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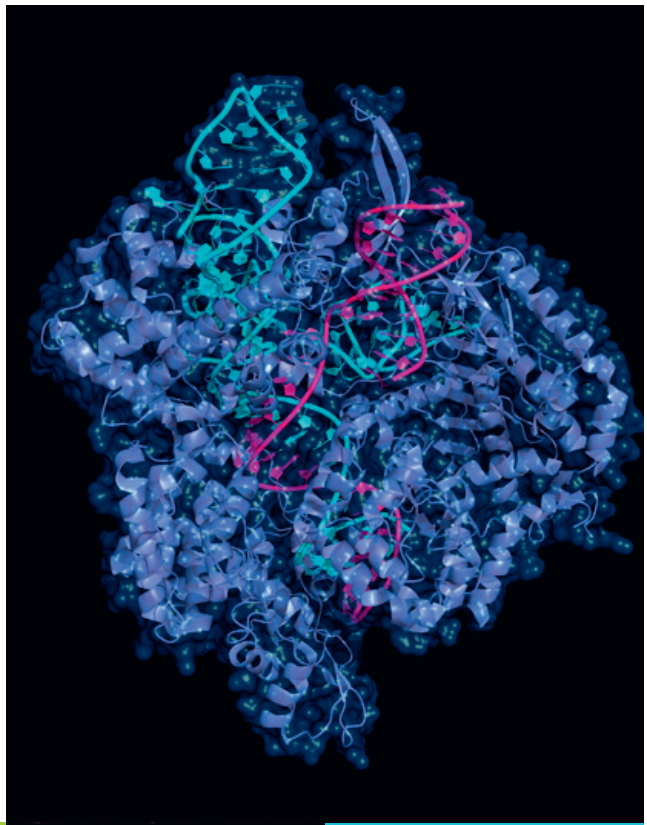
Issue 93 Summer 2019

EMBL etc.

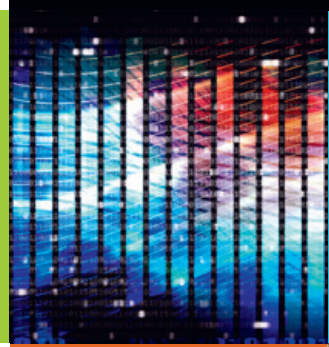
Code

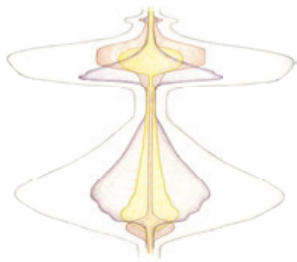
Contents

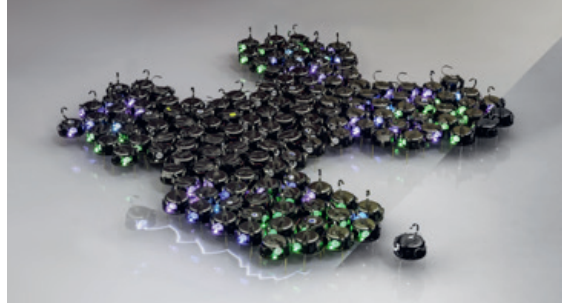


Nucleus

Feature stories







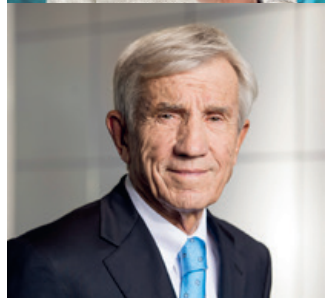
Synapse

News stories

Cultures

EMBL community stories

Alumni




MASSIMO DEL PRETE/EMBL

Editorial

Codes are everywhere. In biology, the most obvious examples might be the codes in DNA and RNA, but whenever scientists seek to understand how a system works, or piece together observations to reveal deeper truths, they're cracking codes of one kind or another.

In this issue, we explore how CRISPR-Cas9 – a tool for editing the DNA code – is used at EMBL (p. 14), and Science and Society speaker Tim Lewens analyses the ethical side of gene editing (p. 50). We also meet members of the EMBL community who are teaching children and teenagers how the nucleotides in DNA store information, using an even more beloved set of fundamental building blocks: Lego bricks (p. 46).

We find out how computer code is providing more efficient ways to access and analyse biological data (p. 24), and how EMBL scientists are gaining new scientific insights by using computer algorithms for analysing language (p. 20). We also report on a new search engine for microbial genomes (p. 7), and EMBLers share the lessons they learned on their coding journeys (p. 42).

Finally, we take a look at the codes used in different worlds. We celebrate twenty years of EMBL's technology transfer partner, EMBLEM, which takes fundamental science into the commercial sphere (p. 36). Manfred Lautenschläger, funder of the EMBL Lautenschläger Summer School, discusses his code for giving (p. 48), and we explore codes from various disciplines as an artist and a historian visit EMBL (p. 28).

Edward Dadswell
Editor

Word to remember

Mitochondria

Plural noun
(singular *mitochondrion*)

Pronunciation:
/ˌmaɪtəˈkɒndrɪə/

Often described as the powerhouses of the cell, mitochondria are cellular components that produce the cell's energy currency, adenosine triphosphate (ATP).

You inherit your mitochondria almost exclusively from your mother (p. 50), and they may play a role in ageing (p. 34).

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New functionalities for cells

EMBL scientists create membraneless organelle to build proteins in a living cell

Typical cellular processes are seen as encapsulated, isolated, and are represented as repetitive structures in a city. The making of a new organelle is highlighted as a new building that is more dynamic and flexible, and is not fenced.

GEMMA ESTRADA GIRONA

BY IRIS KRUIJEN

For the first time, scientists have engineered the complex biological process of translation into a designer organelle in a living mammalian cell. Research by the Lemke group at EMBL – in collaboration with JGU Mainz and IMB Mainz – used this technique to create a membraneless organelle that can build proteins from natural and synthetic amino acids carrying new functionality. Their results allow scientists to study, tailor and control cellular function in more detail.

"The organelle can make proteins by using synthetic non-canonical amino acids. Currently we know of more than 300 different non-canonical amino acids – compared to 20 that are naturally occurring. We are no longer restricted to the latter ones," says co-first author Gemma Estrada Girona. "The novelty we introduce is the ability to use these in a confined space, the organelle, which minimises the effects on the host."

Wobbly wall-less organelles

Translation is too complex to be contained in one single organelle surrounded by a membrane. Therefore, inspiration was drawn from phase separation: the process responsible for the formation of membraneless organelles *in vivo*, such as nucleoli or stress granules. Phase separation is used by cells to locally concentrate specific proteins and RNAs. Even though these wall-less organelles have wobbly boundaries, as they interact dynamically with the surrounding cytoplasm, they can still do very precise tasks. The team combines phase separation with cellular targeting to create their membraneless organelle and to make sure that only one organelle per cell is formed.

Edward Lemke – visiting group leader at EMBL, Professor at JGU Mainz and Adjunct Director at the IMB – led the project. He concludes: "In the end, we aim to develop a technique to engineer synthetic cellular organelles and proteins that do not affect the host machinery at all. We want to create a tool that does not have any uncharacterised effects. The organelle should be a simple add-on that allows organisms to do custom-designed novel things in a controlled fashion."

Reinkemeier, CD*, Girona, GE*, Lemke, EA. *Science*, 29 March 2019. DOI: 10.1126/science.aaw2644

FULL VERSION ONLINE: BIT.LY/embl-93-01

Global microbial signatures for colorectal cancer

Colorectal cancer is characterised by consistent changes in our gut bacteria across continents, cultures and diets

BY IRIS KRUIJEN

Cancers have long been known to arise due to environmental exposures such as unhealthy diet or smoking. Lately, the microbes living in and on our body have entered the stage as key players. The role that gut microbes play in the development of colorectal cancer – the third most common cancer worldwide – is unclear. To determine their influence, association studies aim to map how the microbes colonising the gut of colorectal cancer patients are different from those that inhabit healthy subjects.

A study led by EMBL scientists focused on a process in which certain gut bacteria turn bile acids that are part of our digestive juices into metabolites that can be carcinogenic. "We used a rigorous machine learning analysis to identify microbial signatures for colorectal cancer," says EMBL group leader Georg Zeller. "We validated these signatures in early cancer stages and in multiple studies, so they can serve as the basis for future non-invasive cancer screening."

Wirbel, J, Pyl, PT *et al. Nature Medicine*, 1 April 2019. DOI: 10.1038/s41591-019-0406-6

Thomas, AM, Manghi, P *et al. Nature Medicine*, 1 April 2019. DOI: 10.1038/s41591-019-0405-7

FULL VERSION ONLINE:
BIT.LY/embl-93-02

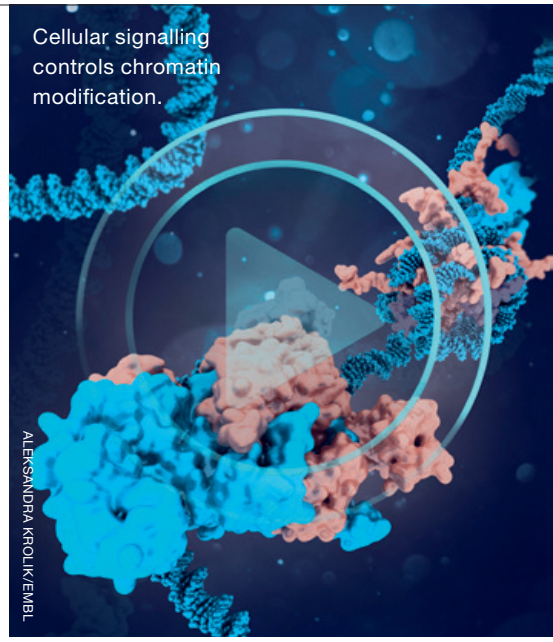
Transcription factors controlled by DNA sequence

EMBL scientists gain mechanistic insights into how cellular signalling controls gene regulation

BY PATRICK MÜLLER

In cells, DNA exists in a highly compact form. The scaffolding that enables this packaging of DNA is made of proteins known as histones. More than 50 years ago, it became apparent that chemical modifications to these proteins are associated with gene activation. One example of such a modification is acetylation – the addition of an acetyl chemical group. However, precisely how cellular signals initiate this modification remained unclear.

To reveal the underlying mechanism, a team led by Daniel Panne – a former group leader at EMBL Grenoble – studied p300, an enzyme that transfers acetyl groups and regulates cell growth and division. The team found that transcription factors – proteins that control the expression of genes – are the mediators between acetylation and cellular signalling. Transcription factors are known to control where in the genome particular genes are expressed,



Cellular signalling controls chromatin modification.

ALEKSANDRA KROLIK/EMBL

and when. Now, the scientists have discovered that the sequence of the DNA determines where the histone is acetylated.

Ortega, E *et al. Nature*, 15 October 2018. DOI: 10.1038/s41586-018-0621-1

FULL VERSION ONLINE:
BIT.LY/embl-93-03

A DNA search engine for microbes

New search engine allows researchers to identify antibiotic resistance genes or mutations in real time

BY OANA STROE

Researchers at EMBL-EBI have combined their knowledge of bacterial genetics and web search algorithms to build a DNA search engine for microbial data. The search engine could enable researchers and public health agencies to use genome sequencing data to monitor the spread of antibiotic resistance genes. The search engine, called Bitsliced Genomic Signature Index (BIGSI), fulfils a similar purpose to internet search engines, such as Google. The amount of sequenced microbial DNA is doubling every two years but, until now, there was no practical way to search the data.

This type of search could prove extremely useful for understanding disease. Take, for example, an outbreak of food poisoning, where the cause is a *Salmonella* strain containing a drug-resistance plasmid (a 'hitchhiking' DNA element that can spread drug resistance across different bacterial species). BIGSI allows researchers, for the first time, to easily spot if and when the plasmid has been seen before.

Bradley, P *et al. Nature Biotechnology*, 4 February 2019. DOI: 10.1038/s41587-018-0010-1

FULL VERSION ONLINE:
BIT.LY/embl-93-04

New method to study gene expression in yeast cells

Scientists develop high-throughput yeast single-cell RNA sequencing method

TOBIAS WÜSTEFELD

The strands of RNA within a single yeast cell can now be studied across the entire genome.

BY JOSH TAPLEY

A group of scientists, including EMBL's Lars Steinmetz, have developed an inexpensive yeast single-cell RNA sequencing (yscRNA-seq) method that is sensitive enough to explore the architecture of RNA transcription in individual yeast cells.

The team's new protocol has significantly reduced the cost of yscRNA-seq to $12 per cell. They used it to measure the expression of genes in clonal yeast populations and to investigate any differences between the cells. The expression levels of cell-cycle and metabolic genes were found to vary the most. These variations gave individual cells a competitive advantage and an increased ability to withstand corresponding environmental challenges.

The scientists believe the new protocol could potentially replace older, conventional RNA-seq techniques. Additionally, it allows microbiologists to answer complex transcriptional questions that the older processes could not, such as the identification of more rarely expressed genes that would be lost in the data of conventional RNA-seq.

Nadal-Ribelles, M, Islam, S, Wei, W, Latorre, P *et al. Nature Microbiology*, 4 February 2019. DOI: 10.1038/s41564-018-0346-9

FULL VERSION ONLINE:
BIT.LY/embl-93-05

Role reversal: RNA controls protein function

EMBL scientists identify RNA regulating protein behaviour in switch of normal roles

BY JOSH TAPLEY

Ribonucleic acids (RNAs) perform many important roles within cells, mainly ensuring that proteins are made in the right quantities at the right times. Usually, the fate of an RNA is controlled by RNA-binding proteins. However, EMBL scientists in the Hentze group have uncovered a counter-example in which the RNA controls the fate of the protein instead.

In human and rodent cells, the molecule vtRNA1-1 regulates the function of the protein p62. This protein plays a key role in autophagy – the 'self-eating' process by which cells recycle their unnecessary or dysfunctional components. These components are broken down into their biological building blocks, such as amino acids, and used to build new structures within the cell. When vtRNA1-1 binds to p62 it prevents autophagy. When a cell is starved of amino acids, less vtRNA1-1 binds to p62 and autophagy increases. This process allows a cell to increase its supply of vital biological construction material when resources are sparse.

Strands of RNA can bind to proteins to prevent the cell from carrying out autophagy – 'self-eating'.

TOBIAS WÜSTEFELD

Horos, R, Büscher, M *et al. Cell*, 14 February 2019. DOI: 10.1016/j.cell.2019.01.030

FULL VERSION ONLINE: BIT.LY/embl-93-06

ATP affects proteome-wide solubility

Scientists develop technology to measure how ATP concentration affects protein solubility in cells

BY JOSH TAPLEY

A collaboration between EMBL Heidelberg's Savitski team and GSK's Cellzome has developed a new technology to study how the concentration of a molecule affects the solubility of individual proteins on a proteome-wide scale. They used Solubility Proteome Profiling (SPP) to show that adenosine triphosphate (ATP) affects the solubility of at least 25% of the solubility-transitioning proteins in mammalian cells.

The researchers discovered that ATP preferentially affects the solubility of proteins that are positively charged, naturally disordered, nucleic acid-binding and part of membraneless organelles. The susceptibility of a protein to solubilise depends on its localisation to the different types of these organelles.

In future studies, SPP could be used to measure how drugs affect protein solubility. This would allow scientists to assess the effectiveness of drugs that aim to dissolve protein aggregates – clumps of misfolded proteins that are associated with diseases such as Alzheimer's or Parkinson's.

Sridharan, S, Kurzawa, N *et al. Nature Communications*, 11 March 2019. DOI: 10.1038/s41467-019-09107-y

FULL VERSION ONLINE: BIT.LY/embl-93-07

Cell death trigger in tuberculosis bacteria

Suicide system in tuberculosis bacteria might hold key to treatment

BY IRIS KRUIJEN

Tuberculosis (TB) is one of the top ten causes of death worldwide. In 2017, 10 million people around the world fell ill with TB and 1.3 million died. The genome of the bacterium that causes TB holds a special toxin–antitoxin (TA) system with spectacular action: once the toxin is activated, all bacterial cells die, stopping the disease. An international research team co-led by the Wilmanns group at EMBL Hamburg investigated this promising feature for therapeutic targets.

When the bacteria are growing normally, the toxin's activity is blocked by the presence of its corresponding antitoxin. But under stress conditions such as lack of nutrients, dedicated enzymes rapidly degrade the antitoxin molecules. This activates the toxin proteins in the cell and slows down the growth of the bacteria, allowing them to survive the stressful environment.

Disrupting the system

One particular TA system has a more drastic effect: in the absence of the antitoxin, the toxin kills the bacteria. As this system holds potential for therapeutic targets, researchers from EMBL Hamburg, the IPBS at the CNRS/Université de Toulouse, and the Francis Crick Institute in London joined forces to study this TA system in more detail.

"Our collaborators in Toulouse were already able to extend the lifetime of mice infected with TB by activating the toxin in a controlled way," says Annabel Parret, EMBL staff scientist in the Wilmanns group, who led the project. "If we find molecules that can disrupt the TA system – and thus trigger cell death – in TB patients, that would be the perfect drug." The team will now screen thousands of small molecules to see if they have this capability. However, the structure of the TA system is so stable that it will be a big challenge to find an entry point where they can go in to break it.

Freire, DM, Gutierrez, C *et al.* *Molecular Cell*, 18 February 2019. DOI: 10.1016/j.molcel.2019.01.028

FULL VERSION ONLINE:
BIT.LY/embl-93-08

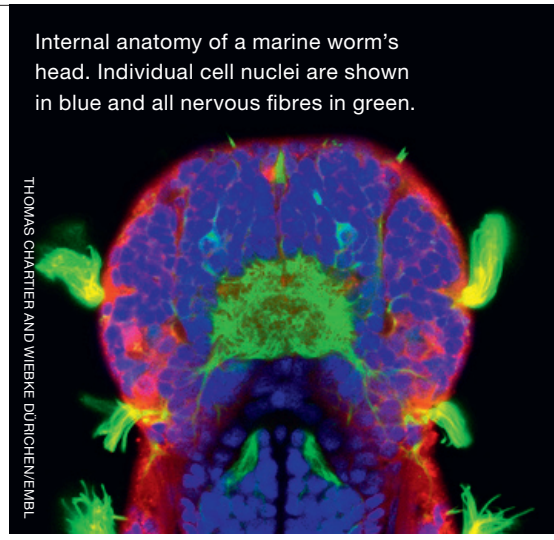
A worm's sense of the world

EMBL researchers discover that four organs in a marine worm's head can sense different chemicals

BY EMMA STEER

We sense the world around us using primarily our eyes, ears and nose. Marine worms, on the other hand, have long been thought to understand the world very differently – primarily by detecting chemicals in the ocean water that surrounds them. Now, researchers in the Arendt group have recorded nerve cell activity in the head of the marine worm *Platynereis dumerilii*. The worm's small size and transparency mean that all of the nerves and neurons within the head can be imaged at once. They found that cells located in four particular areas of the head reacted when the worms were exposed to different chemicals.

Alcohols, sugars, amino acids and an ester that smells like pears were tested. The group identified these four areas of the head as the worm's chemosensory organs, capable of detecting different chemicals in the surrounding environment. The worm's antennae could detect each chemical equally well, whereas three other organs responded to each chemical differently.



Internal anatomy of a marine worm's head. Individual cell nuclei are shown in blue and all nervous fibres in green.

THOMAS CHARTIER AND WIEBKE DÜRICHEN/EMBL

Chartier, TF *et al.* *Open Biology*, 31 October 2018. DOI: 10.1098/rsob.180139

FULL VERSION ONLINE:
BIT.LY/embl-93-09

Many gut microbes may originate in the mouth

Even in healthy people, many oral microbes traverse the gastrointestinal tract and colonise the gut

BY JOSH TAPLEY

A collaboration involving EMBL scientists has identified many shared microbial strains in saliva and stool samples from several hundred people across three continents. The research shows that the barrier between oral and gut microbiomes is weaker than expected and highlights evidence of oral–gut transmission of several microbes thought to play direct roles in the progression of colorectal cancer.

The scientists found that, although patients suffering from colorectal cancer or rheumatoid arthritis did indeed show higher levels of oral–gut transmission, it is actually very common in healthy people too. Scientists must now assess whether interventions in the oral microbial community could impact the gut microbiome and its effects on human health.

Schmidt, TSB, Hayward, MR *et al.* *eLife*, 12 February 2019. DOI: 10.7554/eLife.42693

FULL VERSION ONLINE: BIT.LY/embl-93-10

Using light to stop itch

Itch is easily one of the most annoying sensations. For chronic skin diseases like eczema, it's a major symptom

BY IRIS KRUIJEN

The specialised nerve cells that sense itch are located in the upper surface of the skin. Linda Nocchi, Paul Heppenstall and colleagues at EMBL Rome have developed a light-sensitive chemical that binds only to those cells. When the affected area of a mouse's skin is injected with the chemical and then illuminated with near-infrared light, the itch-sensing cells withdraw from the skin. This stops the itch and allows the skin to heal. "We hope that one day our method will be able to help humans suffering from a disease like eczema, which causes chronic itching," says Heppenstall.

Nocchi, L *et al. Nature Biomedical Engineering*, 17 December 2018. DOI: 10.1038/s41551-018-0328-5

FULL VERSION ONLINE: BIT.LY/embl-93-11

Genomes of all known UK species to be sequenced

The genomes of 66,000 UK species are to be sequenced as part of a global effort to sequence all known eukaryotic species on Earth

BY GEORGIA HINGSTON

The genetic code of 66,000 UK species will be sequenced by the Wellcome Sanger Institute in a major collaboration with EMBL-EBI and other partner organisations as part of the Earth BioGenome Project, a global effort to sequence all 1.5 million known species of animals, plants, protozoa and fungi on Earth.

The project – the UK contribution to which is known as the Darwin Tree of Life Project – launched on 1 November 2018. Once the genomes are sequenced, EMBL-EBI will assist in annotating them and assessing how the data can be stored and accessed. The project will create a new foundation to drive solutions for preserving biodiversity and sustaining human societies.

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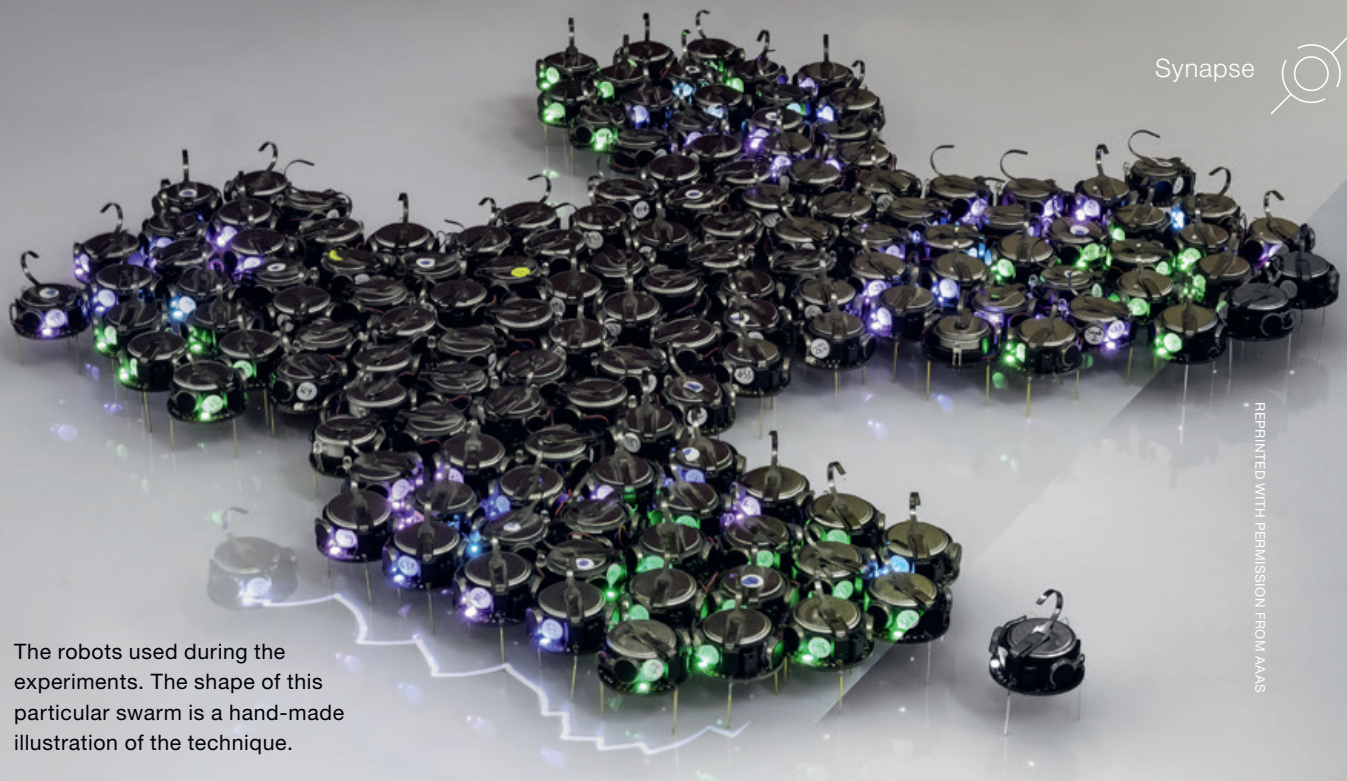

The robots used during the experiments. The shape of this particular swarm is a hand-made illustration of the technique.

Hundreds of tiny robots grow bio-inspired shapes

Scientists build self-organising features into robot swarms to study shape formation

BY IRIS KRUIJEN

Hundreds of small robots can work in a team to create biology-inspired shapes, purely based on local communication and movement. To achieve this, researchers from EMBL, the Centre for Genomic Regulation (CRG), and Bristol Robotics Laboratory introduced the biological principles of self-organisation to swarm robotics.

The only information that the team installed in the coin-sized robots involved basic rules on how to interact with their neighbours. In fact, they specifically programmed the robots in the swarm to act similarly to cells in a tissue. Those 'genetic' rules mimic the system responsible for the Turing patterns we see in nature, like the arrangement of fingers on a hand or the spots on a leopard. In this way, the project brings together two of the fascinations of British scientist Alan Turing: computer science and pattern formation in biology.

Turing's rules

The swarm forms various shapes by relocating robots from areas with low morphogen concentration (morphogens are virtual molecules that carry the patterning information) to areas with high morphogen concentration – called 'Turing spots'. This leads to the growth of protrusions reaching out from the swarm. "It's beautiful to watch the swarm grow into shapes – it looks quite organic. What's fascinating is that there is no master plan; these shapes emerge as a result of simple interactions between the robots," says Sabine Hauert from the University of Bristol.

While inspiration was taken from nature to grow the swarm shapes, the ultimate goal is to make large robot swarms for real-world applications. Imagine hundreds or thousands of tiny robots growing shapes to explore a disaster environment after an earthquake or fire, or sculpting themselves into a dynamic 3D structure such as a temporary bridge that could automatically adjust its size and shape to fit any building or terrain. However, there is still a long way to go before we see such swarms outside the laboratory.

Slavkov, I, Carillo-Zapata, D *et al.* *Science Robotics*, 19 December 2018. DOI: 10.1126/scirobotics.aau9178

FULL VERSION ONLINE:
BIT.LY/embl-93-13

Foundation stone laid for EMBL Imaging Centre

The foundation stone ceremony for the EMBL Imaging Centre took place on 1 April 2019.

EMBL

A foundation stone ceremony has been held for the new EMBL Imaging Centre, located on EMBL's Heidelberg campus

BY MATHIAS JÄGER

The new EMBL Imaging Centre, to open in 2021, will give researchers access to the most modern microscopy technologies available. "EMBL was set up in order to promote molecular biology across Europe, and to be a centre of excellence for Europe's leading young molecular biologists," says EMBL Director General Edith Heard. "Training, technology development and providing services to scientists are key aspects of EMBL's missions. The new EMBL Imaging Centre embodies these missions and extends them to users across Europe and from around the world."

Open to visitors

The centre will be for state-of-the-art high and ultra-high resolution electron and light microscopy techniques, including new developments not yet commercially available. It will be open to visiting researchers from all over the world. This means EMBL's expertise in imaging technologies and data analysis will pass on to other locations, promoting scientific discovery in EMBL's member states and beyond.

An interactive exhibition is also planned, which will be housed in the openly accessible part of the building. The exhibition will allow the public to get insights into molecular biology and the power of imaging technologies, as well as how the research done at EMBL affects everyday life.

A large collaboration

The EMBL Imaging Centre is made possible by a collaboration between the German Federal Ministry of Education and Research (BMBF), the State of Baden-Württemberg (MWK), and EMBL, and by contributions from industry partners (Thermo Fisher Scientific, Leica, ZEISS), and donations from the Boehringer Ingelheim Foundation and HeidelbergCement.

The foundation stone ceremony on 1 April was opened with a speech from EMBL Director General Edith Heard, followed by speeches from state secretary Christian Luft (BMBF); Baden-Württemberg's State Minister for Science, Research and the Arts, Theresia Bauer; the president of Leica, Markus Lusser; the Chairman of the Managing Board of HeidelbergCement, Dr Bernd Scheifele; and by Dr Jan Ellenberg, project leader for the EMBL Imaging Centre and head of EMBL's Cell Biology and Biophysics Unit.

FULL VERSION ONLINE:
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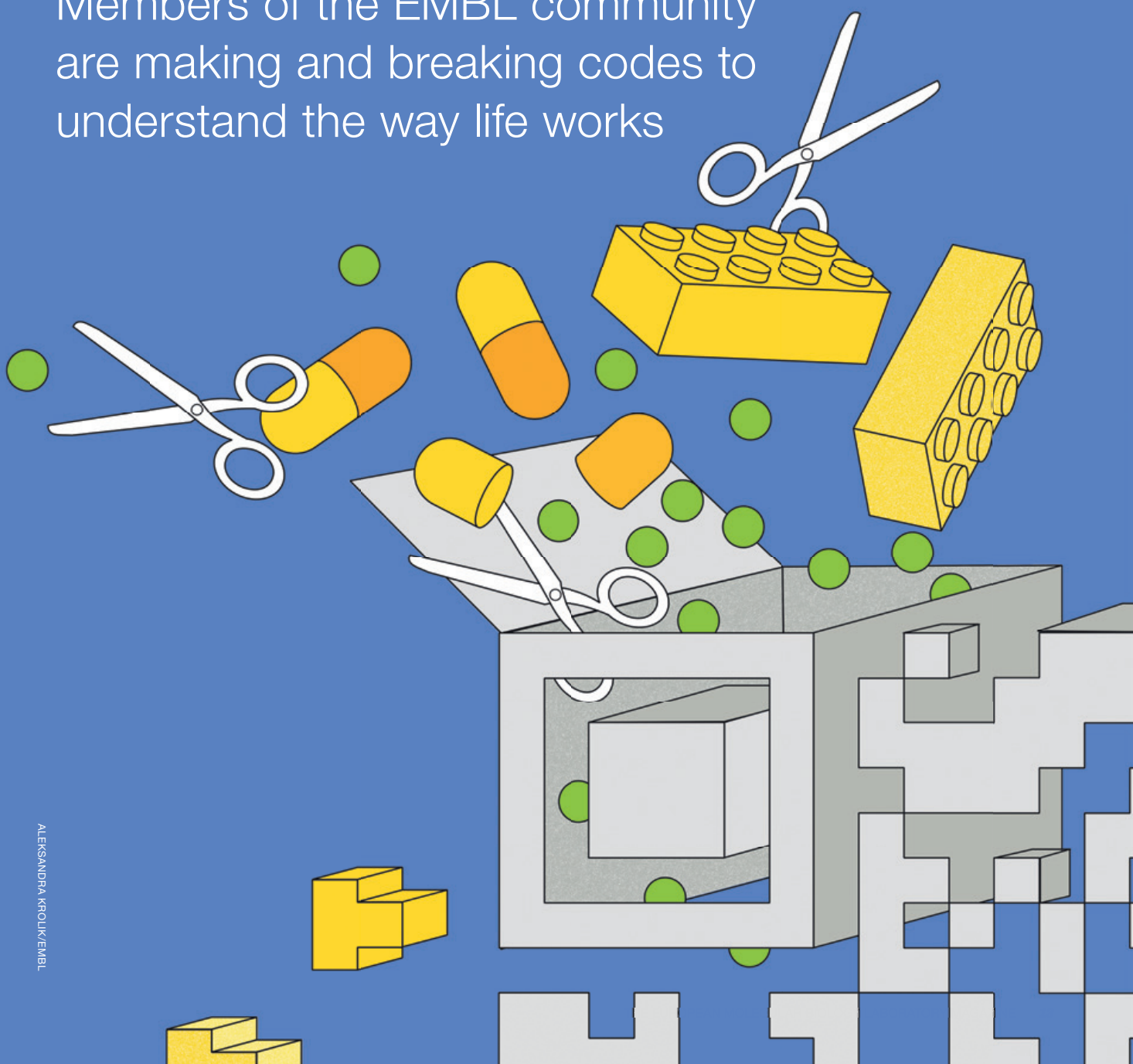
Codemaking, codebreaking

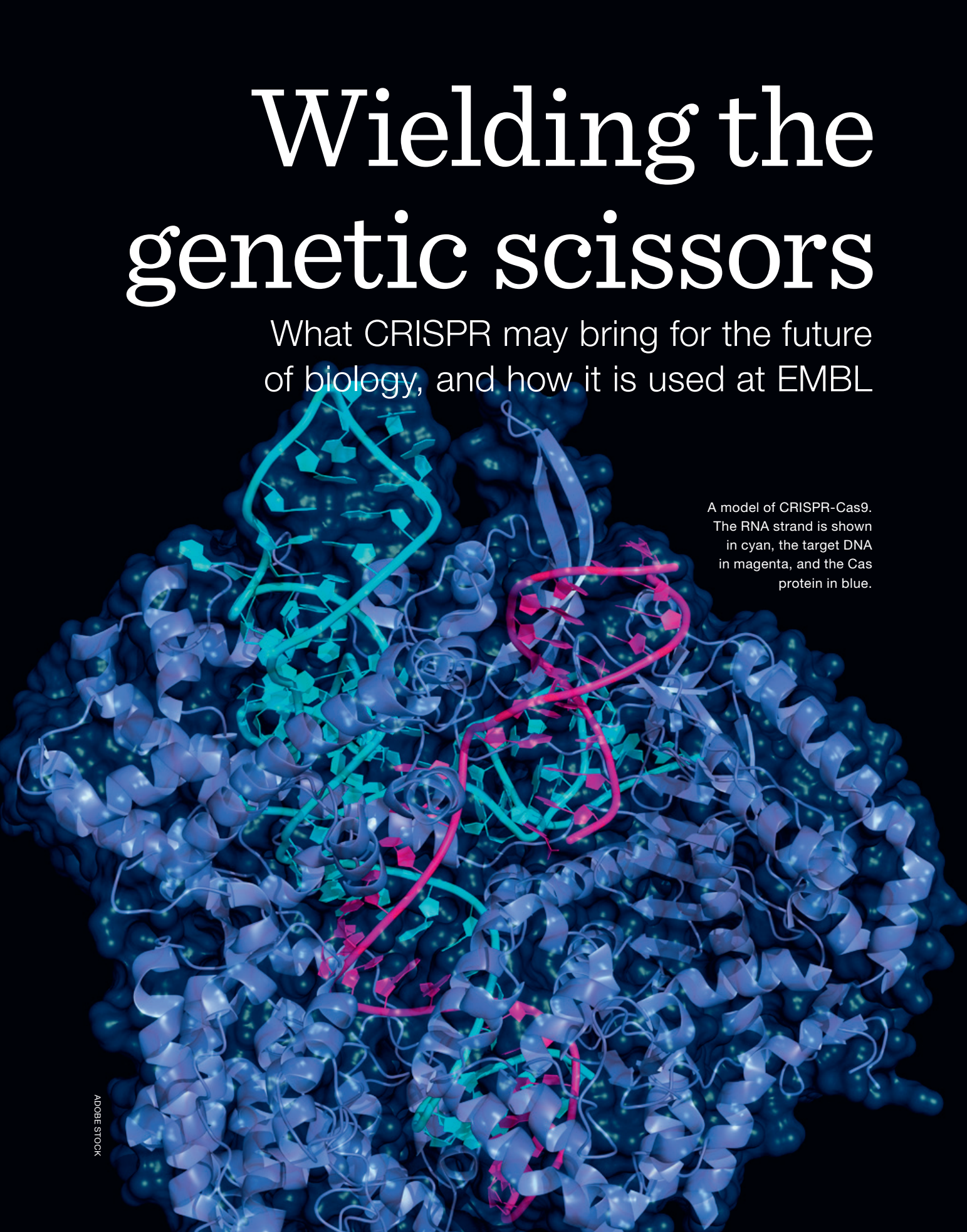
Members of the EMBL community are making and breaking codes to understand the way life works



ALEKSANDRA KROLIK/EMBL

Wielding the genetic scissors

What CRISPR may bring for the future of biology, and how it is used at EMBL



A model of CRISPR-Cas9. The RNA strand is shown in cyan, the target DNA in magenta, and the Cas protein in blue.

ADOBE STOCK

BY FABIAN OSWALD

One of the most popular metaphors used to describe CRISPR-Cas9 – often referred to simply as 'CRISPR' – is that of a pair of genetic scissors: a cut-and-paste tool at the molecular level. Based on an ancient bacterial defence mechanism, its enormous potential for gene editing has only been discovered during the last decade and has revolutionised biology. CRISPR is built from an individually designed RNA strand and a DNA-cutting protein, Cas9 (see infographic, p. 19). Three important qualities make this tool invaluable for the life sciences: it is cheap, easy to use and very precise. With CRISPR it's possible to target any known DNA region and deactivate a gene or introduce a new one. From medical therapy to fundamental research, CRISPR has a large range of applications and is used by research groups at EMBL to address important questions in biology.

Investigating synergy between cancer cells

To what extent do mutations in cancer cells interact with one another? That's one of the questions that EMBL's Korbel group is trying to answer using CRISPR. "This is the principle of epistasis. In other words, we want to know whether one mutation in cancer can affect another mutation and if there is synergy between them," says group leader Jan Korbel. This is done by using cell lines originating from the same donor, but with different gene mutations. By deactivating a gene using CRISPR, the scientists can observe how this affects other genes.

"We also reconstruct fairly large-scale rearrangements in the genome that we have previously predicted to have a functional effect," says Korbel. "Here we use the gene scissors to break the genome and remake it. The attempt is to repeat what we have observed in a disease. We make these rearrangements and anticipate a functional effect on gene expression."

Studying CRISPR's side-effects

CRISPR is a very versatile tool and can be used in all types of organisms, from yeast to mammalian cells. EMBL's Steinmetz group use this flexibility to their advantage. "We do a fairly broad coverage of the CRISPR-Cas 9 landscape," says group leader Lars Steinmetz. "We use it to study natural variants, to do genetic screens, and we think about how it could be used more safely for therapeutic editing applications."

The Steinmetz group studies the impact of single-nucleotide polymorphisms (SNPs) on phenotypes – that is, an organism's observable characteristics. SNPs are cases where a single DNA base has been substituted for another – a T instead of a C, for example – at a specific location in the genome. SNPs can have biomedical effects, such as increasing susceptibility to certain diseases or affecting the body's response to treatment. To study the effects of SNPs on an organism, the Steinmetz group carry out large-scale experiments. "CRISPR enables us to do that with high efficiency. We developed an approach >>

MARIETTA SCHUPP/EMBL

Jan Korbel, Senior Scientist and Co-Director of the Molecular Medicine Partnership Unit.


MARIETTA SCHUPP/EMBL

Lars Steinmetz, Senior Scientist and Director of the Stanford | EMBL Life Science Alliance.

>> where we can engineer 10,000 to 100,000 different SNP variants in genomes of yeast," says Steinmetz. One goal of the project is to improve the methodology of CRISPR editing by increasing the efficiency of DNA repair at the cut site. This makes it more probable to get the desired edit.

Another project in the Steinmetz group involves research on off-target edits – unwanted side-effects of CRISPR gene editing. At the stage when a mouse embryo consists of only two cells, they modify one of these cells using one of several different CRISPR editing techniques that are under investigation. The genomes of the cell populations derived from these two cells are then compared. This makes it possible to determine which mutations are natural background mutations and which are caused by off-target edits. The number of off-target effects reveals the accuracy of different editing methods and makes it possible for the researchers to start finding ways to improve them.

Fruit flies for science

The fruit fly – *Drosophila melanogaster* – remains a model organism of choice for biological research, and is widely used at EMBL. Alessandra Reversi, a research technician in the Ephrussi group, provides gene-editing services in fruit flies, creating genetically modified strains for scientists across EMBL.

"Using CRISPR is the best strategy for genome editing," says Reversi. "The advantage of CRISPR is that you can now modify the *Drosophila* genome with even single-nucleotide precision. Compared with previous strategies, editing the fruit fly genome with CRISPR is more precise, and much easier, faster and cheaper. With this technique, scientists no longer need to perform time-consuming screens in order to identify flies with the desired modifications."

Fruit flies are not the only organisms for which EMBL provides gene-editing services. EMBL Rome has a Gene Editing and Embryology Facility that uses CRISPR to provide the whole of EMBL with gene-editing services in mice.

Editing the epigenome

A relatively unusual application of CRISPR is epigenetic editing, which is being carried out in EMBL Rome's Hackett group by postdoc Cristina Policarpi and PhD student Valentina Carlini. Epigenetics refers to the chemical


LYUDMILA DIMITROVA-PATERNOGA/EMBL

EMBL Research Technician Alessandra Reversi.

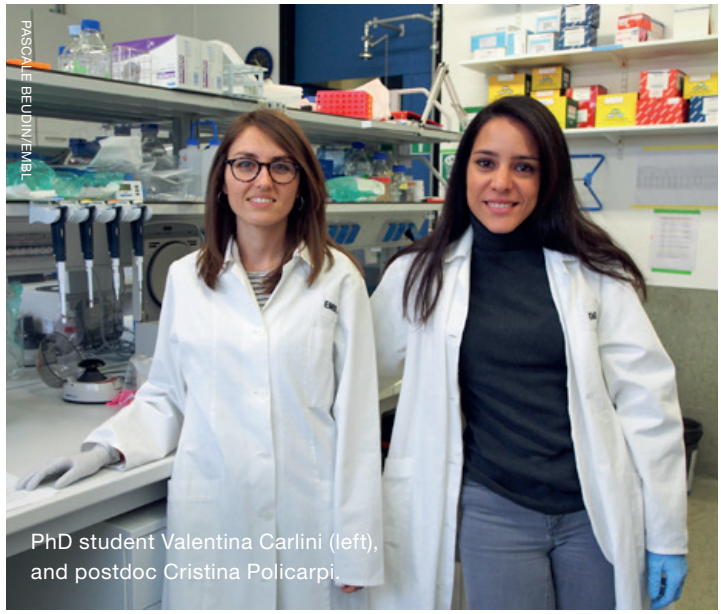
changes that affect gene expression without actually altering the DNA sequence. One key type of epigenetic change is DNA methylation – the addition to the DNA molecule of a chemical group containing one carbon atom and three hydrogen atoms. Other types of epigenetic change involve chemical modifications of histones – the proteins around which our DNA is wrapped.

The Cas9 proteins used in Policarpi and Carlini's research have been modified so that they are unable to cut DNA: instead, they recruit other proteins. These recruited proteins then alter the epigenome through DNA methylation or histone modifications. "The main goal of the project is to understand how all these epigenetic marks contribute towards gene expression and genome organisation," says Policarpi. "We add or remove epigenetic marks only in small parts of the genome and we don't touch anything else, so we're sure that we're studying only the contribution of those marks to gene expression and regulation."

In another project in the Hackett group, CRISPR is used to knock out single genes in a pool of mouse cells – a different gene in each cell, until the 20,000 genes in the mouse genome have been covered. This makes it possible to study the effects of the absence of any gene on a phenotype of interest. An experiment on such a large scale is only possible with a tool like CRISPR. Policarpi has to laugh: "Otherwise you would spend your whole life and that of your children and grandchildren in the lab!"

What lies ahead

There are still problems to overcome in the use of CRISPR. "The main concerns are editing at high efficiency and the issue of on-target editing accuracy," says Steinmetz. "You have to worry about off-target effects: apart from what I wanted to achieve, what else did I do to the cell by manipulating the system and introducing a new enzyme? These concerns get really important when you want to go into any form of therapeutic application."


PASCALE BEUCHAT/EMBL

PhD student Valentina Carlini (left), and postdoc Cristina Policarpi.

"You have to worry about off-target effects"

Political and public concerns focus mostly on germline gene editing with CRISPR, where genes are edited so early in an organism's development that the changes are copied into all future cells, including sperm and egg cells. This means the edited genes will be passed on to future generations. These concerns have spiked since the case in November 2018 in which Chinese researcher He Jiankui claimed to have edited the genomes of two human embryos, using CRISPR to introduce a gene that would increase HIV resistance. This action was widely condemned by the scientific community as an experiment on humans that could have potential off-target effects, while its benefits remain questionable.

"There's of course a huge ethical debate about whether one should do germline editing in humans," explains Korbel. "My standpoint and EMBL's standpoint is that this should not be done. Introducing changes into a human being before he or she is born creates a huge >>


CARRIE TANG

Ewan Birney, Director of EMBL-EBI, Joint Head of Research and Senior Scientist.

>> issue of consent, as these mutations would remain in the germline for future generations, with consequences that are not clear. My position would be to have a moratorium for some years to come, to better understand the rates of errors that are introduced during gene editing with CRISPR, and to have a full ethical discussion."

Regulations and expectations

Ewan Birney, director of EMBL's European Bioinformatics Institute (EMBL-EBI), agrees that this type of science should be closely regulated. He points out that, in many countries, couples who carry a serious genetic disease and who are conceiving by *in vitro* fertilisation (IVF) can choose to implant only those embryos that do not carry the disease. This procedure is called pre-implantation genetic diagnosis, and is subject to strong national regulation. "The CRISPR approach would add an extra step of introducing CRISPR technology at the first-cell stage," Birney explains. "This would be followed by screening for a successful edit. Although this is technically possible, there are currently virtually no serious genetic diseases where pre-implantation diagnosis would not work but CRISPR would."

Birney highlights that society must be able to trust in legislation to guarantee the ethical use of a new technology like CRISPR. "In the UK, the Human Fertilisation and Embryology Authority provides regulation enshrined in UK law in this area. Other countries in Europe have analogous legislation and regulation. This allows new technologies, such as mitochondrial donation [see pp. 50–51], to be developed in a way that is medically safe, scientifically and ethically sound, and supported by society."

One problem of national regulation is that technology is advancing at a rapid pace and political decisions are not keeping up. "The legal framework in Germany is fairly old," says Korbel. "The Embryonenschutzgesetz, the embryo protection law, was written prior to the discovery of CRISPR, so the set of techniques and tools that scientists now have in their hands is way beyond what the legislators anticipated. That implies that the law should be reviewed."

While the prospect of eugenics or designer babies in the near future is unsettling, CRISPR itself is only a tool and therefore its effects depend on how responsibly – or otherwise – it is used. "There is still the potential to fix thousands of mutations that affect somatic cells in the human body. These diseases could be eliminated or prevented before they occur," says Steinmetz. "It's fascinating how this technology can work across systems, in a mammalian cell as well as in yeast or bacteria. The potential is enormous and I have no doubt that it's going to change the way we think about our healthcare, the kind of food we eat, the way we live."

If you are a journalist and wish to arrange an interview with any of the scientists featured in this article, please contact: pressoffice@embl.de

READ ONLINE:
BIT.LY/embl-93-15

READ EWAN BIRNEY'S BLOG POST ON THE ETHICS OF CRISPR:
BIT.LY/embl-93-15a

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

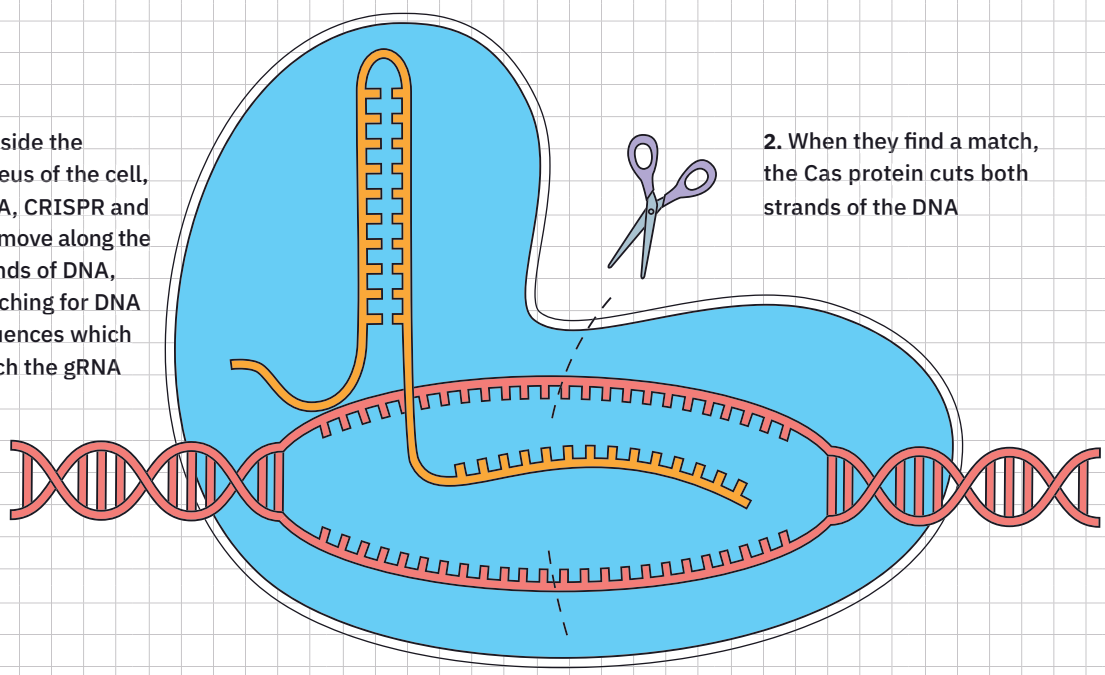
DNA Base – a natural building block which makes up DNA

Cas – a protein which can cut DNA

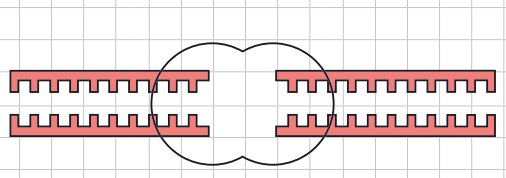
CRISPR – a strand of RNA, copied from a matching region of bacterial DNA and folded into a hairpin bend

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

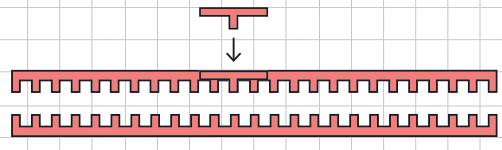


3. Changes to the DNA can be made at the site of the cut



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

Programming: language

How computer processing of human language is harnessed by EMBL scientists

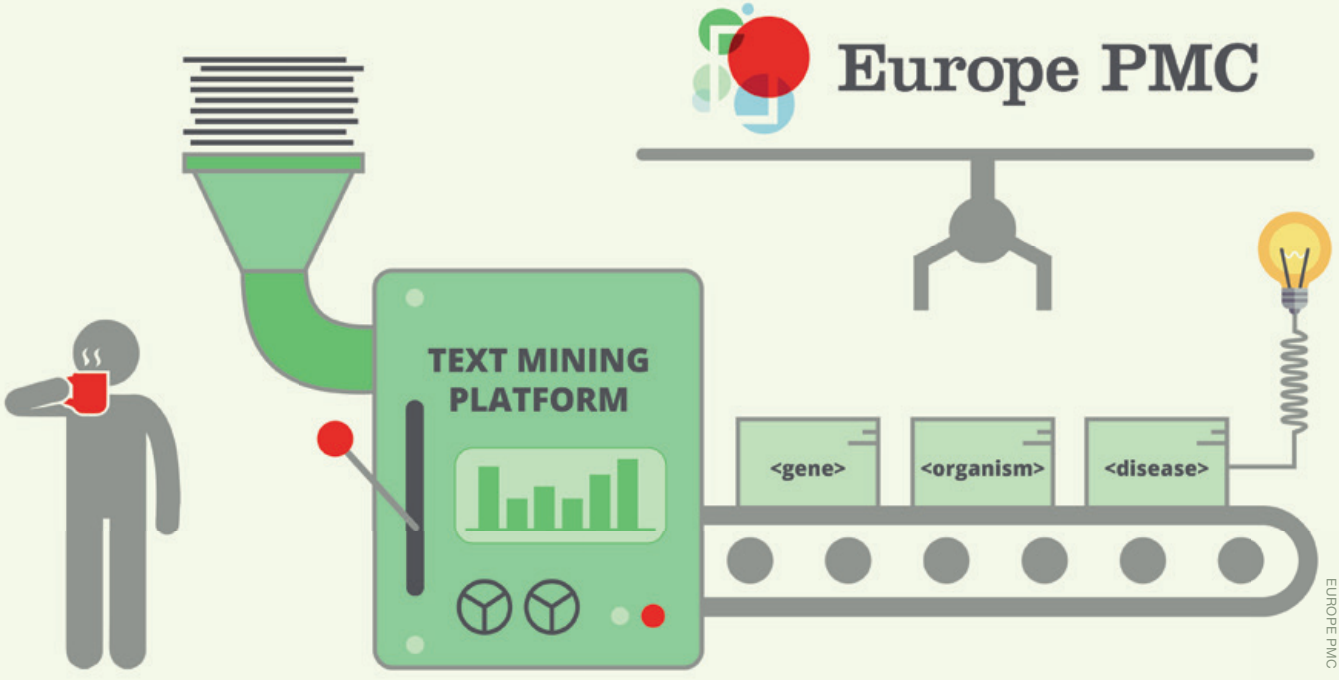
BY JOSH TAPLEY

Text mining technology at Europe PMC speeds up scientific discovery by identifying key elements from large collections of text.

"We have 35 million records; that's about seven times the size of English Wikipedia," says Maria Levchenko, community manager at Europe PMC. "We're in a very good position to utilise text mining."

Hosted by EMBL's European Bioinformatics Institute (EMBL-EBI), Europe PMC is a database for life science literature. It aims to provide free, worldwide access to scientific research. To handle its vast collection of textual data, Europe PMC is one of the increasing number of organisations capitalising on the technological gold rush of text mining: using computer software to comb through existing text and extract new knowledge.

One of Europe PMC's main goals is to use text mining to accelerate scientific discovery.



"You could be researching genes, proteins or organisms, and with our tool SciLite [scientific highlighter] you can see them at a glance," says Levchenko. "We also link publications to data so it's easy to go from one to the other." These tools help scientists generate new insights from existing research, without spending the many lifetimes it would take to read all of the relevant scientific publications themselves.

Europe PMC is also a key contributor to Open Targets – a collaboration between industrial and academic institutions uncovering new links between genes and diseases (see p. 41). By combining genetic theory and text mining, Open Targets hopes to identify genes that could be potential targets for new disease treatments. "It's a public–private partnership," says Levchenko. "It's companies working together to make discoveries happen, and the lion's share of its new gene–disease associations comes from text mining here at Europe PMC."

A word cloud produced by mining the text in this issue of *EMBLetc.* By displaying more frequently used words at larger sizes, we can quickly learn about the content of the magazine and about EMBL as an organisation.

Reading between the lines

However, handling scientific publications presents a unique set of challenges. "Biology literature can be very messy from a text mining standpoint," says Xiao Yang, Europe PMC's text mining specialist. "There are lots of abbreviations, acronyms and big, ambiguous words." Context is also important. "The same gene in *Drosophila* and humans has the same name," says Levchenko, "but you often need to distinguish between these two very different things."

There is also more to finding new gene–disease associations at Open Targets than just searching publications for mentions of genes and diseases. For example, when analysing "Gene A does not cause disease B", the computer must be able to tell that the relationship is negative. In order for Europe PMC to overcome these challenges, their computers need a deeper understanding of how we communicate.

"Human language is ambiguous, fuzzy and imprecise," says Katja Ovchinnikova, a natural language processing (NLP) expert at EMBL Heidelberg. NLP is the area of computer science that translates the meaning behind our natural language – how we typically speak to one another – into a form that computers can understand and use. It often involves the use of machine learning algorithms that give a computer an 'intuition' for language, like a child learning their mother tongue. "You don't say to children, 'These words mean the same thing, these words mean opposite things,'" says Ovchinnikova. "They just listen to speech and pick it up." Like children, the computers used by modern biologists learn how to understand our language by experiencing a million conversations.

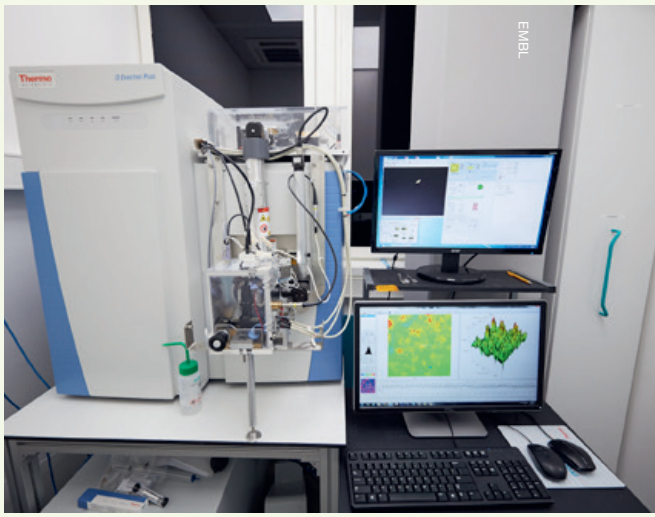
Fluent microbe

The cornerstone of NLP is identifying how different words are related. One way to do this is by studying word context: which other words does a word often appear close to? Strings of words that appear together often enough to provide more information about a text than the individual words separately are called *n*-grams. For example, 'New York City', a 3-gram, tells you more about the locations of apartments in a database than its individual words.

>>

>> n-grams can even be applied beyond conventional words. The Iqbal group at EMBL-EBI use n-grams – known as k-mers in computational biology – in their search engine Bitsliced Genomic Signature Index (BIGSI). BIGSI substitutes microbial genetics for human language, using genes as k-mers and their nucleotides as words. Seeing a gene for antibiotic resistance as a k-mer of its nucleotides and searching for it with BIGSI quickly shows you all of the datasets and species in which this gene has been reported before.

The big challenge when switching from human to genetic language is that new microbial genomes often contain new 'languages' that have never been seen before. BIGSI, unlike many NLP technologies associated with human language, was therefore developed with an emphasis on scalability to rapidly expanding vocabularies.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MALDI-IMS technology in the lab.

Beyond language

But why stop at words and letters? "Any sort of input can be handled with the same computer science," says Ovchinnikova. She and the Alexandrov team at EMBL Heidelberg are using NLP algorithms to extract knowledge from a large-scale community knowledge base for spatial metabolomics called METASPACE.

METASPACE contains spatial maps of the metabolites in many types of tissue. Metabolites are small molecules that are used by cells to steer their internal processes such as energy production, anti-tumour activity or intracellular communication. Hundreds of scientists from around the world use METASPACE to share the metabolomics data they produce using MALDI imaging mass spectrometry (MALDI-IMS).

MALDI-IMS data represent a tissue as a 2D grid of pixels, each about the size of a typical cell. A laser is used to release molecules from the area of tissue corresponding to each pixel. These molecules are then sucked into a mass spectrometer and analysed. The resulting mass spectra reveal which molecules were present in each pixel.

Making sense of MALDI-IMS data can be a challenge. However, the team has found that the NLP algorithm Word2Vec, originally developed at Google to measure the relationships between words, is surprisingly


JOSH TAPLEY/EMBL

A representation of a network of connected elements such as words or metabolites. Stronger relationships can be represented by shorter distances between elements or thicker lines connecting them.

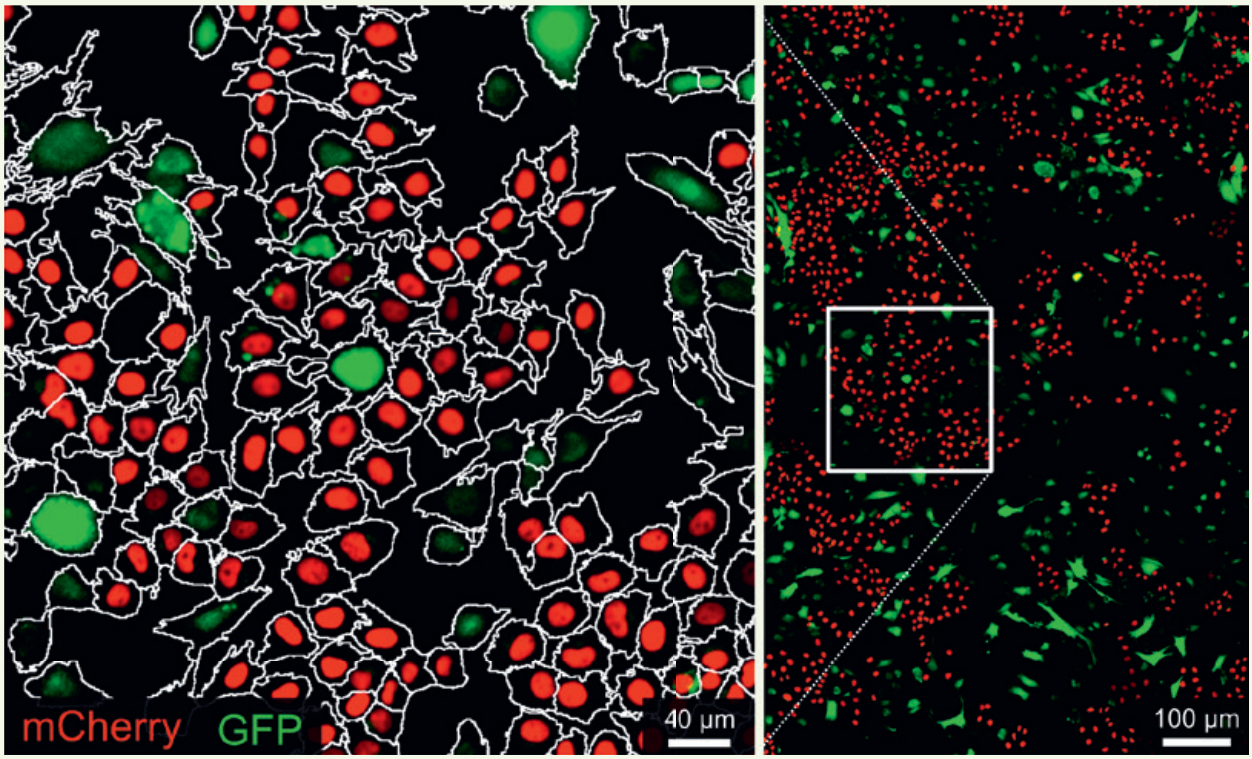

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Illustration of the spatial heterogeneity of two types of co-cultured cells. The Alexandrov team uses MALDI-IMS to look at the metabolites in each cell and predict which cell is of which type.

well suited for mining the terabytes of data in METASPACE. Analysing spatial metabolomics data, it turns out, has a key similarity with analysing textual data: both aim to find patterns in datasets full of a large number of related but spatially distributed objects.

Cell.txt

Word2Vec uses a sliding 'window' that moves across a body of text and records which words are often found close together. "If two words occur in the same window, they are said to occur in the same context," says group leader Theodore Alexandrov. "If words often occur in the same context, they are related."

The algorithm has proved adaptable to a wide range of research topics. "We're modelling a cell as a text document and a metabolite as a word in this document. We want to find functionally related metabolites, so we're applying Word2Vec to the 2D spatial context of metabolites seen in the MALDI-IMS data."

Metabolites that are identified together when a cell performs a particular task could be a part of, or related to, the same reaction or metabolic pathway. Cancer cells, for example, have their metabolisms reprogrammed and accumulate particular metabolites, sometimes called 'oncometabolites', that are remarkably different from those found in healthy cells. The team aims to use the data from METASPACE to build a Word2Vec-powered network of metabolite relationships. By looking at which metabolites are related to known oncometabolites, this network will hopefully allow scientists to identify new ones not yet associated with cancer.

Research like this has great potential for other applications in the clinic. But the current focus for Alexandrov and Ovchinnikova is to explore how combining NLP algorithms with biological techniques can help answer fundamental research questions. Indeed, these algorithms – and the computing power that drives them – are helping researchers throughout EMBL to take the science designed to help computers make sense of language and use it to deepen our understanding of biology.

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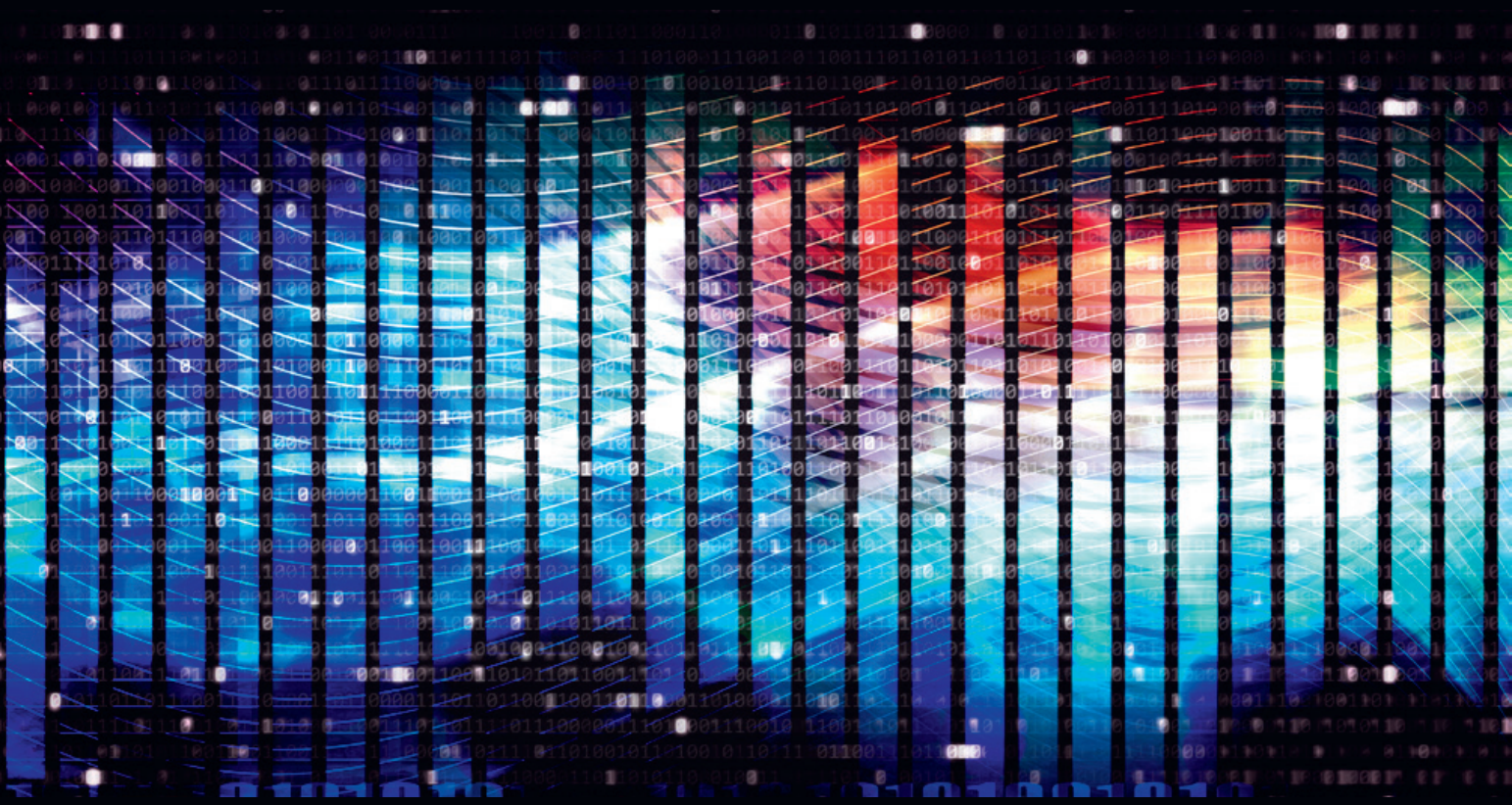

How coding opens up scientific data

The increasing importance of code in the biological sciences

SPENCER PHILLIPS/EMBL

BY GEORGIA HINGSTON

Ask most people how scientific discoveries happen and they will probably describe a scientist wearing a white coat, working in a lab with microscopes, pipettes and the odd animal model. While lots of biological research is still carried out in this kind of environment, the role of coding in biology is becoming just as important as traditional wet-lab science. Bioinformatics allows researchers to analyse vast datasets and track trends or discrepancies in the data in a way that has never been possible before. As the size and diversity of data grow every day, so the tools we develop to analyse the data become more robust and more useful.

Developing algorithms and application programming interfaces (APIs), which help scientists spot such trends, also plays a key role in bioinformatics research. Here, we explore a few examples of how coding, algorithms and APIs open up scientific data and drive new biological discoveries.

Coding can predict cancer development

Moritz Gerstung is a group leader in cancer data science research at EMBL's European Bioinformatics Institute (EMBL-EBI). He and his team use code in their work every day to analyse genetic data. Their aim is to understand different types of cancer and, ultimately, help develop improved treatments and cures.

"The human genome is so large – 3 billion base pairs long – it's 20 times the Encyclopædia Britannica," explains Gerstung. "As researchers, we need to identify the specific sites in the genome that are mutated in cancer cells. That's just a tiny fraction of the whole genome – about 0.0002%. We need computational methods to enable us to find these variants; we can't just point to them manually. And when we ask the more specific question, 'Are the variants that we're seeing truly causing cancer?', it's code that can help us find the answers by looking at not just one, but many hundreds or thousands of genomes. Comparing genomes and finding regions that are recurrently mutated across many cancers is a good indication that a certain part of the genome is driving cancer development."


Moritz Gerstung.

MARY TODD BERGMAN/EMBL

"This may open a window of opportunity for early cancer diagnosis"

Collaborating with the Wellcome Sanger Institute, the University of Cambridge and other international organisations, Gerstung and his team discovered that it's possible to identify people at high risk of developing acute myeloid leukaemia (AML), an aggressive blood cancer, years before the disease develops.

"What we have shown is that many of the genetic aberrations you find in AML are actually occurring a decade or more before diagnosis, which was previously totally unobserved," says Gerstung.

By analysing data and a large number of blood samples from the European >>

JON MOULD

Oliver Stegle.

"Now we can analyse everything in one go"

>> Prospective Investigation into Cancer and Nutrition (EPIC) study, Gerstung's team was able to discover a pattern of genetic changes that happen long before AML appears in an individual, and which differs from the typical mutations seen in the natural ageing process.

"We have indications that this genetic lag may also be found in other types of cancers," says Gerstung, "and this insight may open a window of opportunity for early cancer diagnosis."

Algorithms show us who we are

It can be a long and complex process to understand the relationships between our genome, environmental factors such as air quality or geographical location, and phenotypic expression – that is, our observable characteristics such as eye colour or height. Until recently, scientists had to come up with a very specific hypothesis to reach a conclusion about how just one environmental factor interacts with genetic variables and impacts our phenotypes.

Now Oliver Stegle and his group, who study statistical genomics and systems genetics, have developed an algorithm that enables researchers to simultaneously use hundreds of environmental factors to understand genotype–phenotype relationships.

"Now we can analyse everything in one go," says Stegle, "meaning we can find and identify interplays between genomes, environment and phenotype in a comprehensive manner."

The algorithm, called the structured linear mixed model (StructLMM), can be applied to human datasets to, among other things, provide a finer characterisation of high-risk groups for certain diseases, and to help identify the most relevant environmental factors.

In the future, this method will offer a more comprehensive way of incorporating environmental influences into genetics studies, and will also increase the number of discoveries of variants whose function depends on environment or lifestyle.

Accessing vital information

EMBL-EBI freely provides more than 200 biological databases to researchers worldwide, and received approximately 58 million data requests per day in 2018. With both the volume of biological data and the number of requests rapidly increasing, algorithms are not only essential for analysing scientific data, but also for accessing it.

Youngmi Park, a software engineer and Project Lead in the web production team at EMBL-EBI, developed EBI Search, a full-text search engine application programming interface (API), which allows researchers to rapidly

GEORGIA HINGSTON/EMBL

Youngmi Park.

access relevant data held in EMBL-EBI databases with minimal programming or at the touch of a button. An API is an interface that delivers a request to a source, like a waiter in a restaurant taking your order to the kitchen, and brings back the requested information, like the waiter bringing food to your table.

"Scientists can continue focusing on the quality of data"

"EBI Search equips users with a tool that allows them to search through vast amounts of data," says Park, who is also one of the four team members dedicated to maintaining and developing the API. "The resources [databases] are then enabled to present the data in a way that is beneficial and customised to their users."

Many of EMBL-EBI's data resources, including Ensembl Genomes and RNAcentral, have integrated Park's central Search API directly into their systems.

"This is a good strategy for everyone," says Park. "It allows scientists working on the data resources to spend more time developing other useful tools for their users and to focus on curating data. By applying the EBI Search API to data resources, our scientists can continue focusing on the quality of data rather than the running of software systems, all while users are able to access relevant research data in a single search."

Not only can EBI Search retrieve requested data, it can also cross-reference information between EMBL-EBI data resources. For example, when a scientist looks up a specific gene in Ensembl – a genome data resource – EBI Search is able to cross-reference that gene with relevant protein sequences, chemical structures, and scientific literature references. Such tools ultimately enable an increased pace of research, providing researchers around the world with rapid access to the biological data they need.

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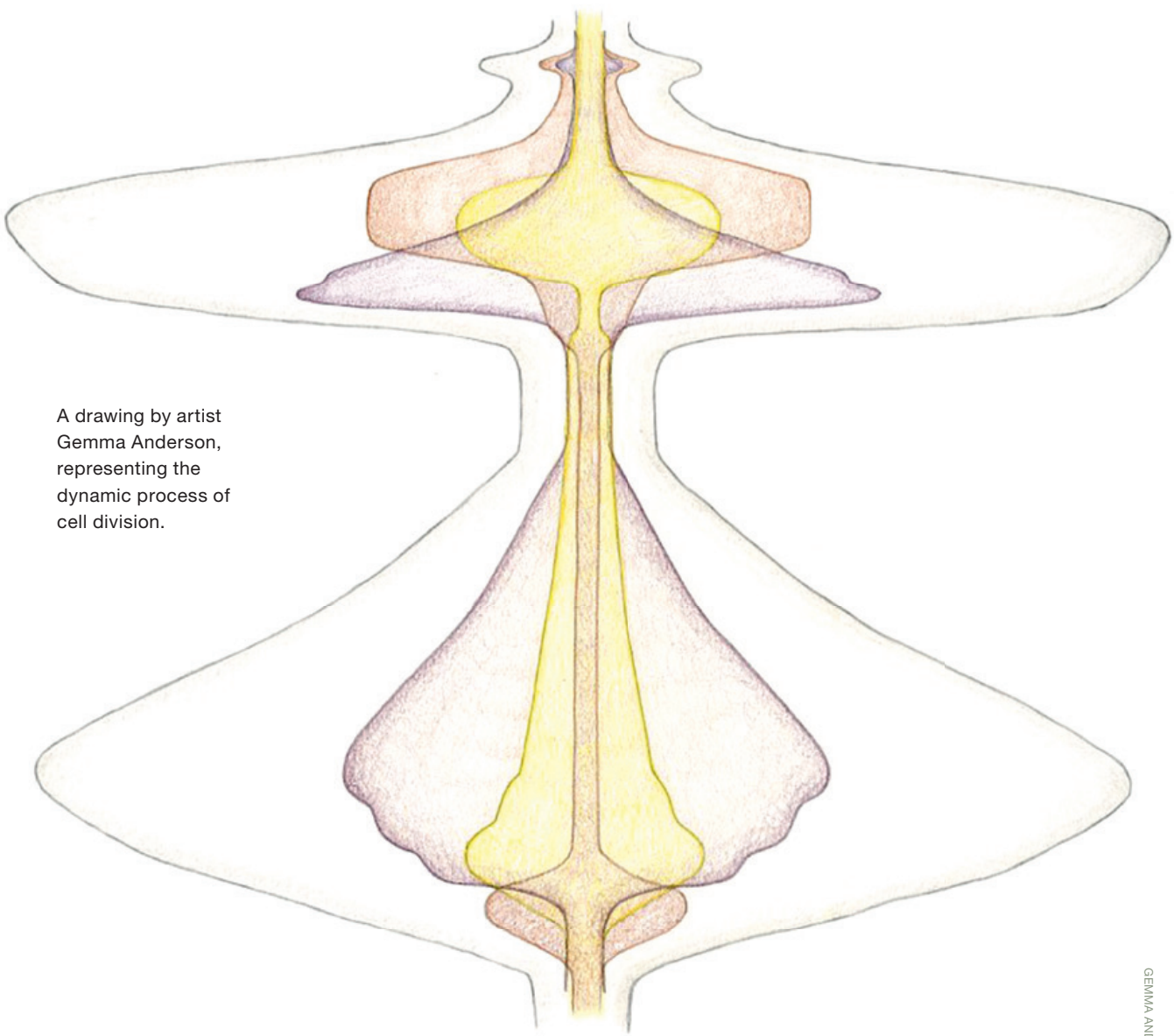
Drawing knowledge



A drawing by artist Gemma Anderson, representing the dynamic process of cell division.

GEMMA ANDERSON

A conversation about art–science collaborations and the importance of drawing in biology

BY FABIAN OSWALD

What could bring an artist and a science historian together and make them visit a research institute for molecular biology? The embryo of a fruit fly, of course.

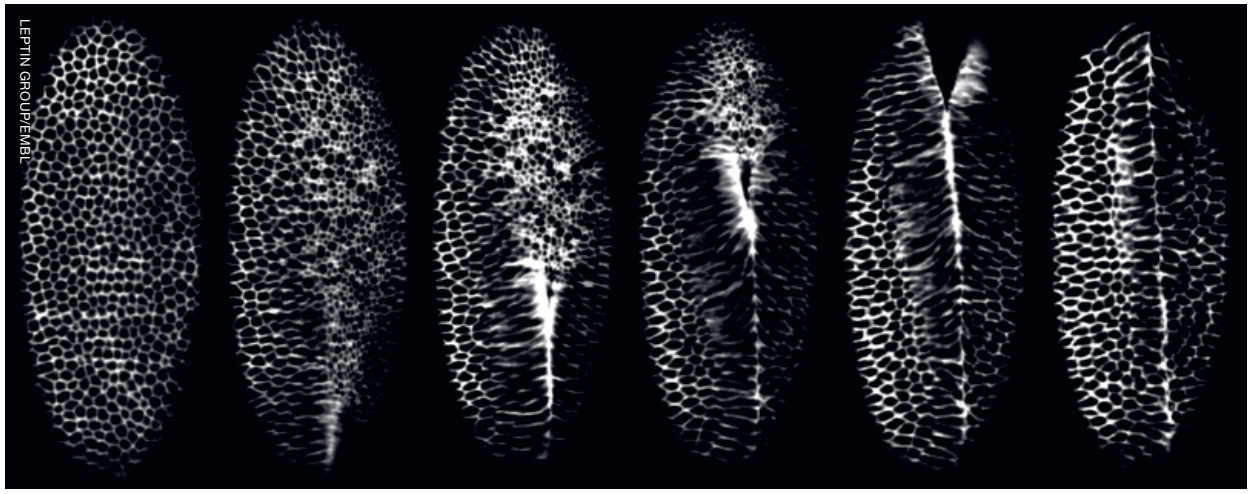
Researchers with the academic backgrounds of Gemma Anderson and Janina Wellmann are not usually seen at EMBL. Anderson is an artist and postdoctoral research fellow currently working at the University of Exeter, UK, on a collaborative project involving art, science and philosophy. In her art and her research, she focuses on drawing as a way of generating knowledge, especially in biology. Wellmann is a historian of science and author of *The Form of Becoming: Embryology and the Epistemology of Rhythm, 1760–1830*. In this book, Wellmann describes how scientific observation is limited when confronted with living, moving systems, and discusses the way creative decisions influence the scientific process. Both Anderson and Wellmann are fascinated by dynamic processes in biology. "Our common interest is the question: how do you depict changes over time and how do the processes of visualising and making it intelligible co-evolve?" says Wellmann. Anderson and Wellmann want to find a way to include time and change in a two-dimensional drawing: a challenge that overlaps the worlds of science, art and philosophy.

This common interest brought them to EMBL after Anderson attended a talk by EMBL group leader Maria Leptin. The talk was on embryogenesis and gastrulation – the process during which the embryo folds inward, transforming from a hollow ball of cells to a multilayered structure. Anderson was immediately fascinated.

Drawing to understand

During their week at EMBL, Anderson and Wellmann observed the work of the Leptin group in the laboratory. While Anderson gathered ideas and information so she could start drawing, Wellmann was particularly interested in the technology used to visualise the development of the fruit fly embryo. Anderson and Wellmann also spoke to scientists individually about the processes they were studying. "In the lab, they image the three-dimensional body of the embryo," says Anderson. "But, just like with the map of the world, they then do a cartographic projection as a 2D image and flatten it, so you see the whole surface." She started working on some first sketches based on these conversations, facing the challenge of drawing a part of the process that could not be properly visualised with the microscope. "In the process of gastrulation, part of the surface goes inside and then you don't see it any more. So, in their images, you just get this line where that's happening. I've been trying to make a drawing that actually includes that inside surface as well."

An important aspect of Anderson's view of art–science collaboration is that drawing should not be understood as a way of merely illustrating or decorating scientific thought. Wellmann shares the same opinion. "It's not that you use drawing as an illustration of something you have thought of before," she explains. "Your thoughts about it evolve together with the ability to represent it." Drawing can also create a personal connection between a scientist and the object of study, which is missing when the image is taken by a scientific instrument. "If you try to draw something that you're working on, what you decide to keep and what you decide to leave out are quite intellectual decisions," says Anderson. "Drawing also shows you what you understand, and you can then show that understanding to others." This is why, during her visit, Anderson actively encouraged >>



The development of a fruit fly embryo.

Gemma Anderson (left) and Janina Wellmann.

>> scientists to explain their research to her through drawing.

Sourabh Bhide, a postdoc in the Leptin group, says: "Between the first day of their visit and the last, my opinions shifted a lot. In the beginning I thought: 'I really don't know how this is going to help.' But, in the end, I realised that it made me think so much about the process when I was actually trying to put it down on a single sheet of paper."

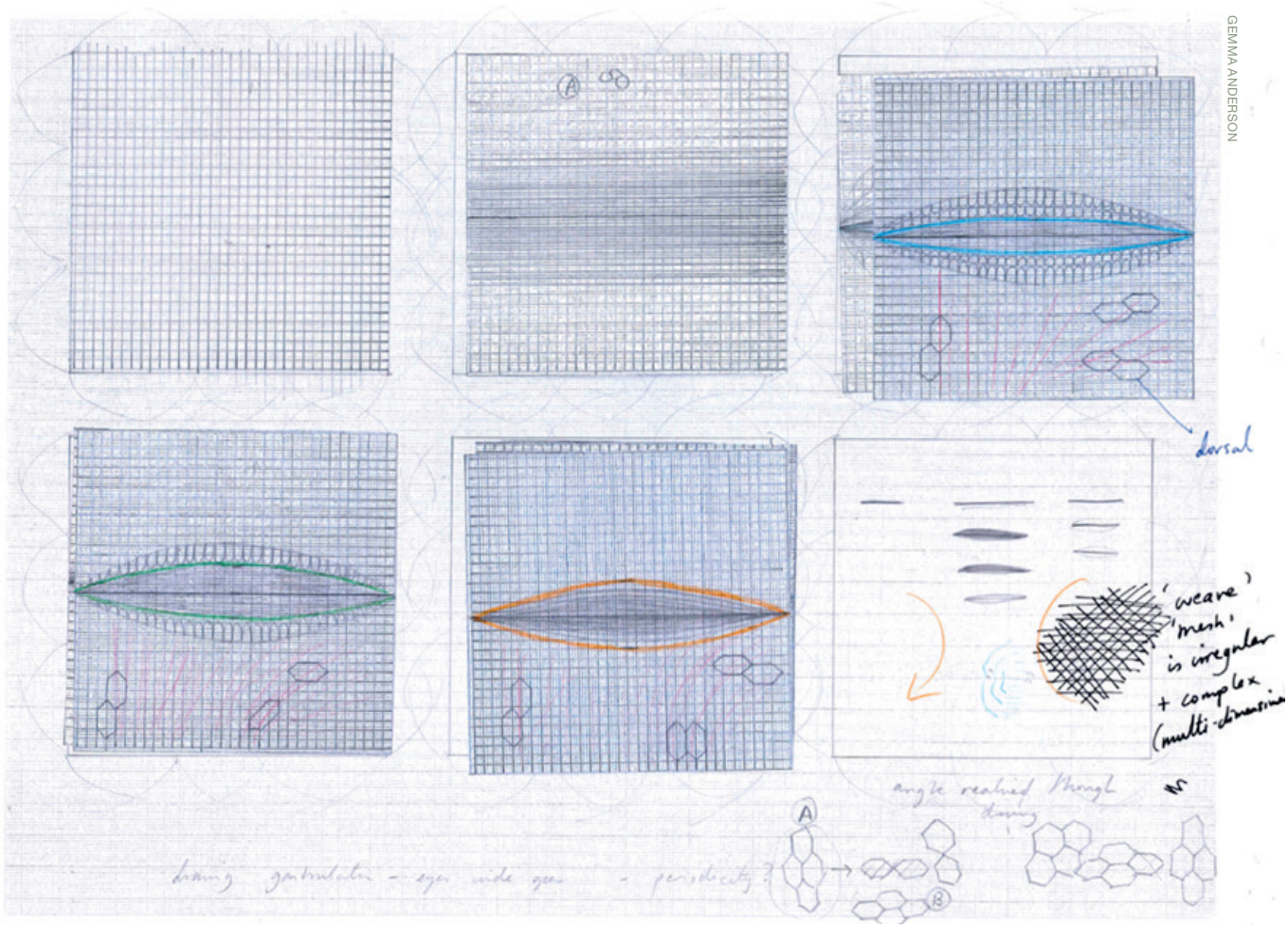
Ideas made visible

This explanatory quality of drawing is what makes it such a useful tool during interdisciplinary encounters. Where language is not enough, because it is encrypted in the jargon of individual research fields, visual communication can help to break that code. During their visit, Anderson and Wellmann talked to EMBL group leader Robert Prevedel, who works on developing new microscope technologies. This brings him together with biologists, physicists and computer scientists, all of whom have to somehow explain their ideas and needs to each other. "They use basically everything that they have at hand," explains Wellmann. "They do drawings, they doodle, they try to clarify the concepts when they talk about things. You're dependent on a mixture of all kinds of representations and ways of making your ideas intelligible in words, drawings, gestures."

Another observation made during the conversation with Prevedel was that biologists draw very differently from physicists when they're explaining something. These differences between disciplines also apply to the perception of images: during their visit to the laboratories, Anderson and Wellmann followed the preparation and use of the SPIM microscope – based on a technology developed at EMBL that uses a thin sheet of light to illuminate only one plane of a sample at a time, minimising damage to the sample caused by light. Wellmann noticed that scientists had very different opinions on how to define what they were seeing. While some referred to the images of the SPIM microscope as data, others saw them as a model. "We had to figure out during the conversation that, when we were talking about images, we meant different things," she explains.

Replacing the observer

Drawing used to be the preferred visual tool for biologists. Nowadays, it has largely been replaced by modern tools with increasing technological complexity, ranging from photography to three-dimensional data visualisation. Wellmann is fascinated by



GEMMA ANDERSON

Anderson's sketches showing the gastrulation process.

the philosophical issues that are opened up by these new imaging technologies. As an example, she describes the elimination of the 'observer' from the scientific process. Visual information is now captured by machines using specialised software, and only the result of this machine-driven observation is then interpreted by scientists. Anderson has questions on this topic as well: "If you're not doing optical observation, and it's basically a machine translating data into pixels, then what do we mean when we say that we see something, and who is seeing? I find this human–computer mediation really interesting."

Anderson and Wellmann both seem very inspired by their week at EMBL. "What is fascinating is to have the chance to be exposed to an environment that is unusual to me," says Wellmann. "I have to be attentive, to be observational and really look and see and try to understand." She observes that, to scientists, this sort of interaction is unusual as well, but is very well received.

Explaining his work through drawings to someone without a biological background has been an interesting experience for Bhide. "Usually we only interact with other scientists," he says. Bhide has promised Anderson that he will continue drawing in the future, and will report back on how this has changed his understanding of his work.

FULL VERSION ONLINE:
BIT.LY/embl-93-18

READ GEMMA ANDERSON'S BLOG POST ABOUT THE EMBL VISIT:
BIT.LY/embl-93-18a

Decoding ageing

Ageing, longevity, the naked mole-rat and us

BY CELLA CARR

It was more by serendipity than design that Alessandro Ori came to be studying the molecular mechanisms associated with ageing and longevity. During his postdoc at EMBL, he ventured down a research rabbit hole that was to shape the course of his career in ways he hadn't anticipated, leading not to rabbits but to the naked mole-rat, *Heterocephalus glaber*.

Prior to becoming a group leader at the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI), in Jena, Germany, Ori worked on mass spectrometry-based proteomics in the Beck Group in Heidelberg for five years. One of the group's main areas of research was the nuclear pore complex – a large complex of proteins that allows the transport of molecules into and out of the cell's nucleus. This led to a collaboration

KERSTIN WAGNER/FLI

EMBL alumnus Alessandro Ori in the lab.

KAROL SZAFRANSKI/FLI

Naked mole-rats.

with Martin Hetzer of the Salk Institute in California, USA. Hetzer was interested in studying how the nuclear pore was affected by ageing.

"It was one of many side projects I was working on at the time," Ori explains. "As part of my postdoc I developed mass spectrometry techniques to quantify precisely the proteins that form the nuclear pore. Working with Martin Hetzer, we decided to look at the brains of young and old rats. Then the project expanded in scope from the nuclear pore to a proteome-wide analysis, and we also started to integrate genomics approaches. I found myself somehow sidetracked into the ageing field, and it suddenly became very important!"

When the time came for Ori to leave EMBL, Lenhard Rudolph at FLI was looking for someone to set up a proteomics facility there, and to work on proteomics in the context of ageing. Ori realised that this was no longer a side project but a great opportunity to immerse himself more fully in this area of research.

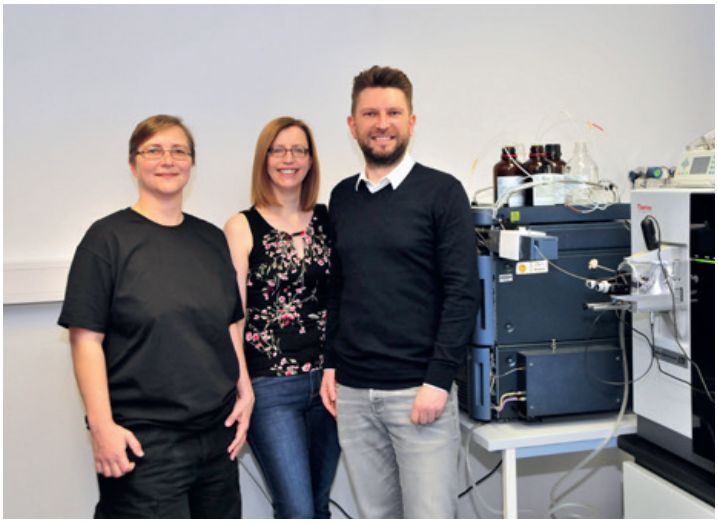
Small but long-lived

At first glance, a small, wrinkly, hairless rodent with tiny eyes and ears might seem to have little in common with humans. Or with bees, for that matter. However, like us, naked mole-rats are exceptionally long lived relative to their body mass (up to 30 years, compared to 2–3 years for mice and about 12 for guinea pigs). And, like bees, they have a eusocial lifestyle: they live in colonies comprising a queen, several breeding males, and up to 300 male and female workers. They are native to the savannahs of East Africa, where they live underground in extensive tunnel systems.

"I found myself sidetracked into the ageing field"

Naked mole-rats have a number of special characteristics that differentiate them from other rodents, and indeed from humans, and make them fascinating subjects for study: they are fertile throughout their lives and are highly resistant to infection, as well as to diseases such as cancer and diabetes. These traits, combined with their extraordinary >>

KERSTIN WAGNER/FLI



EMBL alumni Alessandro Ori and Joanna Kirkpatrick, with collaborator Ivonne Heinze (left).

"I think we can find the magic bullet"

>> longevity, make them one of the most interesting model organisms for ageing research.

Do they age?

They live long, but do they age? This question was a source of much debate and speculation in the scientific community, and one that Ori and his collaborators sought to answer definitively. Using a combination of proteomic and genomic approaches, they compared liver samples from naked mole-rats with those from guinea pigs and humans. They also compared the livers of young and old naked mole-rats.

"We found that naked mole-rats and closely related species showed differences in their mitochondria – the cellular components that generate energy," says Ori. "Our data also clearly showed age-dependent changes in protein levels in the livers of young and old individuals. The molecular signature is actually similar to other organisms; it's just that it's happening at a different pace. It's slower."

Perhaps one of the most significant findings of Ori's research is that ageing affects similar molecular pathways in the livers of naked mole-rats and humans. Specifically, ageing affects a group of proteins responsible for eliminating toxic substances from the body. However, whether or not these pathways affect the health of old naked mole-rats remains to be investigated.

Extending healthspan

Ultimately, the goal of ageing research is not necessarily to extend lifespan in humans, but to extend healthspan: the part of life that we live healthily. "The overall aim is to find fundamental molecular mechanisms that have a causative role in the ageing process," explains Ori. He emphasises the importance of causation: "We need to identify the molecular changes that are causing ageing, not those that are a consequence of ageing. This has always been one of the trickiest things in the ageing field. If you compare only young and old – extreme age groups – you cannot distinguish that."

Ori is clear about what is needed if this research is to translate into clinical applications. "If we can find some early event that has a cascade effect, we can try to intervene pharmacologically. You don't want to have interventions that are effective only if administered from the beginning of life. That's not what a successful intervention would look like. The aim is to identify populations or age groups that are at risk, and to extend their healthspan by treating them in old age."

As Ori returns to his lab, and his naked mole-rats, he is optimistic that he is on the right path: "If we can understand the fundamental mechanisms of ageing at the proteome level – both the causes and the consequences – I think we can find the magic bullet."

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BIT.LY/embl-93-19

Cultures

Alumni

ALEKSANDRA KROLIK/EMBL

Twenty years of EMBLEM

Reflecting on the past and looking to the future of technology transfer at EMBL

BY CELLA CARR

"Ultimately, what drives us is to make an impact on human health and to secure the best interests of EMBL," says Gábor Lamm, reflecting on the 20th anniversary of EMBLEM, EMBL's technology transfer partner. EMBLEM was established in May 1999, and Gábor has been at the helm as Managing Director almost since its inception.

Technology transfer is the bridge that takes innovative science from the lab and sees it through the process of development into commercial products – novel drugs, therapies, diagnostics and medical devices – that can be used for the benefit of society. It is one of EMBL's key missions.

The decision to establish a company to handle technology transfer at EMBL was made in 1998. One of the reasons for this decision is that commercial activity would jeopardise EMBL's special status as an intergovernmental research organisation. EMBLEM was therefore set up as a company that operates according to German rather than international law, and which pays corporate tax in Germany. It is thus free to pursue commercial interests and to make decisions independently of EMBL.

A close eye on science

That's not to say that there isn't a close relationship between EMBLEM and EMBL. On the contrary, Gábor and his team are proactive in identifying potential commercial opportunities. "We're at EMBL all the time," Gábor says. "The Faculty Seminars, where the different groups talk about their research, are very important for us, as are the faculty retreats. We interact with – and take good ideas from – people at all levels, from PhD students to senior scientists."

Training scientists is also an important part of EMBLEM's work. All new PhD students receive training on various aspects of technology transfer, including patenting,

MARIETTA SCHUPP/EMBL

The EMBLEM team: (left to right) Jürgen Bauer, Yvonne Meyer, Birgit Kerber, Annabelle Grimm, Gábor Lamm, Christina Böhm, Thorsten Schneider and Ilka Singer.

public disclosure, and the various types of open-source licences.

Securing EMBL's commercial interests

EMBLEM's technology transfer remit spans a broad spectrum of activities. These include identifying and protecting intellectual property, facilitating the establishment of spin-off companies from EMBL, licensing technologies to third parties, marketing and contracting scientific consultancy services, and developing collaborative research agreements.

Collaborations are extremely valuable for EMBL scientists. "In the late 2000s we realised that just doing licence agreements was not enough," says Gábor. "With collaboration agreements, an industrial partner brings something to the table that's valuable for EMBL scientists, and the scientists contribute something that the industrial partner doesn't have. We have a joint collaboration on a focused project. It's a mutually beneficial arrangement."

Two key questions

Every innovation is unique and presents its own distinct challenges. However, in all cases the team at EMBLEM ask two key questions at the outset. First, what is the fastest way to ensure that this technology is deployed in the market? And, second, what is the best way to ensure that this technology is made available as broadly as possible to benefit society?

"The answers to both of those questions define everything else that we do," explains Gábor. "They define the intellectual property >>

>> protection and commercialisation strategy: is the innovation going to be protected by a patent or by other means? If a patent, in which territories and with what scope? Is it going to be a single patent family, or do you build a patent portfolio around this topic? Who are the potential licensees? Will you put it into a start-up, or license it to an established company? Are you going to have multiple and exclusive licences? All of these decisions follow on from the answers to those two simple questions."

EMBL Ventures and the EMBL Technology Fund

From the start, Gábor was convinced of the importance of having a venture capital vehicle associated with EMBL. The EMBL Technology Fund, managed by EMBL Ventures, was established to invest in life science start-ups emerging from EMBL and, importantly, from its member states. The first EMBL Technology Fund was raised in 2002. It amounted to €26 million, which was invested in 13 portfolio companies. Three of these originated at EMBL. The second fund, amounting to €40 million, was raised in 2011. It was invested in 11 portfolio companies, one of which was Luxendo (see p. 40).

"EMBLEM helps us with technology transfer, licensing and contracts. We're very lucky to have EMBLEM as part of EMBL, and it's just a pleasure working with our EMBLEM colleagues."

Ewan Birney
Director of EMBL-EBI, Joint Head of Research and Senior Scientist

In 2006, the EMBL Technology Development Fund was created. This is a classic 'proof-of-concept fund' to develop early inventions to a stage of commercial potential. The initial investment was about €1.7 million, which funded 11 proposals and resulted in four spin-off companies. These have already returned around €8 million to EMBL, attracted €24 million of additional external investment, and seen the creation of over 50 new jobs. By any measure, that is a good return on investment.

Milestones on the road to success

EMBLEM is now among the top five technology transfer entities for the life sciences in continental Europe. In 2004, EMBLEM recouped all of EMBL's previous investments in technology transfer, and since then the company has returned an

EMBLEM in numbers

May 1999 – May 2019

1060
invention disclosures – around 50 per year

929
EMBL inventors – around every third EMBL scientist, accounting for turnover

450
priority patent applications filed; over 40% then licensed

250
patents granted

annual surplus to EMBL, amounting to over €40 million over the past 20 years. This money is earmarked for further collaborations between science and industry, across EMBL groups and sites. "To put this in context, it usually takes at least 10 years for a tech transfer company to break even," says Gábor. "And many never make a cent."

The company passed another significant milestone in 2018, when it generated in excess of €10 million from licensing, collaboration, service and consultancy contracts. "The monetary part of what we do is important, but by no means is it the main criterion when we make decisions," says Gábor. "If you only have the money in sight, you're going to lose the big picture. Our focus has always been the mid- and long-term sustainability of the activity, and to return value to EMBL and to society."

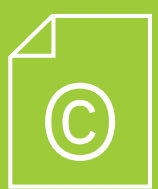
The success of any company depends on the people behind it. At EMBLEM, a small team of highly trained scientists – many with postdoctoral research experience; most having also worked in industry – are driven by a passion for science and a desire to make a positive impact. "We are innovators, bridge-builders and service providers," says Gábor. "We don't sit around and wait for things to happen."

"EMBLEM is committed to bringing together researchers from academia and industry. My research has benefited from a decade of their excellent support, and I look forward to working with them in the future."

Lars Steinmetz
Senior Scientist and Director of the Stanford | EMBL Life Science Alliance

Looking to the future

EMBLEM's many successes over the past 20 years are cause for pride and celebration, but there is no room for complacency. Gábor Lamm is looking to the future. "We want to maintain a high level of service for EMBL, and to expand our business offerings. We'd also like to develop new initiatives to foster innovation, and to develop commercially viable opportunities. We want to help deepen EMBL's relationships with industry, and to support the institute in achieving its goals." With quiet confidence he concludes, "We're good at what we do." This is surely an understatement, but the results speak for themselves, without any need for embellishment. >>



100
copyrights secured

4000
licence and collaboration agreements concluded

400
commercial licensees, with every second licensee a recurring customer

€100 million
income generated, including share disposal

20
start-ups created

Spotlight on Luxendo

"It was obvious that this technology was a breakthrough," says EMBL group leader Lars Hufnagel, of the light-sheet microscopes developed in his lab at EMBL. The MuVi SPIM (multi-view single-plane illumination microscope) and InVi SPIM (inverted view SPIM), developed in collaboration with EMBL group leader Jan Ellenberg, sparked intense interest in the scientific community. Inundated with requests from scientists who wanted to come to EMBL to use the technology, or acquire it themselves, Hufnagel realised he needed to get the technology into the market. Fast.

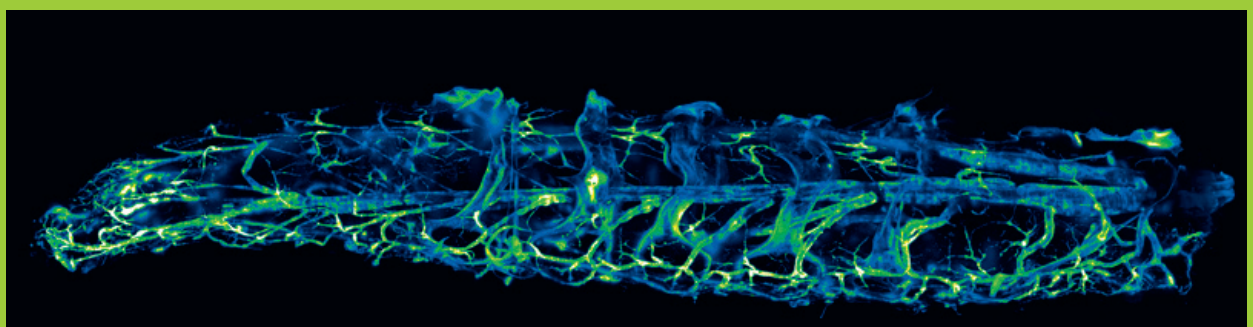
Hufnagel and Ellenberg were building on the work of Ernst Stelzer, the former EMBL group leader who developed the first generation of SPIM microscopes at EMBL and filed the first patent on the technology in 2002. "What was missing in the early prototypes was usability by biologists," says Jürgen Bauer, EMBLEM's Deputy Managing Director. "When Lars brought the technology to the next level of development, and generated instruments that were more robust and usable – closer to a product – we agreed that this would be a perfect basis to turn this into a spin-off company."

Mutual benefits

The resulting company – Luxendo – was created in September 2015 and venture capital funded by both the EMBL Technology Fund, managed by EMBL Ventures, and Life Sciences Partners, one of the largest life science venture investors in Europe, based in Amsterdam. Luxendo was acquired by the global scientific instrument manufacturer Bruker after only a year and a half. "Bruker recognised that we had a good team, and they kept it and expanded it," says Hufnagel. Luxendo continues to be hosted on the EMBL campus in Heidelberg. "Initially there was a lot of knowledge from my lab going into this company," says Hufnagel. "But now Luxendo finds better solutions, builds better components, which we integrate. That knowledge now flows back to EMBL."

"This is a great example of excellent science coming together with perfect engineering competence to build a solution for scientists to answer biological questions," says Bauer. "The Luxendo story exemplifies the unique ecosystem at EMBL, which, together with EMBLEM and EMBL Ventures, allows innovations to be fast-tracked to prototype stage and then spun out into a start-up, which makes EMBL technology rapidly available to the scientific community and commercial partners."

"The Luxendo story exemplifies the unique ecosystem at EMBL"



DIMITRI KROMM, HUFNAGEL GROUP; DANIEL RIOS, LEPTIN GROUP/EMBL

This MuVi SPIM image reveals a fruit fly larva's developing tracheal system – the network of tubes that transport oxygen and other gases around the fly's body.

Open Targets: a paradigm for collaboration

"This is collaboration at its best," Birgit Kerber, Business Development Manager at EMBLEM, says of Open Targets. "It's a role model for large public–private partnerships and exemplifies how EMBL and EMBLEM together are successfully interacting with industry."

Open Targets was established in 2014 and is based at the Wellcome Genome Campus in Cambridge, UK. It brings together partners from academia and industry to develop innovative approaches to drug target identification and prioritisation, using human genetics, genomics and other omics data. There are currently five pharma and two academic partners, one of which is EMBL's European Bioinformatics Institute (EMBL-EBI), whose world-leading competencies are essential to Open Targets.

"There's nothing going on in the life sciences, either in the research space or the development space, that is not impacted by bioinformatics," says EMBL-EBI Director Rolf Apweiler, "and we have the expertise in large-scale data analysis and provision of these services to the scientific community."

"It's a very intense collaboration, and that's why it's so successful"

SPENCER PHILLIPS/EMBL

Shoulder to shoulder

EMBLEM is responsible for the business development side of Open Targets, and Kerber plays a lead role in getting new industry partners involved. "Open Targets works extremely well. It has established a portfolio of more than 50 interlinked projects and has published more than 20 articles across three therapeutic areas: oncology, immunology and neurodegenerative disease," she says. "Scientists from academia and industry are working shoulder to shoulder on these projects. It's a very intense collaboration, and that's why it's so successful. We're operating in what's called the pre-competitive space, where there's room to share information, and that is beneficial to everybody."

Open Targets hit the headlines earlier this year, with the announcement that researchers had identified thousands of genes that are key to cancer survival. The unique collaborative framework of Open Targets generates important results like these, and helps to facilitate and accelerate their translation into the development of new, safe and efficacious drugs.

Kerber is focused on the future. "Expanding the breadth of Open Targets, and having more Open Targets-like initiatives in other spaces – that's a good prospect," she says. "It's a visionary initiative."

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Top tips for teaching

Overwhelmed as a biologist getting to grips with computer programming? EMBLers are here to help!

BY JOSH TAPLEY AND OANA STROE

Computer programming is not always a part of the undergraduate life science curriculum. But, for many, coding skills have become a necessary tool in the biologist's toolkit.

If you find yourself thrown in at the deep end during your PhD or later, you are not alone. Here, members of the EMBL community who went through similar situations share their top tips for people at the beginning of their coding journey.

MARIETTA SCHUPP/EMBL

Florian Huber

Postdoc, Heidelberg

I started coding during my PhD, when I collected a lot of imaging data and had to learn how to analyse it myself. Now I'm using statistical learning techniques to predict drug mode of action in bacteria.

In biology, people mostly use the programming languages Python or R, but which you learn tends to depend on what the people in your team are already using.

MY TOP TIP: Keep a notebook! Notebooks are like lab books for coding. You can write explanations around your code, which are highly useful to remind yourself later of what you did and why. They also make it easier to reproduce your work, which is very important in science.

Andrew Hercules

UX Designer, EMBL-EBI

I've always been interested in writing, so I first approached coding as a way of making my blog stand out. There are simple projects that you can try out in a few languages, just to get a feel for them and see which you prefer. It's definitely worth taking the time to do them at the beginning. These days, I work as a User Experience Designer, so I use code to understand and build our front-end technologies.

MY TOP TIP: Coding is a marathon, not a sprint. Google is great, but the amount of available information can be daunting when you're just starting out. With the right mentality though, you'll get there.

RODICA PETRUSEVSCHI/EMBL

yourself to code!

COURTESY OF MIQUEL MARIN

Miquel Marin

Postdoc, Barcelona

I started programming seriously during my master's and PhD. I joined a group that was purely computational, so learning how to program was a necessity! My colleagues gave me lots of helpful tips, but nowadays you mostly learn by yourself from online tutorials and internet forums. Now I'm a biological modeller, so I write programs that implement specific mathematical models in order to simulate biological processes.

MY TOP TIP: Use version control software, like GIT, from the very beginning. This is something I learned later that would've helped me. It's good whether you are working in a group or by yourself, because it keeps everything tidy.

Tom Boissonnet

PhD student, Rome

After discovering programming during a fun undergraduate module on Java, I kept learning by myself and attempted to make an old game I played as a child. During my master's, I had the opportunity to devote a year of study to programming, and I quickly realised all the things I had been doing wrong! In the lab I'm in now, we use different techniques to understand how the retina works, and we need a lot of computer analysis. I'm trying to make some general software that would work for everyone. It's a big challenge, but I'm really enjoying it!

MY TOP TIP: Try lots of different projects and be curious! Break down code that works to get a better understanding of what it's doing. It's about developing an intuition for good code.

ANASTASIIA VLASIUK

COURTESY OF GIOVANNI DALMASSO

Giovanni Dalmasso

Postdoc, Barcelona

I started my master's thesis in a lab doing high-performance computing. I knew basically nothing about programming! I had helpful colleagues, but most of the time I was on my own. Now, 90% of what I do involves programming. In my current lab we make simulations of biological processes such as the growth of a mouse limb. We use programming to handle almost everything, from mathematical modelling to data visualisation. I mostly use Python, but I'm also starting to use CUDA. This is a programming language specifically designed for taking advantage of a computer's graphics processing unit (GPU). It's really powerful for using GPUs to do many easy tasks really fast. Using CUDA, some programs that used to take hours, or even days, now take seconds!

MY TOP TIP: Write down some of your code with pen and paper. Writing on paper makes you really think about what your code is supposed to be doing and helps you understand it better.

Jan Kosinski

Group leader, Hamburg

My first contact with coding was in high school. I wrote simple games like Snake or Pong in Turbo Pascal. The serious coding started during my postdoc, when I used Python and JavaScript to develop a computational pipeline and an interactive web application. These days, I use code for many different things, including automating daily tasks and generating scientific figures and movies. The movie about the nuclear pore complex that I made for the EMBL YouTube channel was generated entirely with a Python script!

MY TOP TIP: Give meaningful, self-explanatory names to things. I used to write cryptic code that I couldn't understand half a year later. Save yourself the time and hassle – use meaningful names.

MARIETTA SCHUPP/EMBL

MASSIMO DEL PRETE/EMBL

Toby Hodges

Bioinformatician, Heidelberg

I learned a language called Perl at the beginning of my PhD, but moved over to Python soon after my doctoral studies. Now I apply programming mostly by teaching. Most people find coding difficult at the beginning, so there's no shame in asking for help. People who consider themselves programmers are still googling things 20 times a day!

MY TOP TIP: Learn the programming language that people around you are using! The best thing you can have is a person next to you whom you can ask for help when you can't figure out what's going wrong.

Malvika Sharan

Bioinformatician, Heidelberg

I was a bit clumsy in the lab, so computer programming was a way to stay in science and experiment in different ways! Now I really enjoy teaching it because I can relate to the struggles of people just starting out, and I can really help them.

MY TOP TIP: Come to one of Bio-IT's two-day programming courses. We start from the very beginning, making people comfortable with opening the terminal and running code, and then expand from there. If I'd had these two days, I think I would have saved several months of my life!

COURTESY OF MALVIKA SHARAN

Malvika and Toby coordinate EMBL's Bio-IT community

Toby: Bio-IT is a community-building and support project for computational biology and bioinformatics at EMBL. We run networking events for people to have conversations that hopefully lead to collaborations. We also train staff with our beginner and intermediate courses on command-line computing, programming in Python and R, and using version control software. Occasionally, we also do specialised courses like 'Image Processing with Python' or 'Machine Learning with R'. Our courses are open to all EMBL staff, but I recommend signing up to the Bio-IT mailing list [see below] because they tend to fill up quickly!

Malvika: The most active people in our community are the experts. That's great, but we'd like more learners to stay in the community after their courses. I want to make beginners in programming and bioinformatics more comfortable exchanging ideas and helping each other. This year, I've tried to identify how to bring them in by providing training or networking in the areas that they feel are important.

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bio-it@embl.de

Building engagement

How Lego can help you learn the fundamentals of DNA

BY CELLA CARR

Who can resist the lure of a pile of shiny, colourful Lego bricks? The iconic children's toy has fuelled countless imaginations and furnished the construction of a vast array of complex structures, including detailed replicas of the Kennedy Space Center, London's Houses of Parliament, and even da Vinci's *Mona Lisa*. Yet its individual parts are simple: small plastic bricks that can be joined together. Like Lego, DNA can also be broken down into simple components: organic molecules called nucleotides, or bases, denoted by the letters A, T, C and G.

JEFF DOWLING/EMBL

Nick Goldman, group leader and Joint Head of Research at EMBL-EBI.

This similarity dawned on Nick Goldman, group leader and Joint Head of Research at EMBL's European Bioinformatics Institute (EMBL-EBI), while he was trying to come up with a suitable visual aid to explain how DNA can be used to store digital information. He tested some ideas with his son, who was 14 at the time, and he has since run a number of masterclasses for similar age groups. "For DNA we essentially have four letters of the alphabet, and it occurred to me that you can demonstrate DNA's information content using four different colours of Lego bricks, without having to create the structure of the DNA or the helix," he explains. "Lego works incredibly well because you can make it easily, and of course everyone loves playing with Lego."

Coding at the Technoseum

Last October, the team at EMBL's European Learning Laboratory for the Life Sciences (ELLS) got to wondering if Goldman's ideas might be adaptable for an even younger audience. While preparing for a public science day at the Technoseum in Mannheim, Germany, they were quick to realise the appeal of Lego as a public engagement tool. "The theme of the event at the Technoseum was coding, and the obvious focus for us was DNA," says Agnes Szmolenszky, Head of ELLS. "We knew Nick Goldman had been using Lego for educational purposes, and we took up the idea and developed activities for the science day."

MARIETTA SCHUPP/EMBL

The ELLS team: (left to right) Eva Haas, Hana Mujkovic, Shweta Gaikwad and Agnes Szmolenszky.

This was something of an experiment for ELLS in terms of assessing the method's effectiveness for a young age group, but the activity received an enthusiastic response from both children and adults. Even very young children took part, by working together with older siblings to complete encoding and decoding tasks. "At the Technoseum event, most of the other activities related directly to computer programming," says Eva Haas, Education Officer at ELLS. "Ours was a little different, so it had novelty value."

Scalable and adaptable

The ELLS team are now looking at ways of developing the Lego activity for secondary school students (16 years and over), introducing concepts such as mutation and replication. "We like it because it's very flexible," says Szmolenszky. "We're already testing a more advanced version, and we're thinking about offering this as a hands-on activity as part of our school visitor programme."

Shweta Gaikwad of ELLS has also used Lego to teach teenagers about the science behind using DNA as an information storage system. "Explaining the science behind DNA can be really simple or really detailed," she says, "and you can scale the activity up or down for different age groups."

Every area of scientific endeavour has its own unique challenges. It is perhaps inevitable that when using Lego to teach science to teenagers, a certain proportion of the target audience will ignore the science bit and set about building a castle or a battleship instead. And, reflecting on the scalability of the teaching method, Nick Goldman says wryly, "What's not scalable is carrying a lot of Lego around. I went over to Belgium once with a suitcase full of Lego – it's a bit inconvenient!"

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The donor's code

The main funder of the EMBL Lautenschläger Summer School reflects on codes of conduct around giving

MLP SE

Manfred Lautenschläger.

BY FABIAN OSWALD

Manfred Lautenschläger began his career by selling insurance to university graduates, and in 1971 he co-founded the financial services company Marschollek, Lautenschläger und Partner AG, soon becoming one of Germany's most successful businessmen of the time. In 1999, he retired from business operations and set up the Manfred Lautenschläger-Stiftung, a foundation that supports numerous philanthropic projects around the world. Here, he reflects on his code of conduct as a donor.

What motivated you to support the EMBL Lautenschläger Summer School?
I've always admired young people's energy and enthusiasm. When I heard about the summer school, I thought: "Great! I will support that." Now there are applications from all over the world – the demand is huge. Giving young people some guidance, that feels great.

Is there a code of conduct that you follow when donating?
Yes, certainly. My foundation is very broadly oriented. One focus is promoting understanding among people. I built the Heidelberg-Haus in Crimea, where older women that were kidnapped as young girls by the Nazis can meet and receive medical attention. I'm part of the board of trustees of the Documentation and Cultural Centre of

German Sinti and Roma in Heidelberg, and honorary senator at the Centre for Jewish Studies Heidelberg. Science is very important to me, along with cultural events like the Heidelberger Frühling, now the third largest classical music festival in Germany, or Enjoy Jazz, the largest jazz festival in Europe. These are all things that I can promote as a donor. Where the public sector is not willing or able to get involved, there is a lot that can be done with selective funding. It is important for me to decide for myself whom I support. I want to know the individual projects.

Is there a code of conduct that you expect from the institutions you support?
I think that science should be free. I don't control anything. I take a look at the people beforehand and ask myself: are they really passionate about their work? How trustworthy do they seem? That's important. And I've never been disappointed. A scientist must work freely, and also has every right to fail.

How did you decide to start your foundation? Was there a key moment?
Not a key moment, no. I had become very rich, a billionaire. That is not the case any more, but I am still wealthy. I do not need all that money, my children do not need all of it, because they are all self-sufficient. So, it seemed natural to use it for the common good. That has rewarded me greatly, because I got in touch with people whom I would never have met otherwise: scientists, artists, and getting to know the world of the Sinti and Roma, or the Crimean Peninsula. This has made my life beyond 60 as exciting as my professional life was. I can imagine few countries in which I would have been as successful as in Germany. I'm committed to contributing to the preservation of what we have here. I think it is an obligation, for people who can afford it, to contribute to this.

"A scientist must work freely, and also has every right to fail"

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BIT.LY/embl-93-23

EMBL'S CODE OF GOOD PRACTICE FOR DONOR RELATIONS:
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Friends of EMBL

Friends of EMBL is a network for anyone interested in the life sciences, and in supporting EMBL's research and missions. Members engage in a close relationship with EMBL and support various areas of our work with their annual donations, focusing in 2019 on the advancement of women in science. For his longstanding support, Manfred Lautenschläger received the Honorary Membership of the Friends of EMBL in 2018. For more information visit embl.org/friends

ALEKSANDRA KROLIK/EMBL

The EMBL Lautenschläger Summer School

From 15–26 July 2019, undergraduate students from scientific fields outside biology will learn about current research in the life sciences. This year's focus will be on the possibilities for high-end imaging to contribute to new insights in a broad range of research areas. The EMBL Lautenschläger Summer School has been made possible by a substantial gift from the Manfred Lautenschläger-Stiftung and by further generous donations. See embl.de/training/undergraduates/summer_school

Editing the ethical code

Professor Tim Lewens challenges the human genome's unique place in bioethics

BY JOSH TAPLEY

Tim Lewens was always going to be a scientist. That is, until a gap year spent reading philosophy books left him with cold feet. He switched to philosophy during his first week at university, but immediately feared he had made a huge mistake leaving science behind. "Philosophy of science turned out to be a really fortuitous thing for me," says Lewens, now a professor of the subject at the University of Cambridge, UK. "It was exactly what I would have aimed at doing, had I known it existed!"

What are mitochondria?

Mitochondria are specialised components of most eukaryotic cells – cells that have a nucleus bound by a membrane. They convert the chemical energy gained from food into a form cells can use: adenosine triphosphate. Mitochondria are thought to have originated as free-living bacteria that were incorporated into larger eukaryotic cells around two billion years ago. There they formed a symbiotic relationship, providing energy in exchange for protection.

Due to their origins as organisms in their own right, mitochondria in human cells have their own DNA – a genome of 37 genes. Over time, many genes essential for mitochondrial function have migrated to the cell's nucleus. Mitochondria are typically passed only from mother to child, as there are many more mitochondria in egg cells than in sperm cells, and in many species there are mechanisms to destroy paternal mitochondria that enter the egg cell.

In February, he gave a Science and Society talk at EMBL Heidelberg entitled 'Blurring the germline – from genome editing to transgenerational epigenetic inheritance'. In the talk, Lewens highlighted the special form of ethical concern that surrounds making heritable changes to the human genome. He then explored other heritable changes to human germline cells – cells that pass on their characteristics to offspring – suggesting that the genome should be just one part of a wider discussion about how we make decisions that impact future generations.

Differing definitions

Institutions around the world have differing stances on intentionally editing germline cells. The UNESCO International Bioethics Committee says "interventions on the human genome should be admitted only for preventive, diagnostic or therapeutic reasons and without enacting modifications for descendants".[1] By contrast, the US National Institutes of Health "will not fund any use of gene-editing technologies in human embryos",[2] whether those alterations are heritable or not. In the UK, however, one form of heritable germline modification – mitochondrial donation – has been legal since 2014.

Defects in the mitochondrial DNA of a woman's egg cell can lead to a range of systemic diseases that can be fatal for her children. Women in the UK can have the nucleus of their fertilised

egg cell placed inside the cell of a donor which has had its nucleus removed. All cells in the resulting embryo will have the mother's nuclear DNA, but the donor's functioning mitochondrial DNA. Not only will the child be disease free, but they will pass on the donated, healthy mitochondrial DNA to their own offspring: an inherited, and likely irreversible, germline modification.

This treatment is possible because the UK Department of Health decided that "genetic modification involves the germ-line modification of nuclear DNA (in the chromosomes) that can be passed on to future generations".[3] Therefore, in the case of specific techniques that have had their safety thoroughly tested and which remain subject to strict, ongoing regimes of regulatory approval, editing mitochondrial DNA is legal.

However, very similar diseases caused by faulty genes inside the nucleus, rather than the mitochondria, cannot legally be treated by gene editing. Lewens argues that, because of cases like these, altering the nuclear genetic code should not necessarily constitute an immovable ethical line. Rather, genuine concerns over editing the human genome should fall into the wider framework of how we balance the needs and risks associated with any decisions that affect future generations.

In some cases, we may never know for sure if the decisions we make are the right ones. "Consider Fred, a man living fifty years in the future," says Lewens, in our interview after his talk. "Is his life better or worse because we used some controversial technology now? Well, if we hadn't, then the same Fred simply wouldn't exist." Should we care about some less personal, average wellbeing per capita then? "In that case, it would be best to have just a few people who were all super happy!" As Lewens puts it, when it comes to measuring the success of our decisions, "We're often not even sure what the criterion is, let alone if we can be confident whether or not we've achieved it!"

Risk and reward

Instead, Lewens argues, we should focus on the present and look at factors such as whether there are ways to achieve similar benefits to a new biological technology with less risk. "In general, if you look at why people's health fails," says Lewens, "it can be due to well-understood but hard-to-action problems: people not eating the right kinds of food or not doing enough exercise, poor patient data-processing in hospitals, etc. In some cases, new technologies might not provide the best solutions."

This is one part of Lewens' wider ethical framework for assessing the risks for future generations. "In ethical deliberations," he says, "it's often not worth trying to build your argument upwards from your foundational beliefs [e.g. all gene editing is right or wrong], because the next person probably won't agree with them." Instead, he tells me, the most important factors are compassion and open discussion, taking into account as many opinions as possible and carefully measuring benefits, costs and risks. "When any new technology has costs and benefits, it's sensible not just to make sure the benefits outweigh the costs, but that the people who suffer most from the costs gain the most from the benefits too."


EMMA GILBY

Tim Lewens is a professor of Philosophy of Science at the University of Cambridge, UK.

1. BIT.LY/embl-93-24a
2. BIT.LY/embl-93-24b
3. BIT.LY/embl-93-24c

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Awards & honours

EMBL-EBI Director **Ewan Birney** was made a Commander of the British Empire in the Queen's New Year Honours list, in recognition of his services to computational genomics and leadership across the life sciences.

Peer Bork and **Christoph Müller**, Joint Heads of the Structural and Computational Biology Unit, have been elected members of the Academia Europaea. **Peer Bork** has also been awarded the Heinz P.R. Seeliger Prize, and an honorary professorship at Fudan University, Shanghai, China.

Ana Rita Brochado and **Lisa Maier**, both formerly of the Typas group, received funding from the Deutsche Forschungsgemeinschaft, via the Emmy Noether Programme, to start their own independent junior research groups. **Lisa Maier** also received the Robert Koch Postdoctoral Award for Microbiology in November 2018.

In March 2019, group leader **Sara Cuylen-Häring** received a Career Development Award from the Human Frontier Science Program.

In 2018, **Robin Diekmann**, postdoctoral fellow in the Ries group, was a winner of the Tycho Jæger Prize in Electro-Optics, awarded by the Norwegian Physical Society.

Jan Ellenberg, Head of the Cell Biology and Biophysics Unit, has been elected a member of the Leopoldina – Nationale Akademie der Wissenchaften.

Camille Goemans, postdoctoral fellow in the Typas group, has been awarded an EMBO Long-Term Fellowship.

In December 2018, EMBL Director **Matthias Hentze** received the Ilse and Helmut Wachter Award from the Medical University of Innsbruck, Austria, for his pioneering work on RNA biology.

Toby Hodges, Bioinformatics Community Project Manager in the Zeller team, and **Malvika Sharan**, computational biologist in the Gibson team, were joint winners of The Carpentries 2018 Community Service Awards. **Toby Hodges** has also been named an AAAS Community Engagement Fellow for 2019, and in January 2019 **Malvika Sharan** was accepted into the latest cohort of Mozilla Open Leaders.

In April 2019, **Katharina Imkeller**, visiting postdoctoral researcher in the Huber group, received a Bayer Pharmaceuticals Promotional Award from the Society for Biochemistry and Molecular Biology.

Andrea Imle, postdoctoral fellow in the Diz-Muñoz group, was awarded a 2019 L'Oréal-UNESCO for Women in Science fellowship.

Yacine Kherdjemil, postdoctoral fellow in the Furlong group, has been awarded an EMBO Fellowship for postdoctoral research.

In December 2018, group leader **Jan Korbel** received the Heidelberg Molecular Life Sciences Investigator Award. The award recognises Heidelberg-based researchers for outstanding work in the life sciences.

Maria Lukarska, formerly a PhD student in the Cusack group, was awarded a Prix de Thèse in June 2019 by Université Grenoble Alpes.

Mikhail Savitski, team leader and Head of the Proteomics Core Facility, was included in *The Analytical Scientist*'s Top 40 Under 40 Power List for 2018.

Ewa Sitarska, PhD student in the Diz-Muñoz group, has been awarded an Add-on Fellowship for Interdisciplinary Life Science by the Joachim Herz Foundation.

In December 2018, **Janet Thornton**, group leader and Director Emeritus of EMBL-EBI, was named Vice President of the European Research Council's governing body.

Tobias Wenzel, postdoctoral fellow in the Merten group, has been awarded an Open Science Fellowship. The Open Science Fellows Program is a joint initiative of Wikimedia Germany, the Stifterverband and the Volkswagen Foundation.

Alumni

Celebrating alumni worldwide


EMBL

On 19 July, we will celebrate EMBL's talented and diverse community of alumni by holding the first ever EMBL World Alumni Day. EMBL's new Director General, Edith Heard, will discuss the role of alumni in EMBL's future, and we'll take a virtual tour to connect with members of the alumni community around the world. Follow the link below for more details.

In this issue, we profile the winners of the John Kendrew and Lennart Philipson Awards (pp. 54–55), honoured for pioneering work in cancer immunotherapy and structural biology. We also invite you to nominate members of the alumni community for next year's awards. Nominations should be sent to alumni@embl.de by 29 July.

As we reflect on the idea of code in biology, we meet members of the alumni community who are decoding the ageing process (p. 32), using computer code to control a system for photographing ferns (p. 56), and writing books and holding school workshops to explain the DNA code to children and teenagers (p. 58).

Over the coming months we'll be holding 'EMBL in...' events in Australia, France, Spain, Sweden, and the USA, and we'd love to see you there. All dates can be found on the back cover.

Finally, this year marks the twentieth anniversary of the EMBL Alumni Association. If you're not currently a member, we invite you to join! We have well over 4000 members already, and will have a special deal for the 5000th.

Mehrnoosh Rayner
Head of Alumni Relations

EMBL WORLD ALUMNI DAY:
BIT.LY/embl-93-25a

EMBL ALUMNI AWARDS:
BIT.LY/embl-93-25b

Alumni Association Board elections

A big thank you to the 34 candidates who stood in the elections in May, and to the 637 Association members who voted.

The newly appointed board: (first row) Fátima Gebauer (Chair), Christian Engel (Vice-Chair), Anne-Marie Glynn (Vice-Chair), Angel Chong (Treasurer), Julius Brennecke, Marina Chekulaeva, Mark Green, (second row) Johanna Höög, Anne-Sophie Huart, Isabel Palacios, Ramesh Pillai, Kai Simons, Ernst Stelzer, Pavel Tomancak, and Erin Tranfield.

2019 alumni awards

Scientists honoured for contributions in cancer immunotherapy and structural biology

BY CELLA CARR

A revolution in cancer drug therapy

In the course of a research career spanning several decades, Patrick Baeuerle, currently Executive Partner of healthcare investment firm MPM Capital, has spearheaded the development of a novel class of biological drugs for treating cancer. This kind of drug offers hope in cases where conventional treatments have poor outcomes. "There has been a revolution in cancer therapy. In addition to chemotherapy, radiation and small molecule targeted inhibitors, clinicians now have a fourth addition to their arsenal, and this is immunotherapy," says Baeuerle.

MAVERICK THERAPEUTICS

Patrick Baeuerle, winner of the Lennart Philipson Award.

"There has been a revolution in cancer therapy"

Immunotherapeutic drugs activate a patient's immune system to recognise and eliminate cancer cells. Under Baeuerle's leadership, scientists at the biotechnology companies Amgen and Micromet developed antibodies known as 'bispecific T cell engagers' (BiTEs), which essentially form a bridge between immune cells called T cells (which have an innate ability to target tumours) and cancer cells. Bringing the two types of cell into close contact using a BiTE antibody greatly facilitates the destruction of cancer cells.

As Baeuerle explains, the BiTE antibodies are simple in concept. "They bind with one arm to cancer cells and the other arm grabs on to T cells. By making that connection, a T cell is able to kill the cancer cell that is temporarily associated with it. The T cell can then do the same thing again and again, killing multiple cancer cells. This explains the enormous potency of this class of immunotherapy. Just micrograms per day yield very robust responses in patients."

One of these BiTE antibodies, blinatumomab, was approved in record time by the US Food and Drug Administration for adults suffering from relapsed or hard-to-treat cases of acute lymphocytic leukaemia. It has also shown positive outcomes in patients with non-Hodgkin lymphoma. The ongoing research in this area is indicative of a shift towards a new paradigm for treating cancer.

The structural biology of bacterial communities

Rather than living as single cells in monocultures, most bacteria on Earth exist in multicellular communities called biofilms. Tanmay Bharat, currently a group leader at the Sir William Dunn School of Pathology at the University of Oxford, UK, is at the forefront of research applying advanced cryo-electron microscopy (cryo-EM) imaging to understand these biofilms. "It's an underexplored area of fundamental biology, because of the technical difficulties in studying cells that are part of a biofilm community," says Bharat. "In terms of practical applications, the structures that we resolve could potentially be used as targets for antimicrobial drugs." To this end, he has been developing novel cryo-electron tomography (cryo-ET) techniques for high-resolution structural refinement of molecular structures.

While carrying out his PhD research at EMBL, in the laboratory of John Briggs, Bharat described for the first time the structure of the lattice of proteins that mediate the assembly of immature retroviruses; an essential first step in understanding how such viruses mature to become infectious. He also generated insights into the structure and assembly of filovirus pathogens such as Marburg and Ebola viruses. "As the birthplace of cryo-EM, EMBL has always been a supportive environment for

THE ROYAL SOCIETY

Tanmay Bharat, winner of the John Kendrew Award.

"It's an underexplored area of fundamental biology"

cryo-EM research, so with the advancements in microscope and detector technologies, we were able to apply our image processing tools to solve longstanding problems in pathogenic virus assembly," he says.

Another important recent outcome of Bharat's research was the development of image analysis tools for tomography at the Medical Research Council Laboratory of Molecular Biology (LMB), in Cambridge, UK, in collaboration with Sjors Scheres and Jan Löwe. The imaging and image analysis tools that Bharat has been developing will be used to resolve structures of important antibiotic target molecules *in situ* directly in bacterial cells.

FULL VERSION ONLINE:
BIT.LY/embl-93-26

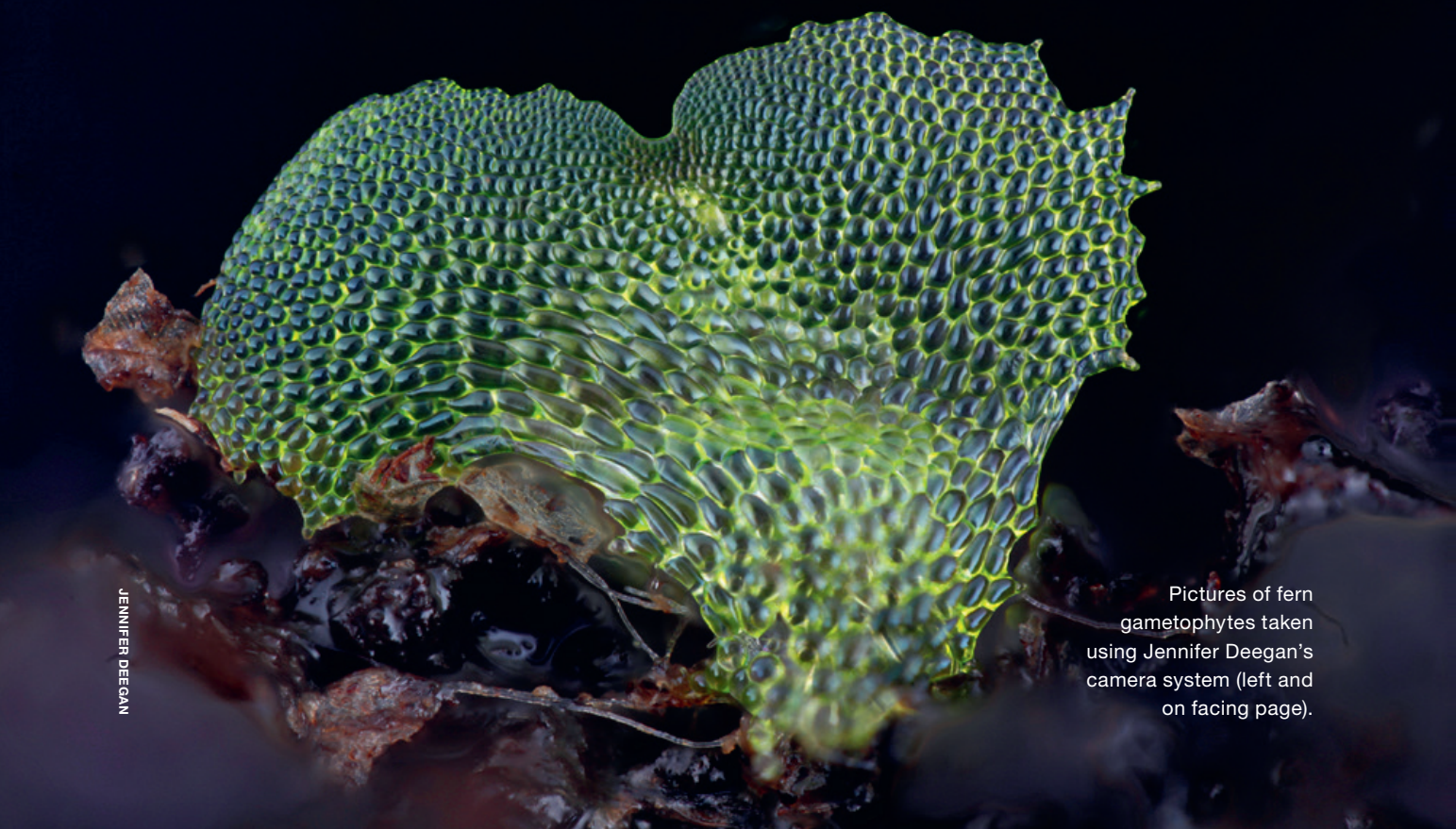
Fun with fern photography

EMBL alumna Jennifer Deegan built a prize-winning system for photographing ferns

BY FABIAN OSWALD

After several years in the Gene Ontology project at EMBL's European Bioinformatics Institute (EMBL-EBI), Jennifer Deegan left work to raise her son. However, she soon started to miss science and was happy when she could rejoin her previous research group as a volunteer. She went on to pursue a very different kind of scientific career, involving code, a second-hand electric motor and home-grown fern specimens.

A lot of Deegan's work was spurred on by EMBL's nine-year rule, which limits the duration of employment at EMBL to nine years for most staff. When Deegan left after eight years, she was going on maternity leave without expecting to have another job for the foreseeable future. However, the administrative staff at EMBL-EBI encouraged her to at least have a small business idea that she could work on.



JENNIFER DEEGAN

Pictures of fern gametophytes taken using Jennifer Deegan's camera system (left and on facing page).

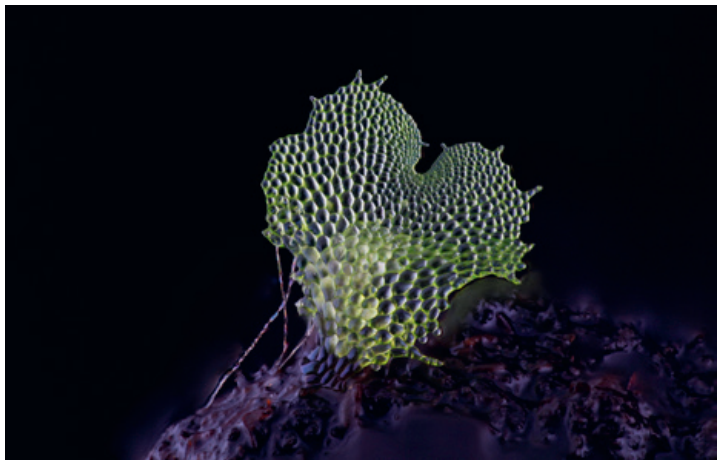
"EMBL-EBI really set me on a good road in many different ways," says Deegan. "After leaving, I bought the Canon DSLR camera that was the foundation of all of my future work. It took a long time to come back to academic science, via garden photography and a stint in garden design, but the camera was the thing that brought me round to the right place in the end."

With the support of her previous research group, Deegan started to develop a macrophotography system at home. Her goal was to take photos of fern gametophytes: the tiny plants – around 2 mm in size – in which a fern's sexual reproduction phase plays out. The problem with photographing fern gametophytes is the high magnification that is needed to capture them on camera. This causes a very shallow depth of field, which means that while one small area of the specimen is focused, the rest sinks into a blur. Until now, biologists have relied only on drawings of fern gametophytes, as it was not possible to take useful photographs.

Deegan and her group received a grant from the University of Cambridge OpenPlant Fund to proceed with the project. This also required that the progress of her work be carefully documented with videos, which are available on a YouTube channel called Chlorophyllosophy.

Deegan developed a system that would move the camera progressively closer towards the specimen. After every tiny step of 10 µm (0.01 mm), the camera would take a photo, resulting in about 40 photographs with different areas in focus. The photos were then merged into a single, fully focused picture. Setting up this system required a lot of experimentation with hardware and coding, work which Deegan enjoyed very much.

"My favourite part was when I stripped a stepper motor out of an old flatbed scanner and had to figure out by experiment how it worked. I had to write code to make the stepper motor move, and then figure out from the movements which of the five wires was which, and how they joined up inside the motor. I then had to write more code to make the motor move in single steps in the right direction. That was a lot of fun."



JENNIFER DEEGAN

JENNIFER DEEGAN

EMBL alumna Jennifer Deegan.

Deegan relied on the experience she had gathered while coding at EMBL-EBI, along with advice from her computer scientist husband. Deegan coded the system to work with an Arduino or a Raspberry Pi computer. Both systems were documented and are available online to anyone who wishes to build their own system.

The project proceeded to win the 2017 Biomaker Spirit trophy, a prize for inventors of electronics equipment for biomedical science.

After building her macrophotography system, Deegan is still coding. "The microscope code requires constant adjustment for my different photographic specimens, so that's a nice thing to do as I'm battling with my tiny plants," she says. In addition to her scientific work, she writes scripts to process orchestral sheet music for the community orchestra that she, her son and her husband play in. She's also teaching her son how to code.

"It's amazing the things that can grow out of a beginner's Java course!" says Deegan.

READ ONLINE:
BIT.LY/embl-93-27

READ MORE ABOUT THE MICROSCOPY PROJECT AND THE PEOPLE WHO CONTRIBUTED TO IT:
BIT.LY/embl-93-27a
BIT.LY/embl-93-27b

Bringing science to life

Storybook characters teach children about DNA

NEIL CHAPMAN AND LISA MULLAN

Lisa Mullan with an illustration from the Dinky Amigos Adventures.

BY CELLA CARR

When Lisa Mullan left her role as Scientific Training Officer at EMBL-EBI in 2006 to focus her energies on family life, she decided to revisit an idea that had occurred to her many years before: the creation of a set of cartoon characters to teach children about DNA. "I saw some bases drawn out and I thought, 'They look like little people!'" she says. Much drawing, writing and testing of ideas ensued, culminating in the creation of the Dinky Amigos: four characters called Alina, Crispin, Tristan and Gina, who get up to all kinds of adventures in the human body.

Mullan has now created two series of books: the Dinky Amigos Adventures, targeted at children from the age of four upwards, and the *My DNA Diary* series for older children (9–12 years), which introduces more of the chemistry of DNA. Her writing involves multiple iterations, distilling down the content, testing it on her non-scientist husband and their children, and going back to the drawing board again.

Bringing DNA into the classroom

Mullan's passion as a science educator is clear: "I love science and I love teaching – seeing those lightbulb moments." Not content to simply put her books out into the world and hope for the best, she also runs workshops in schools. "It's amazing what the children learn," she says. "In follow-up writing exercises, even children who were struggling in class produced work that would be appropriate for a high-grade student. And teachers have been surprised at the level of engagement by students with challenging behaviours." For Mullan, simply wearing her lab coat during workshops arouses curiosity in young audiences. She recalls with a smile one little girl who came up to her and proclaimed: "I've never met a scientist before. This is the best day of my life!"

NEIL CHAPMAN

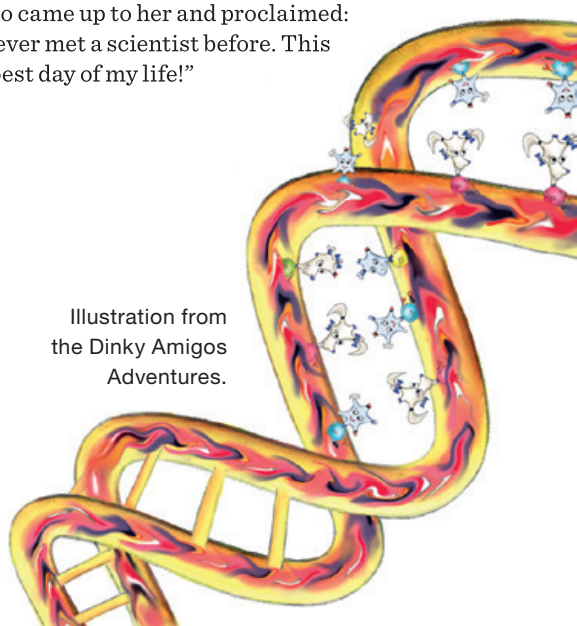


Illustration from the Dinky Amigos Adventures.

EMBL's coding past

Visualising 3D protein structures on the graphical workstations, 1999.

Write once, read many – these CRV discs were used largely as early portable data backups.

As at present envisaged, these facilities will include:

1. A medium size central computer in the Heidelberg Laboratory. This computer will be linked to a projected large computer operated by a neighbouring institute. The possibility of joint operation of the large computer is under consideration.

2. Dedicated mini-computers, integrated into the central computer system, for control and data processing of various experimental projects.

3. Small or medium size computers at the two EMBL outstations.

EMBL

Excerpt from an EMBL job advert from 1975: installations to be overseen by EMBL's first 'Head of Computing'.

Biological research equipment controlled by a Macintosh, circa 1990.

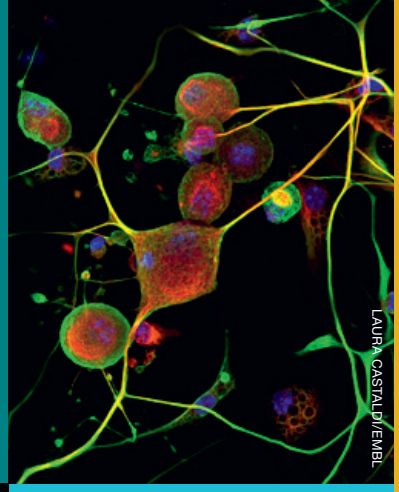
EMBL alumnus Jörg Schultz and current EMBL group leader Peer Bork in 1999.

EMBL

Events

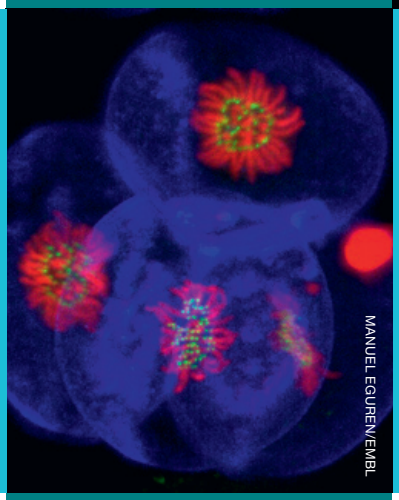
August
28–29

EMBL Heidelberg
EMBL Conference:
A Life for Science – Symposium in Memory of Fotis Kafatos


LAURA CASTALDI/EMBL

September
22–25

EMBL Heidelberg
EMBO Workshop:
Creating is Understanding: Synthetic Biology Masters Complexity


MANUEL EGUREN/EMBL

October
7–9

EMBL Hamburg
EMBO Workshop:
Tools for Structural Biology of Membrane Proteins

October
8–10

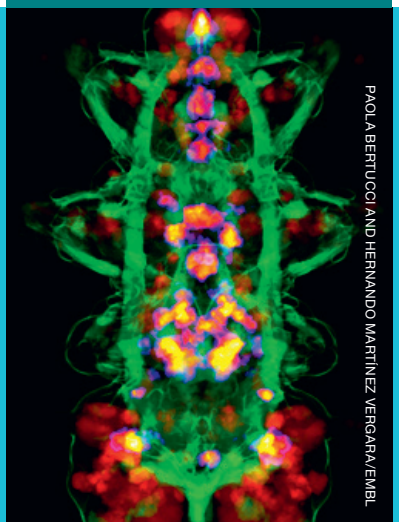
EMBL-EBI
EMBL Course:
Exploring Biological Sequences

October
9–12

EMBL Heidelberg
EMBO | EMBL Symposium:
Seeing is Believing – Imaging the Molecular Processes of Life

November
4–6

EMBL Heidelberg
EMBL Conference:
Cancer Genomics


PAOLA BERTUCCI AND HERNANDO MARTÍNEZ VERGARA/EMBL

November
13–16

EMBL Heidelberg
EMBO Workshop:
Precision Health: Molecular Basis, Technology and Digital Health

Upcoming meetings
Alumni

19 July
EMBL World Alumni Day, EMBL Heidelberg

2 September
EMBL in Australia, Brisbane

30 September
EMBL in France, Marseille

7 October
EMBL in Spain, EMBL Barcelona

18 October
EMBL in Sweden, University of Gothenburg

8–9 November
EMBL in the USA, Stanford University, California

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