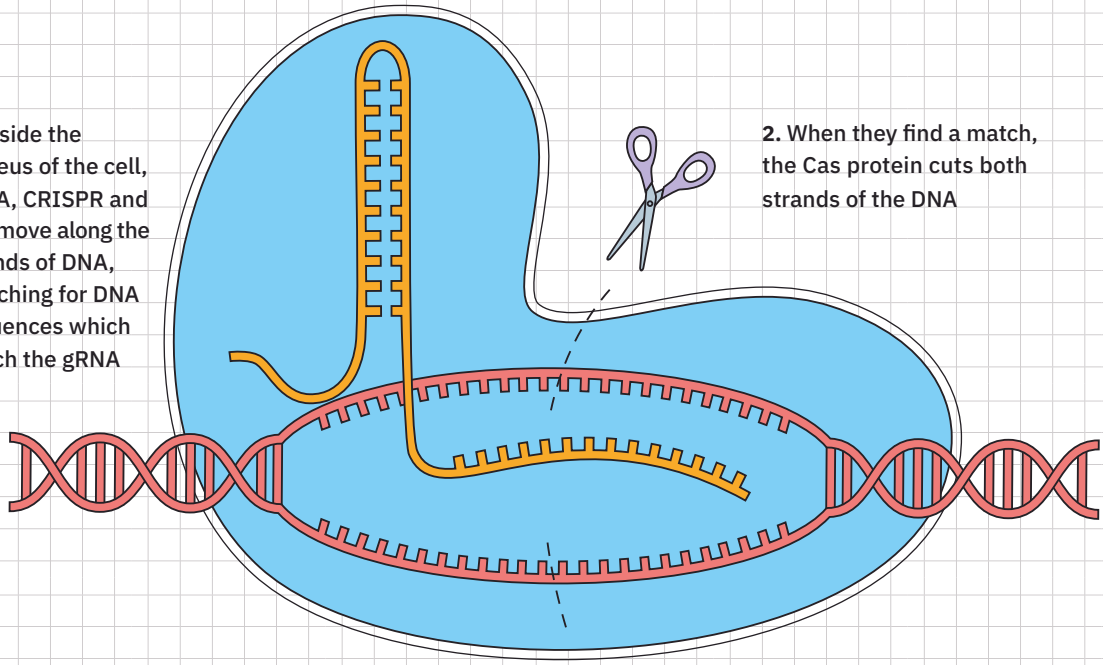
DNA Base – a natural building block which makes up DNA

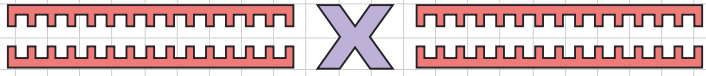
Cas – a protein which can cut DNA

CRISPR – a strand of RNA, copied from a matching region of bacterial DNA and folded into a hairpin bend

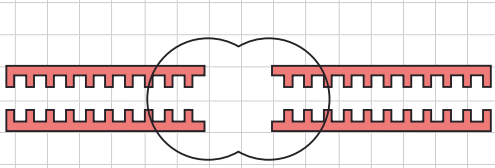
1. Inside the nucleus of the cell, gRNA, CRISPR and Cas move along the strands of DNA, searching for DNA sequences which match the gRNA

2. When they find a match, the Cas protein cuts both strands of the DNA



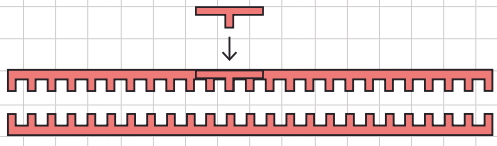


3. Changes to the DNA can be made at the site of the cut



DNA sequence is disrupted

4a. The cell tries to repair the broken DNA but, in doing so, introduces errors into the DNA's code – preventing a functional protein from being made



New sequence is added to the DNA

4b. A DNA sequence that codes for a protein can be inserted into the DNA at the site of the cut

COURTESY OF RÜDIGER TROJOK

EMMA STEER/EMBL

Above: Rüdiger Trojok (right) presenting at the CRISPR.kitchen workshop

>> The event took a new turn, however, when the LGL asked – without explanation – for the DIY CRISPR-Cas kit to be handed over. Trojok and other DIY biologists were keen to know what was going on. "The government didn't want to discuss why they took away the kit," says Trojok. "We didn't know why they were acting so strangely." A week later, a leaked government document surfaced, revealing that several potentially pathogenic bacteria had been discovered in three independently obtained kits. This was closely followed by an official press release from the LGL, but Trojok was still unable to discuss the situation with government officials. "I asked the Bavarian agency to reveal the original data, but they refused," says Trojok. "If they had really found contamination, we didn't know why they wouldn't share this information." Trojok contacted the company who manufactured the kits, asking them to run their own tests. These came back clean, showing only a safe strain of *E. coli* bacterium, which was listed as part of the kits.

EMBL steps in

Clarification was sorely needed, so the DIY biologists approached Vladimir Benes, head of the Genomics Core Facility (GeneCore) at EMBL's Heidelberg site. "EMBL is independent of the company that produced the kit, the DIY biologists who want to use it, and the government that banned it. We just want to know the facts," explains Benes. This independence stems from one of EMBL's founding goals: to be a supranational research centre that is independent of the changing priorities of national governments. "It was an

opportunity for GeneCore to provide a service to one of its member states and manage a conflict by being a neutral party," Benes continues.

From the information that Trojok had gleaned, Benes knew that different identification tests had been used by the LGL and the company involved. Researchers at the LGL tested the identity of the bacterial species using a technique known as MALDI/TOF analysis. This uses mass spectrometry to identify which bacterial molecules are present and then compares them against a known set of bacterial profiles. Meanwhile the company used a method known as 16S sequencing, in which a specific DNA region in the bacterial cells is sequenced and compared against public databanks.

Both analyses are routinely used in professional research labs to identify bacterial species, but each method has its limitations. At GeneCore, whole-genome sequencing is the norm. This method – in which all the bacterial DNA is amplified, sequenced and compared against the genome that the researchers expect it to be – is currently the gold standard in DNA sequencing. According to Benes, this method is the most robust form of analysis to find out what's really in a sample.

Aided by government agencies in Berlin – with whom Trojok has a close working relationship – the DIY biologists provided EMBL with three of the same DIY CRISPR-Cas kits, bought before the CRISPR.kitchen event. Alongside Benes, GeneCore team members Anja Telzerow and Jonathan Landry set to work: Telzerow in the lab – taking all necessary precautions for working with an unknown substance – and Landry at the computer, meticulously analysing the DNA sequences.

Bacterial colonies could be grown from only one of the kits, so it was these that were sequenced and compared with a known *E. coli* genome at GeneCore. Only 30% of the DNA fragments from the kit matched the *E. coli* genome – an unexpected result for a kit supposed to contain only *E. coli*. Yet the exact bacterial species present were difficult to pin down, as large portions of the DNA sequences matched four other bacterial species. Tellingly, three of those were species within the *Enterobacter* genus, a type of bacterium which was also identified by the LGL. But Benes had to be sure of the result – it was vital to confirm the findings with another test. Therefore, the bacterial DNA sequence in question was compared with a subspecies of *Enterobacter*, profiled in one of GeneCore's databases. This gave an 83% match, indicating that the bacterium present in the kit was likely a species of *Enterobacter*. "Without Anja and Jonathan's skills and tenacity, we wouldn't have been able to get the right answers," says Benes.

"The government didn't want to discuss why they took away the kit"

Staying safe

A risk assessment of the kit by the European Centre for Disease Prevention and Control deemed the risk of infection as 'low', and no one was thought to have been harmed as a consequence of this contamination. But some species of *Enterobacter* are known to cause opportunistic infections in ill people or hospitalised patients.

It's still unknown why the company didn't discover the bacteria in their production line. It may be that contamination of the kits occurred during or after the kit had been shipped, as indicated by the company in their official press release. Another explanation, proposed by both Trojok and Benes, is >>

MARIETTA SCHUPP/EMBL

Anja Telzerow working at the biosafety cabinet.

>> that the kits were contaminated during production, and the 16S sequencing method was not robust enough to distinguish between two bacterial genera. Either way, both Trojok and Benes believe that, in this instance, the government was right to ban the product. "I need to be able to trust the source of everything that I order into my lab at EMBL," says Benes. "This should be true for everyone interested in learning more about biology through kits such as these."

In our interlinked societies, bacteria can travel much further and faster than they would be carried by a mere sneeze. Other industries transporting potential bacterial breeding grounds, such as food, must therefore adhere to strict regulations. But companies supplying curious DIY biologists with kits like these are new players to the game – and it's unclear how they are regulated. Where does the freedom to explore and learn end, and the responsibility to protect begin? For Trojok, the answer is clear. Whether it's one person tinkering around with kombucha tea, a company shipping educational biological kits across the world, or an international research organisation such as EMBL, "You have to take responsibility for what you do."

"You have to take responsibility for what you do"

At EMBL, there are stringent regulations in place to allow scientists the opportunity to explore innovative and sometimes off-beat research questions. Within the DIYbio community, Trojok does everything he can to ensure national regulations are put in place, to allow people the chance to safely explore the latest technologies and advances in biology. But, as this situation has shown, there can still be grey areas when sourcing educational kits from companies where the regulations are unclear, or where they differ between countries. For scientists at EMBL, the DIYbio movement provides a conundrum. "As scientists, we recognise and support the urge to explore, ask questions and tinker," says Benes. "But we also hope to see DIY biologists learning in a safe environment – and doing sound science."

FULL VERSION ONLINE:
BIT.LY/embl-92-18

Cultures

Alumni

Humans of EMBL: Outreach

Discover how EMBLers across all sites share their passion for science

BY BERTA CARREÑO

What do rubber ducks, violin bows and school art projects have in common? They all help EMBL researchers explain complex scientific ideas in creative ways. Whether it's people enjoying a pint at the pub or a four-year-old on a day out with her parents, EMBL researchers have fun capturing everyone's curiosity for science.

FULL VERSION ONLINE:
BIT.LY/embl-92-19

HUGO NEVES/EMBL

MATTHEW CONROY

I'm happy to get outside my comfort zone for this – I really enjoy it!

As part of my work, school students email me pictures of their artwork! The **PDB Art** project began by chance: Sameer Velankar, my boss, was telling one of his daughter's school friends about the beautiful molecules in the PDBe database. She asked if she could draw them for her art class at school, so he put me in touch with her. We met and I explained to her how proteins are represented in different ways, and how to use the PDBe website. Six months later, photos of the artworks arrived in our office. They're amazing! It was from here that the project developed into what it is today. I feel that students who gave up science are still getting a flavour of it because this way it's more accessible. It's very different from what I usually do, but I'm happy to get outside my comfort zone for this – I really enjoy it!

Alice Clark
Scientific Database Curator, EMBL-EBI

Doing outreach can be really motivating

I really like explaining my research to people who have a completely different background. They have interesting questions that make me look at my science in new ways. That's one of the reasons why I enjoyed giving a talk at **Pint of Science** in Grenoble. Preparing the presentations, together with Erika Pellegrini, was extremely interesting. We realised how many things we assume people know! Doing outreach can be really motivating. When you spend long days in the lab and the experiments aren't working, it's exciting to hear people ask, "Oh, hasn't anyone done this before?" And you reply, "No, that's why I'm trying!"

Pauline Juyoux
PhD student, EMBL Grenoble

VIRGINIE STROHMEYER

I get to do what I love, and that's a privilege

I really enjoyed being a part of the **EMBL Science Movie Night**. The room was full of interested people who stayed long after the film – *Contagion* – finished, because they had a lot of questions. You get to watch the film beforehand and analyse the smallest bits and pieces – even the smallest pieces of dialogue that no one will listen to! I thought: "Ha! Let me fact check this!" but everything was actually pretty accurate! Working at EMBL, I get to do what I love, and that's a privilege. Scientists build their reputation, publish research, and travel to meet interesting people. I hope we deserve these good things, but I believe we need to give something back to the society that enables this. There are a lot of ways to do this, like teaching or getting involved in science policymaking, but I would recommend participating in outreach activities, because it's a lot of fun!

Philipp Walch
PhD student, EMBL Heidelberg


HUGO NEVES/EMBL


JOANNA PIEPRZYK/EMBL

I explain the concept of protein crystallisation to kids

At EMBL Hamburg's **Night of Science**, I explain the concept of protein crystallisation to kids by getting them to use rubber ducks to imitate how atoms pack into crystals. While the kids play, I use a poster to give a more in-depth explanation for the adults, who usually have a lot of questions. When doing outreach and explaining the biology we do at EMBL, I often hear the question, "When are we going to cure cancer?" I like to reply that science is not only about developing new drugs against cancer – there's also a huge need for basic research. I try to explain how basic research will eventually help to cure cancer, but we first need to understand a whole bunch of things. If we don't know about them, we might miss the next breakthrough – in cancer research or any other field of science.

Sandra Kozak
PhD student, EMBL Hamburg

I performed with a friend as a science busker at Green Man

For a couple of years, I performed with a friend as a science busker at **Green Man**: an electronic and folk music festival in Wales. We used visual and interactive science experiments to demonstrate the practical applications of science – and to start conversations. One of the experiments we did was related to resonance, which is very important in engineering because it can cause bridges to fall down. For example, if you run a violin bow up and down the side of a square plate covered in sand, the sand forms a cross. If you go faster, you get more intricate patterns. We met a guy who designed musical instruments. He told us that when luthiers are carving guitars and violins by hand, they use the same technique to make sure the air is resonating inside the instrument properly. It's a basic way to investigate resonance without using maths!

Antoni Matyjaszkiewicz
Postdoctoral Fellow, EMBL Barcelona

MARETTA SCHUPP/EMBL

BERTA CARREÑO/EMBL

I do my best to challenge people's preconceptions

My grandma was a science teacher and she gave me my first microscope when I was six! We really enjoyed doing experiments together and, in a way, she was doing outreach with me. Now, I do my best to challenge people's preconceptions about science and scientists. Last year I was a tutor for the **Adamas Scienza Summer School**. For two weeks, high-school students join the labs and get a peek at the research going on at EMBL. We actually did experiments that I will use in my PhD project. We used fluorescent dyes to characterise the neurons I was interested in. At the end of the week, the students had a microscope picture of what they'd been doing in the lab that they could take home with them. One of the students told me that she hung the image on her bedroom wall!

Chiara Morelli
PhD student, EMBL Rome

Connection – a painting by Natalia Heirman at Stephen Perse Foundation Sixth Form College.

Art meets structural biology

EMBL-EBI's Protein Data Bank in Europe celebrates art and structural biology

BY OANA STROE

"I've spent my whole life looking at protein structures and there's nothing quite as beautiful. Today, it's so nice to see others inspired by these structures." This is how Janet Thornton, Director Emeritus of the European Bioinformatics Institute (EMBL-EBI) and Senior Scientist, welcomed visitors to the opening of PDB Art 2018 in Cambridge, UK.

The exhibition, entitled 'Artworks inspired by life's building blocks', was organised by the Protein Data Bank in Europe (PDBe). PDBe, based at EMBL-EBI, is one of three sites in the UK, Japan and the USA that host the PDB, a worldwide archive of protein, DNA and RNA structures. Visitors at the art show explored a range of paintings, sculptures and fashion designs created by local school students

Protein-inspired painting.

The 2018 artworks include paintings, ceramics and fashion designs.

Disruption of the Mind – an artwork by Lucy Tunsley, portraying the effects of tau tangles in Alzheimer's disease.

Scientists, art lovers, school students and friends gathered in Michaelhouse Café in Cambridge to celebrate the official opening of the PDB Art exhibition.

and inspired by the 3D protein structures available via PDBe.

A unique collaboration

For the past two years, a team from PDBe has worked with local schools and art societies to inspire pupils with science. After exploring 3D macromolecular structures and discussing with scientists what the proteins do, students were encouraged to create their own artistic interpretations. They explored new ideas using different materials, developing their concepts from the original discussion and creating a diverse collection of final artworks.

"The artistic impulse springs from within, while science is very much focused on the external world," says Liz Tyszka, Young Arts Committee Member for the Art Society CANTAB. "This exhibition brings the two together. The unique character of the project also attracts extremely passionate and talented people – it has been a pleasure working with them and we hope to see the project continue to grow in the future."

PDB Art 2018 was a collaboration with the Leys School and the Perse School in Cambridge, Impington Village College and the Stephen Perse Foundation, with support from the Art Society CANTAB and the Art Society GRANTA.

FULL VERSION ONLINE:
BIT.LY/embl-92-20

Design thinking

MASSIMO DEL PRETE/EMBL

Tabea Rauscher.

EMBL's Design Team Lead on translating scientific discoveries into visual designs

BY MARIANA ALVES

Tabea Rauscher has led EMBL's Design team for the past two years. As well as helping scientists find inspiring ways to present their research, she's working to build a more consistent visual identity for EMBL as a whole. Here she reflects on the process of applying design-led thinking to scientific concepts.

When translating a scientific discovery into a visual design, what is your process?
I think the best designers are listeners as well. So I listen, then I try to learn and understand. After this initial phase I do some research, and eventually I'll check what other designers have created in similar or different fields. After this more inspirational phase, I go into the second phase, which is more output focused: we brainstorm, ideally in a team of two to five people, and decide on two or three concepts we'd like to follow. We then go back to the scientist and discuss which concept is the closest in terms of scientific content. If this is approved by the scientist, we start the final artwork and go into depth and detail and make it really visually appealing. Over the years, I've learned what questions need to be answered to create a focused and tailored output.

Do you think designers need scientific training to be able to ask the right questions?
They need a basic understanding of scientific processes that they either bring with them

or learn by themselves. But every paper is so specific that even a trained scientist would need some time to go into detail and understand all the research.

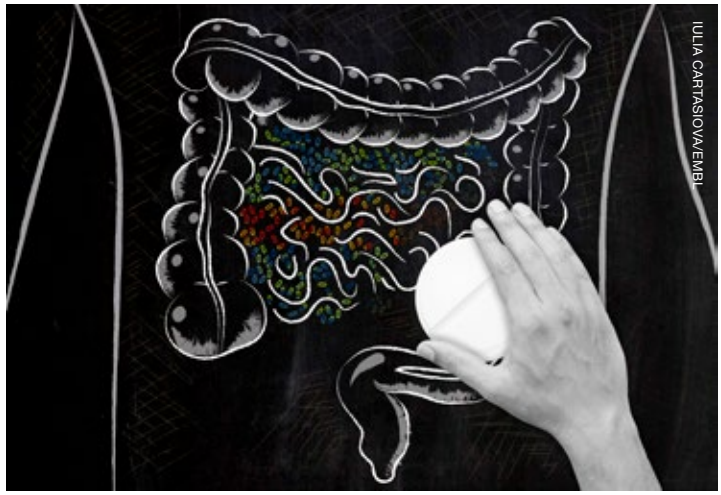
When you study a paper, do you ever realise a figure was not designed in the best way and give constructive criticism to the scientist?
Yes, and I offer scientists training in both general design and creating graphical abstracts and scientific figures. I also offer design consulting two days a week, where scientists call via Skype or just walk in and I'll give them feedback.

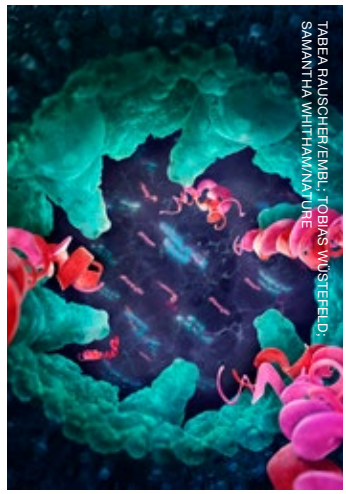
Where do you get inspiration from?
I mainly get inspired by meeting people and friends with different professional backgrounds, going to museums, watching movies, attending conferences, just being a social person – social networks in general. I think good and bad experience is a source of inspiration as well; you connect those experiences with something new in order to create something outstanding and appealing. Plus we're all curious and enjoy what we do. I think I can speak for the whole Design team at EMBL: we all love what we do and that's the best source of inspiration!

What is your preferred biology field, theme or organism to translate into visual designs?
If you're a designer in your heart, it doesn't really matter what kind of field you're working in, as long as you're curious, as long as there's a story to tell, as long as there's relevant content. For me it's just amazing and motivating to understand the content and take the responsibility as a designer to make the complicated and complex data somehow accessible to people – to translate it into a language that everybody can understand or that is understood by the specific group we would like to communicate with.

How would you represent EMBL in one shape, form or image, different from its logo?
That's a tough question! But I think it should be a dynamic network. Visualisation of networks and data is an important part of design – information design anyway – and this type of network is highly dynamic, quite colourful, and very appealing to a wide audience.

How important is interdisciplinary work at EMBL?
Designers love to think, that's what we do all day. There is this outdated idea that designers spend their time moving pixels or switching colours. I really like the Design Thinking approach. This is based around the idea of bringing together people with different professional backgrounds – all of them talented, open-minded, curious and motivated – to explore something new in order to advance society. For me, that's joyful and motivating every day.





Examples of work produced by EMBL's Design team.

FULL VERSION ONLINE:
BIT.LY/embl-92-21

Welcome to EMBL

Six new EMBL leaders share their stories

BY BERTA CARREÑO AND EMMA STEER

Over the past few months, EMBL has welcomed a new group of leaders with diverse academic backgrounds. Among them is an engineer turned biologist, a computer scientist with a background in maths, and an administrator who knows the ups and downs of life in the lab all too well. They're using their skills to approach new challenges from unique perspectives.

Anna Kreshuk

Group Leader, EMBL Heidelberg

Mathematics is aesthetically beautiful, but it's not applied like biology. After my undergraduate degree, I felt maths was a bit too theoretical for me and I wanted to do something of more immediate use. I decided to do a PhD in computer science, focusing on machine-learning methods that could be applied to the life sciences. Sometimes there were times during my PhD when I couldn't see the road ahead. But you just have to put one foot in front of the other and keep going: the view will open when you turn the corner. Becoming a group leader is a very exciting opportunity. In my group, we will develop machine-learning methods and tools for automatic analysis of biological images. Imaging is extremely important in the life sciences, but right now it's also a bottleneck. We want biologists to extract information from images automatically. It's quite abstract, but it can be used for so many things!

MARIETTA SCHUPP/EMBL

FULL VERSION ONLINE:
BIT.LY/embl-92-23

MARIETTA SCHUPP/EMBL

Simone Köhler

Group Leader, EMBL Heidelberg

I saw some images of meiotic nuclei and they were fascinating to me – that's what initially drew me to this field. I also find it inspiring to know that there's so much more to learn about meiosis. This specialised cell division process produces germ cells that have only half as many chromosomes as the other cells in the body. I'm particularly interested in finding out how these chromosomes initially pair, are held together, and exchange genes with each other during this process. As a researcher, I think it really helps if you have a diverse background knowledge, so I'm looking for a group that can bring ideas from different perspectives. I changed fields pretty drastically myself, so I'm very open to others doing the same thing. Also, it's important to stay curious and try things out!

FULL VERSION ONLINE:
BIT.LY/embl-92-22

Rachel Curran

Head of Administration and Operations, EMBL-EBI

I'm a neuroscientist by training. During my PhD, I was using extremely light-sensitive compounds, so I spent a lot of my PhD quite literally in the dark! After a few months as a postdoc, I decided that a career in the lab wasn't for me – I wanted to spend more time with people. My role now is Head of Administration and Operations at EMBL-EBI. In a role such as this, the focus shouldn't just be about the administrative process but also the task that it's supporting. EMBL-EBI is growing and this is really exciting. I want to make sure that the team and I support EMBL-EBI effectively in everything that it does, especially as it continues to grow. I'd also like to explore and further develop the interconnectivity between teams and sites. We're one admin team across EMBL and I think it's really important to work together to understand what we need, and to learn from each other.

OANA STROE/EMBL

At EMBL Barcelona, biologists, physicists and computer scientists work together to understand and simulate the multi-scale connections between genes, cells and tissues. In October, EMBL Barcelona hosted its Inauguration Symposium to officially introduce itself to the city. At this event, journalists, politicians and scientists got the chance to peek inside EMBL Barcelona's new lab spaces and meet the researchers. Donald Ingber, the founding director of the Wyss Institute for Biologically Inspired Engineering at Harvard University, also gave a keynote lecture, which inspired visitors and researchers alike. Here, we catch up with some of EMBL Barcelona's newest recruits.

READ ONLINE:
BIT.LY/embl-92-24a

FERRAN MATEO/PRBB

MARIETTA SCHUPP/EMBL

Miki Ebisuya

Group Leader, EMBL Barcelona

Since I was a child, I've really liked science. After entering the lab at university, I also started to like the process of science. I learned to make a hypothesis, try the experiment, repeat it and then fail! Only once in a while do we succeed, but I really enjoy this process. In my lab, we alter the genetics of cells to recreate and understand what happens during animal development. To do this, we've built artificial gene circuits, where genes are inserted into the genome of cells. Creating these gene circuits is really difficult and in almost all cases it fails. I want researchers in my lab who don't give up – even if they fail a hundred times. This is also why you need to think about your results and plan experiments carefully. If you don't, you can lose a lot of time.

FULL VERSION ONLINE:
BIT.LY/embl-92-24

Vikas Trivedi

Group Leader, EMBL Barcelona

Coming from an engineering background, my approach is to tinker with parts to build units. I also apply this way of thinking when studying embryo development. My research involves understanding how embryos are patterned to form the three body axes: head-tail, front-back and left-right. These axes together define a coordinate system within the developing embryo that lays the foundation for future placement of organs. You can understand the world by making very simple assumptions about it and then testing them. The fun begins when those assumptions or intuitions go wrong, which is often the case! But my priority, when building my team, will always be to ensure a healthy atmosphere in the lab where people can discuss ideas freely and work together synergistically.

FULL VERSION ONLINE:
BIT.LY/embl-92-25

MARIETTA SCHUPP/EMBL

MARIETTA SCHUPP/EMBL

Jim Swoger

Head of Mesoscopic Imaging Facility, EMBL Barcelona

I think it's key for anyone, but especially for scientists, to get out of their comfort zone and live abroad. To experience new work environments is important to grow professionally. I've worked in very international labs and institutes in Heidelberg, Edinburgh and now Barcelona. Here, I'm head of the new Mesoscopic Imaging Facility. We focus on intermediate-size samples that are large enough to be observed with the naked eye, but small enough that you need an instrument to see them properly. The immediate goal is to get the facility running at full capacity with staff and instruments to support the scientists. But I would also like to create a network of imaging facilities or labs that can provide different levels of imaging to study biology and make this available to users. Having a flexible and service-oriented personality is very important – on top of the technical skills, of course!

FULL VERSION ONLINE:
BIT.LY/embl-92-26

The usefulness of useless knowledge

Theoretical physicist Robbert Dijkgraaf discusses the importance of curiosity-based research

BY EDWARD DADSWELL

In 1878, Dutch chemist Jacobus Henricus van 't Hoff gave a lecture titled 'Imagination in Science'. In it, van 't Hoff described his researches into the biographies of more than 200 famous scientists, looking for signs of artistic inclinations among them, which he considered a sign of a healthy imagination. He also looked for evidence of a diseased imagination, such as an interest in superstition or spiritualism, or a tendency towards insanity. In this category, van 't Hoff placed some of science's biggest names, including Ampère, Davy, Descartes, Leibniz, and Newton.

It's an example that theoretical physicist Robbert Dijkgraaf uses in his Science and Society Forum seminar, on the 'Usefulness of Useless Knowledge'. When I speak to him after the seminar, Dijkgraaf emphasises again the importance of imagination and curiosity in science – along with the deadening effect that education can sometimes have, by encouraging people to think in established ways. "Our whole education is a process of confrontation between our imagination and the reality of established facts," he says. "I think the greatest scientists have such an intense curiosity that they're not discouraged by the current practice of the field, and they push the boundaries of knowledge."

Art and science

This effect of education is something Dijkgraaf himself is familiar with. While completing his undergraduate studies in physics, he became disillusioned with the way the subject was taught and began taking more and more time to pursue another of his interests: painting. "At some point my wife said, 'Robbert, I see you painting all day and I don't see you doing any calculations. Perhaps you're doing the wrong thing,'" he explains. Realising she was right, he ended up spending two years studying art at the Gerrit Rietveld Academie in Amsterdam.

It was only after taking some time away from physics that his interest in the subject revived. "I still remember the day I walked into a bookstore and felt, 'Wow, I can read a physics book again!'" says Dijkgraaf. Despite returning to physics, he's clear how much the experience of studying art has helped him. "This detour through art school was actually a shortcut in my development as a researcher," he says. One thing he discovered was the importance

of practising his craft, for example by making sketches. "The important thing is not so much whether the sketches are good or bad, it's that you did the sketches," he explains. That same need to experience the process and do things for yourself applies also in physics. "I discovered that you have to learn a topic yourself, instead of going through a book and following an argument. It's like I can give you instructions for how to walk somewhere, but if you walk the route yourself then you know it and you never forget."

Dijkgraaf – who currently directs the Institute for Advanced Study in Princeton, USA – has recently written a companion essay for a reissue of 'The Usefulness of Useless Knowledge': a 1939 essay by another director of the Institute for Advanced Study, Abraham Flexner. In his essay, Flexner sets out the case for curiosity-based research. Not only does it advance human knowledge – an important goal in itself – but it also generates transformative ideas and technologies, leads to the development of new tools and techniques, brings together the best minds, drives innovation, and acts as a public good. In his seminar, Dijkgraaf cites research indicating that the GDP of a country increases with increases in research spending. "The best grant in the world has been the one that the National Science Foundation gave to Stanford University, to two young graduate students who were working on this new search algorithm in the digital library," he says. "They were the founders of Google, and this less than $5 million grant led to a company that's now close to a trillion in valuation."

Einstein's piano

As our interview comes to an end, I return to the subject of van 't Hoff and his studies of scientists who also had a deep interest in the arts. I'm curious to know whether Dijkgraaf – amid all his other commitments – still finds time for painting. "Yes, I do!" he says, laughing. "I love art, I also love music – I play a lot of music – and I like to write. I feel the mental distance between doing research and painting or playing music is very small."

My final question – "What instrument do you play?" – might well be considered a useless one. What, of any significance, do I hope to learn from it? But then Dijkgraaf tells me that he plays flute and piano, and that one of the pleasures of his job as director of the Institute for Advanced Study is that he has Einstein's grand piano in his living room – the Bechstein piano that was shipped over from Einstein's Berlin apartment when he came to Princeton in 1933.

The fact that Robbert Dijkgraaf gets to play music on Einstein's grand piano might not be especially useful, but somehow it's still the kind of thing you feel better for knowing.

INSTITUTE FOR ADVANCED STUDY

Robbert Dijkgraaf directs the Institute for Advanced Study in Princeton, USA.

FULL VERSION ONLINE:
BIT.LY/embl-92-27

Encounters with Nobel laureates

Meet the EMBL scientists who attended the 68th Lindau Nobel Laureate Meeting

BY BERTA CARREÑO

From 24-29 June, the shores of Lake Constance were witness to a week-long meeting between young scientists and Nobel Prize winners. The seven EMBLers who attended share their experiences.

CHRISTIAN FLEMMING/LINDAU NOBEL LAUREATE MEETINGS

Heena Khatter

Postdoctoral Fellow (EIPOD), EMBL Heidelberg

I had the opportunity to discuss my research with clinicians, geneticists and computational biologists, all of whom have links with structural biology – my field of expertise. I wouldn't have met such a varied panel of experts at any other meeting.

I especially enjoyed a talk given by Michael Bishop and Harold Varmus, where they discussed the significant role that chance played in their careers. They said this wasn't to downplay their hard work, but more to point out that being in the right place at the right time, and being open to new opportunities, are very important for a successful career.

Lara Urban

PhD student, EMBL-EBI

What makes the laureates relatable is their willingness to share aspects of their life that are independent of their scientific breakthroughs. I enjoyed chatting to Elizabeth Blackburn about studying in Cambridge and I exchanged jokes with Michael Bishop about working with poisonous animals. I also admired how Steven Chu talked about the political responsibilities of scientists in combating climate change while we were on a boat trip to beautiful Mainau Island.

As I listened to successful scientists talk candidly about their experiences, with humour and self-awareness, I felt like I was part of their community. For that, I'm very grateful.

Ina Huppertz

Postdoctoral Fellow, EMBL Heidelberg

I had the opportunity to meet Michael Rosbash, who was awarded the Nobel Prize in Physiology or Medicine 2017, along with Michael Young and Jeffrey Hall, for discovering molecular mechanisms controlling the circadian clock. He shared how it felt when Thomas Perlmann from the Norwegian Nobel Committee called him in the middle of the night, disrupting his circadian rhythm, to tell him that he'd won the Nobel Prize. Apparently, he was so shocked that his wife had to remind him to continue breathing!

All in all, the meeting was a source of many wonderful contacts, along with insights into the workings of the Nobel laureates' scientific minds.

EMBLers who attended the 2018 Lindau Nobel Laureate Meeting. Back row, from left: Mathias Girbig, Daniel Rios, Mariana Alves, Elisabetta Cacace. Front row, from left: Ina Huppertz, Lara Urban, Heena Khatter.

Mathias Girbig

PhD student, EMBL Heidelberg

A personal highlight was the lecture given by Joachim Frank, who was one of three scientists awarded the Nobel Prize in Chemistry 2017 for developing cryo-electron microscopy. This is the primary technique I'll use during my PhD project, and I got many insights into this exciting technique and how Frank and others have developed it.

I'm also fortunate that I got the chance to meet so many young and talented researchers. I will keep in mind many discussions, both about science and about other important topics like scientific publishing, politics, and the responsibilities we as young researchers have in our society.

Daniel Rios

Postdoctoral Fellow, EMBL Heidelberg

I was very glad to see the personal side of the laureates – to hear what their concerns were as young scientists and the issues they had to face, either within the lab or in their own lives. Torsten Wiesel was one of the most inspiring scientists for me. He received the Nobel Prize in 1981 for his work on information processing in the visual cortex. Though now retired and aged 94, his excitement was still evident when he recalled the first time he observed a neuron in the cortex respond to a visual stimulus. My favourite take-home message from him: "Hypotheses limit your view on the possible outcomes an experiment may have."

Mariana Alves

PhD student, EMBL Heidelberg

Meeting Nobel laureates has a double effect. You can be incredibly inspired but you can also realise how normal they are and how much of a role serendipity played in their lives. One common theme is that it was never the prize that motivated them. They're not boastful prize winners but individuals incredibly passionate about science.

Lindau was a great experience. There are few moments in life where you can spend one week inhabiting the same lecture hall with 40 Nobel laureates and 600 students from 84 countries. Little by little, meetings like this add bricks to the wall of a scientific world that is more friendly and therefore fruitful.

Elisabetta Cacace

PhD student, EMBL Heidelberg

There were some magic moments where hierarchies were abolished: you could chat about PhD life with fellow young scientists and ask open scientific questions to the person who founded that field of research. Or vice versa: talk science with young peers and PhD life with Nobel laureates. All at the same table, in the same garden, or on the same boat.

What I think was really special about the meeting was spending a week discussing not just science, but the way we do science. I've never perceived so distinctly the responsibilities that scientists hold towards society, and the ways in which society should embrace and protect research.


UNIVERSITY OF LEEDS

Awards & honours

Iain Mattaj prepares for the University of Leeds graduation ceremony.

EMBL Director General **Iain Mattaj** has received an honorary degree from the University of Leeds, UK. Mattaj undertook his PhD research in the Department of Genetics at the University of Leeds in the 1970s.

In May 2018, **François Nédélec** was elected to EMBO membership. He becomes the 18th current EMBL scientist, alongside numerous alumni, to be recognised with membership of the organisation.

Melina Schuh, an EMBL alumna and a director of the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, has received an EMBO Gold Medal. The award is given annually to young scientists for outstanding contributions to the life sciences in Europe.

In July 2018, **Lars Steinmetz** was awarded a grant from the Volkswagen Foundation to study genome organisation in cells where the entire genome has been replaced with synthetic DNA.

In October 2018, EMBL Director **Matthias Hentze** was elected an International Honorary Member of the American Academy of Arts and Sciences in Cambridge, Massachusetts. The Academy was founded in 1780 and recognises people from all disciplines and professions for making extraordinary contributions to society.

Dmitri Svergun was awarded the Guinier Prize at the 17th International Small Angle Scattering Conference. The prize recognises his exceptional scientific contributions to the field of small angle scattering, alongside the positive changes he has made in education and as a mentor to junior researchers.

Laleh Haghverdi, postdoctoral researcher in the Huber and Marioni groups, was awarded the Research Prize by the Peter und Traudl Engelhorn-Stiftung for her pioneering work on methodologies for single-cell transcriptome analysis.

EMBL-EBI Director **Ewan Birney** and EMBL alumnus **Jochen Wittbrodt** have been awarded an ERC Synergy grant for their research into the sources of phenotype variation in a complex vertebrate, the Medaka fish. They will investigate the genetic and environmental sources of variation, as well as the stochastic – or random – variation, which is currently not well understood.

Wolfgang Huber, **Oliver Stegle** and collaborators have been awarded an ERC Synergy grant for their project DECODE, which will study genetic networks in their tissue context *in vivo*, using high-throughput CRISPR knockouts and single-cell sequencing.

Kate Beckham, postdoctoral researcher in the Wilmanns group, received the Jürgen Wehland Award from the Helmholtz Centre for Infection Research (HZI). The Award recognises excellent young researchers in the field of infection biology. Beckham's research focuses on the structural biology of type VII secretion systems in mycobacteria.

Alumni

Translating EMBL expertise across Europe

EMBL

In this issue we meet some of EMBL's most dynamic ambassadors, who are involved in our events in the EMBL member states (pp. 54-57). Read about their extraordinary research, career decisions and motivations – all of which have inspired them to communicate and share EMBL's science, training and services with their scientific communities.

The Council for Advancement and Support of Education (CASE) has recognised the success of last year's EMBL in Norway event, with the event's organisers receiving the 2018 CASE Europe Volunteer of the Year Award (p. 58).

You will also find profiles of alumni whose skills and passions, nurtured at EMBL, now help them to create 3D printed organ models to assist surgeons (p. 20) or develop vaccines against deadly viruses (p. 24).

Finally, we invite you to mark your diaries for our upcoming events in 2019 (see back page and online).

Mehrnoosh Rayner
Head of Alumni Relations

EMBL in Europe

Researchers and EMBL alumni across Europe meet to share ideas and discover research opportunities

BY EMMA STEER AND PATRICK MÜLLER

The only thing finer than reconnecting with old friends is introducing them to new networks. This is the main goal of the EMBL in Europe events. All of these gatherings aim to strengthen ties between EMBL and the wider scientific community in EMBL's member states. This year saw the continuation of these events in Italy, the UK and Spain. Finland also joined the ranks by hosting its inaugural alumni event in October. More than 250 researchers and EMBL alumni gathered at the Biomedicum in Helsinki to build new networks and share ideas. We catch up with some of the organisers and speakers at each of these four events to find out more about their EMBL connections.

ETIENNE ANSOTTE/EUROPEAN COMMISSION

EMBL in Finland: **Marja Makarow** Director of Biocenter Finland

What did your research at EMBL focus on?
I was a postdoc in the lab of Kai Simons from 1981 to 1983, working on cultured kidney cells known as MDCK cells. These cells are polarised, which means that the membranes on opposite sides of the cell look and act very differently to each other. At the time, the presence of these apical and basolateral membranes, as they're known, was a very new finding! We wanted to find out which signals are responsible for trafficking membrane glycoproteins to these different membrane domains.

ELISA LAUTALA

Participants and organisers of the EMBL in Finland event.

As the director of Biocenter Finland, do you still have the chance to go into the lab?
Absolutely not! In 2003 I made the decision to move away from doing my own research. At the time, I was a professor of biochemistry and molecular biology at the University of Helsinki and I was invited to become the university's vice-president for five years. After six months I decided that, if possible, I wasn't going back to the bench. Instead, I'd prefer to take on roles where I'm responsible for all scientific and scholarly disciplines. It was a conscious, but also high-risk, decision.

Since then, I've supported the establishment of two new universities and the Institute for Molecular Medicine Finland (FIMM), I've shaped science policy as the chief executive of the European Science Foundation in Strasbourg, and I was responsible for funding frontier research, as vice-president of the Finnish Research Council (the Academy of Finland). I've also maintained links with EMBL as an EMBL Council member, as president of the European Molecular Biology Conference (EMBC) and as a member of the Alumni Association board.

What did you want to achieve with the EMBL in Finland event?
It's my priority to revitalise Finland's connections with EMBL. Science is renewed by going out to another sector or country and coming back with new ideas, research questions and techniques. As an organiser of this event, I wanted to show young Finnish researchers what opportunities EMBL offers, in terms of its PhD and postdoctoral programmes and the potential for research collaborations. We also wanted them to find out about – and take advantage of – the fantastic research infrastructure that EMBL offers across all of its sites. I think this is a huge opportunity for Finnish science!

How do you think scientific research can further progress?
I want to promote diversity in science and science policy. It's diversity that raises collective intelligence. Gender diversity must be there, but people of different nationalities, cultures and career ages, they must all be there too. When you have these elements in place, then science can advance and the quality of policymakers' decisions increases. Then science can really succeed!

FULL VERSION ONLINE:
BIT.LY/embl-92-28

EMBL in the UK: **Wendy Bickmore Director of the Medical Research Council Human Genetics Unit at the University of Edinburgh**


MARIETTA SCHUPP/EMBL

What's your connection to EMBL and how did it feel to be part of the EMBL in the UK event?
I've been referred to as a 'second generation' EMBL alumna: I haven't worked at EMBL myself, but there's been lots of crossover between scientists working at EMBL and researchers at my own institute. My research topics are also aligned with EMBL's. We study cell and molecular biology in a 3D context and, in particular, try to understand how genes are organised in the 3D space of the nucleus. It's EMBL's high standards, scientific excellence and wonderful facilities that make me want to continue my connection with EMBL. Also, I really enjoy going to EMBL conferences! At this event, I was asked to speak about what EMBL means for research in the UK, and particularly at the University of Edinburgh. I think it was the exchange with other scientists that made this event great.

FULL VERSION ONLINE:
BIT.LY/embl-92-30


MASSIMO DELLE PIETE/EMBL

EMBL in Italy: **Kristina Havas-Cavalletti Group leader at the Institute of Molecular Oncology (IFOM)**

What's your connection to EMBL and how did it feel to be part of the EMBL in Italy event?
I was a postdoc at EMBL Rome from 2012 until 2016, in the lab of Martin Jechlinger, who is now at EMBL Heidelberg. We studied the biological mechanisms behind the recurrence of breast cancer tumours. The EMBL in Italy event was a great opportunity to meet alumni from the Milan area. It's a very dynamic community, with a lot of high-level research being conducted by alumni. There's also a large contingent of women who have come back to Italy and established themselves as group leaders. They're doing a fantastic job, so seeing them present their work was one of my personal highlights. The sense of community at EMBL, and particularly at EMBL Rome, makes you feel part of something bigger and more important than your own research, and that is incredibly special.

FULL VERSION ONLINE:
BIT.LY/embl-92-29

EMBL in Spain: **Lola Ledesma** Group leader at the Centro de Biología Molecular Severo Ochoa (CBMSO)


JOSE ANTONIO PÉREZ/CBMSO

What's your connection to EMBL?
I joined EMBL in January 1996 as a postdoctoral fellow in the lab of Carlos Dotti. I worked there for five years, characterising specialised regions in the membranes of neurons. These regions – known as lipid rafts – contain fats and signalling receptor proteins. We showed that these lipid rafts are crucial for the breakdown of certain proteins within the cell. For example, when the fats that make up a lipid raft change, the production of a small protein important in Alzheimer's disease – known as amyloid beta – is altered.

What was your aim for the EMBL in Spain event?
I think that, for all the organisers of the EMBL in Spain event, EMBL was a place to build networks and make friends. At this event we've continued to build these networks and keep in touch with old friends. We also wanted young researchers in Spain to know more about the opportunities that EMBL can offer them. These scientists are looking for places to start or continue their careers and we want them to know that EMBL is a great place for them to do this.

What did you learn at EMBL?
Being at EMBL was an extraordinary experience – both professionally and personally. It's a paradise for science. This is partly because of the many resources that are available, but also because the people at EMBL are so passionate about their science. Group leaders dare to take on risky and creative projects and there's an excitement that comes with that. This is something that I've tried to keep in mind since leaving EMBL.

FULL VERSION ONLINE:
BIT.LY/embl-92-31

JOSE ANTONIO PÉREZ/CBMSO

Participants and organisers of the EMBL in Spain event.

MEHRNOOSH RAYNER/EMBL

Gareth Griffiths and Rein Aasland receiving their CASE Europe Volunteer of the Year Awards.

Excellent alumni

EMBL alumni Gareth Griffiths and Rein Aasland receive the 2018 CASE Europe Volunteer of the Year Award

BY PATRICK MÜLLER

The organisers of the EMBL in Norway event at the University of Oslo, Gareth Griffiths and Rein Aasland, were presented with the Volunteer of the Year Award from the Council for Advancement and Support of Education (CASE) in August 2018. Rein is currently the head of the Department of Biosciences at the University of Oslo, as well as the vice-president of the Human Frontier Science Program (HFSP). Gareth is a group leader in Rein's department and has been the chair of the EMBL Alumni Association board since 2016.

The EMBL in Norway event, held in September 2017, showcased the role of EMBL, EMBO and HFSP in supporting life sciences worldwide, with particular focus on Norway. Rein and Gareth dedicated a year to mobilising the life science community in Norway to contribute to this event. Speakers included EMBL alumni currently doing research in Norway, EMBL researchers, directors of EMBL partner institutes and a representative from the Norwegian Research Ministry. EMBL students were also included among the speakers, to encourage and motivate other young scientists. To fund the event, Rein and Gareth raised €15,000 from their institutes and the Norwegian Research Ministry, successfully engaging individuals, institutions and government in their goal to advance EMBL. Their award draws attention to the impact that alumni can make with their time, know-how and networks.

READ ONLINE:
BIT.LY/embl-92-32

The year in pictures

March: A new member of the EMBL Events team, Buddy the yeast cell, arrives at EMBL.

July: Celebrating LGBTSTEM Day: the first international day of LGBTQ+ people in science, technology, engineering, and maths.

July: As part of EMBL's Summer Party, EMBL staff and their families trot through the forest surrounding EMBL's Heidelberg site.

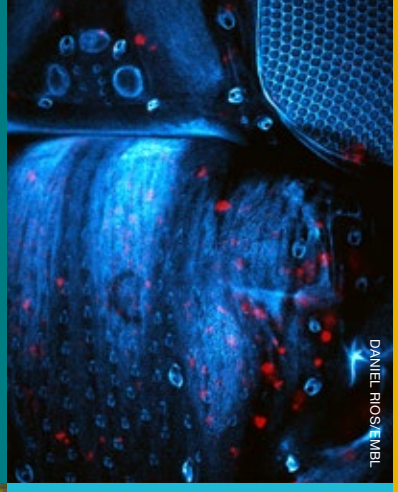
July: Staff and alumni entertain a packed auditorium with heartfelt presentations and performances at the farewell celebration for EMBL Director General Iain Mattaj.

September: People from around Heidelberg and Cambridge visited and learned about EMBL as part of European Researchers' Night.

Events

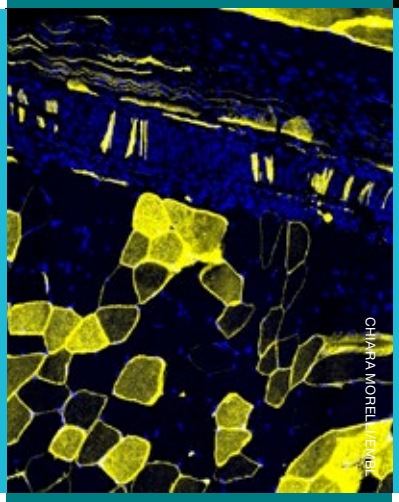
March
7-9

EMBL Heidelberg
EMBL-Wellcome Genome Campus Conference: Proteomics in Cell Biology and Disease Mechanisms


DANIEL RIOS/EMBL

March
17-20

EMBL Heidelberg
EMBO | EMBL Symposium: Synthetic Morphogenesis: From Gene Circuits to Tissue Architecture


CHIARA MORELLI/EVEBI

March
26-29

EMBL-EBI
EMBL Course: Introduction to RNA-Seq and Functional Interpretation

Upcoming meetings
Alumni

1 February
EMBL Alumni Association board meeting and drinks reception, EMBL Hamburg

22 Mar
Annual EMBL Retirees' Afternoon, EMBL Heidelberg

8-9 Apr
Edith Heard Symposium, Collège de Paris

6-7 May
EMBL in Italy, Nouscom, Rome

20 May
EMBL in the UK, Francis Crick Institute, London

March-April
31-3

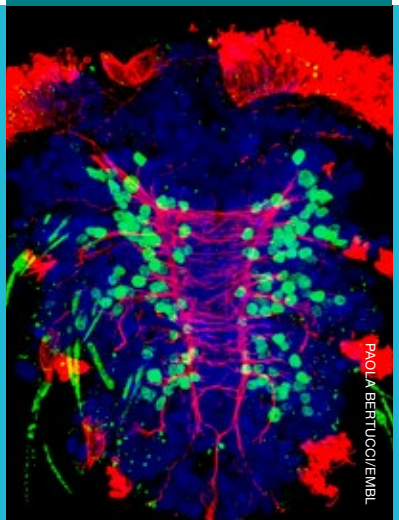
EMBL Heidelberg
EMBO | EMBL Symposium: Reconstructing the Human Past – Using Ancient and Modern Genomics

April
10-13

EMBL Heidelberg
EMBO | EMBL Symposium: Probing Neural Dynamics with Behavioural Genetics

May
13-24

EMBL-EBI
EMBL Course: Computational Molecular Evolution


PAOLA BERTUCCI/EMBL

May
15-18

EMBL Heidelberg
EMBO | EMBL Symposium: The Identity and Evolution of Cell Types

VIEW THE COMPLETE LIST OF EVENTS ONLINE:
embl.org/events