The European Molecular Biology Laboratory Magazine

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EMBL etc.

Failure

At the heart of the scientific method

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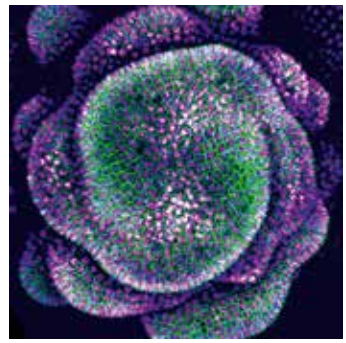

Cultures

EMBL community stories

PHOTO: EMBL/MARIETTA SCHUPP

Editorial

Science is a world of ideas, creativity and scholarly contemplation. But hidden behind the condensed narrative of academic papers one can find countless stories of failures which form an essential part of the research process. Our lead feature in this edition focuses on the work of two researchers from the EMBL community whose struggles illustrate the nature of life in the lab in its human glory. One is a tale of setbacks preceding the discovery of key mechanisms driving the cell cycle (page 14). Another profiles a failed experiment that led to unexpected insights into something else entirely (page 16). These stories carry an important message: that rather than being the opposite of success, 'good' failures are part and parcel of great science.
As always, this edition features a range of other stories, including advice on overcoming feelings of self-doubt (page 40), investigating what it would take to regrow an arm (page 19) and behind the scenes coverage of a stunning exhibition (page 34). We also say farewell to EMBL's senior graphic designer Petra Riedinger, a colleague and friend who retired after more than 40 years of creating graphics, artwork, illustrations and more besides (page 29).

Adam Gristwood
Editor

Word to remember

Auxins

Noun, pronunciation:
/awk-sins/

A family of hormones found in plants that promote growth through cell elongation.
See page 6.

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From the Director-General


PHOTO: EMBL

While I was studying for my PhD, gene cloning in bacteria and yeast were still brand new techniques. My initial goal was to harness these exciting methods to study the molecular basis of a rare human genetic condition. In hindsight, I realised my supervisor had set me an impossible task. Despite my best efforts, the sophisticated assays that I needed simply didn't exist at the time. After reluctantly admitting defeat, I moved on to another project in a neighbouring lab studying gene conversion in the fungus *Neurospora*. I was tasked with cloning a mutant gene in the belief that this could help understand gene conversion at the DNA level. The study was long and arduous: in those days we had to painstakingly make the right enzymes to cut and join strands of DNA rather than buying them. Support from my supervisor, as was normal in the UK at that time, was minimal. We discussed my project twice, once at the beginning, once after my thesis was written. Despite spending several months teaching myself techniques and eventually cloning the gene, I found it could not provide the new information on gene conversion as I and my supervisor had hoped. My project failed.

It could have been easy to get dispirited by these setbacks. But instead such moments made me realise that I was determined to stay in research. As I battled my way to the completion of my PhD and moved on to a postdoc, I had developed a terrific feel for experimental work. As an experimental scientist – like in many other fields of research – you imagine how something works, set up experiments, test your hypotheses and oftentimes they just do not work. One of the most important challenges is to develop the skills needed to know when something is a failure because of unreliable experimentation and when it is a failure of hypothesis. In essence, as scientists we need to learn when to persist and when to give up.

On many occasions things happen that you can't predict. One of the hardest times in my career was a postdoctoral project where I realised that the data on which my study was based were deeply flawed: I strongly suspect that the people who did the prior work faked their data. This only hardened my resolve to carry on and do things the right way, which I was lucky to be able to do in a second postdoc. 'Good' failures, on the other hand, are inevitable when you push in new research directions. In this sense, failure is not something to be afraid of – rather, it is part of a scientific adventure. Knowing when to push on or admit defeat is a judgement call, but one that every one of us can learn to make. The theme of this edition of EMBLetc is inspired by the reality that failure lies at the heart of the scientific method. As Irish playwright Samuel Beckett wrote: Ever tried. Ever failed. No matter. Try again. Fail again. Fail better.

Iain Mattaj,
EMBL Director-General

Spiral growth

Feedback loop behind spiral patterns in plants uncovered

BY SONIA FURTADO NEVES

This flower-like image shows a plant that is not developing quite right. It comes from a study in which scientists at EMBL and the University of Sydney unearthed the molecular feedback loop that creates the spiral pattern of leaves around a stem. The work was published in *Current Biology* in November.

For centuries, artists, biologists and mathematicians have been inspired by the recurring patterns of the plant world: the exquisite symmetry of flowers, the sweeping spirals of seeds, spines and leaves. The plant in this image, however, has gotten its spiral wrong. Instead of several leaves spaced out in a spiral pattern, it has two continuous, spiral-shaped organs developing.

Auxin hotspots

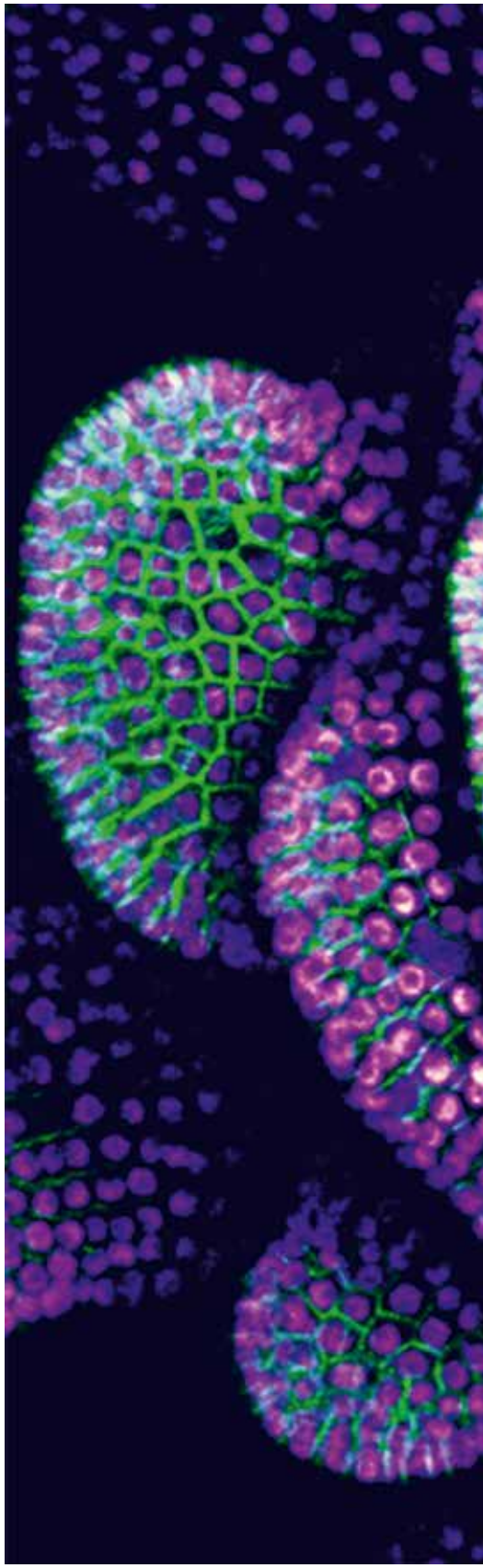
How do plants create such amazing patterns? Based on mathematical modelling and computer simulations, scientists know that if plant organs like leaves or petals are produced at regular intervals, these complex patterns can automatically emerge. So how do plants produce organs at regular intervals? Biologists knew the answer involved cells in the growing plant coordinating with their neighbours to transport the plant hormone auxin to sites where it accumulates. At each auxin hotspot, a new leaf begins to grow. But how are these hotspots formed and maintained?

Neha Bhatia, a PhD student in Marcus Heisler's lab at EMBL, found that if a cell detects a lot of auxin, it makes neighbouring cells transport the hormone towards that cell. This creates a hotspot. At the same time, it depletes auxin levels in the surrounding area, so another hotspot can only form a fair distance away, where that cell's influence is no longer felt. This, the EMBL scientists conclude, is what creates the regular spacing between auxin hotspots, and consequently between leaves.

Surprisingly, Bhatia found that this feedback loop has to be active not just in the cells on the surface of the growing plant, but also in the cells below. If only surface cells can respond to auxin, the auxin seems to build up too much and starts to leak sideways. This gives rise to the wonderful spiral shaped organs in the picture. The EMBL scientists speculate that this could be what happens in some species of *Cereus* cacti, whose leaves are spiral-shaped.

Bhatia N, *et al. Current Biology,* published online 3 November 2016. DOI: 10.1016/j.cub.2016.09.044

MORE ON HEISLER'S WORK:
NEWS.EMBL.DE/?p=8399



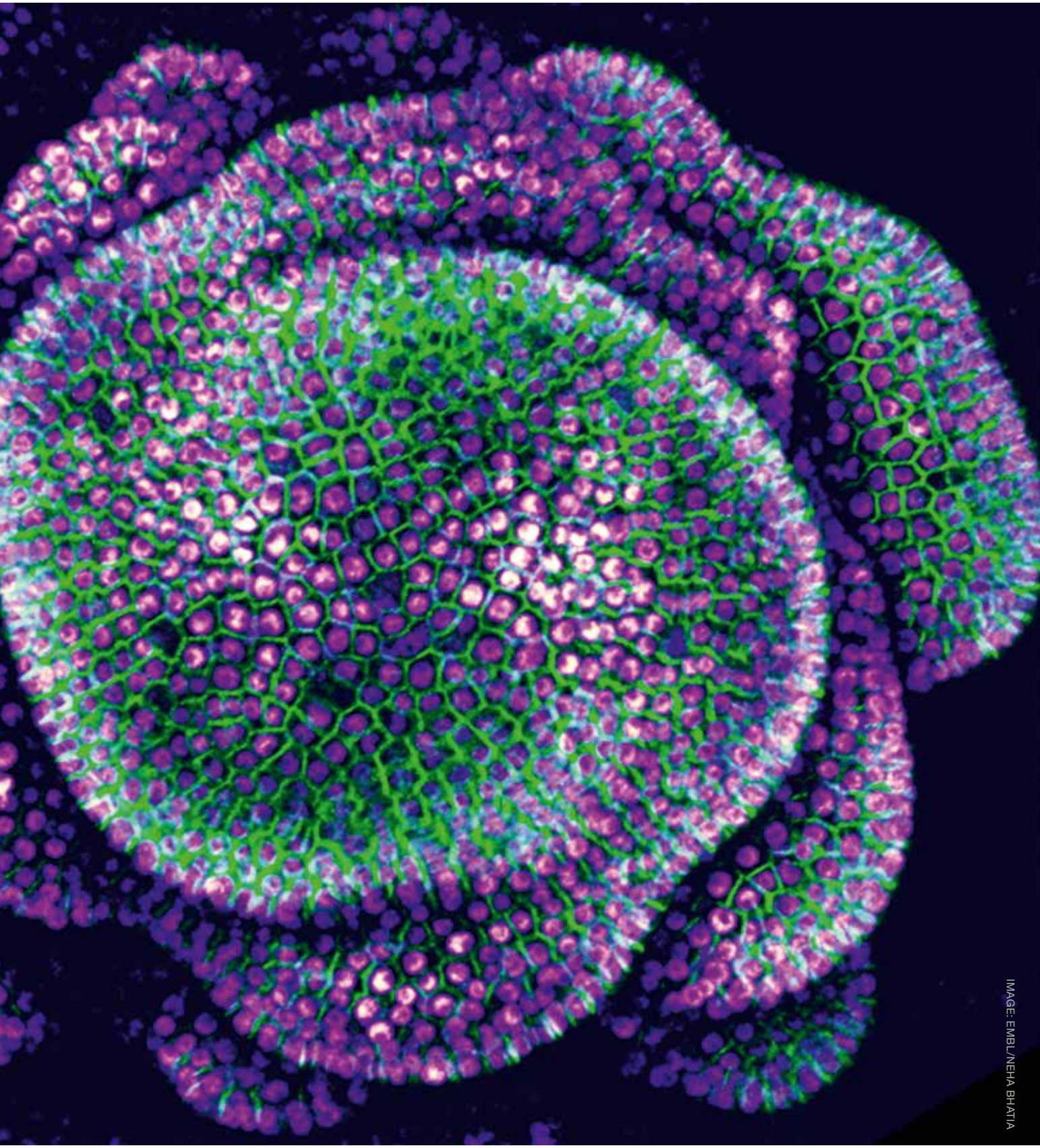


IMAGE: EMBL/NEHA BHATIA

EMBL's Rainer Pepperkok, Eric Karsenti, Peer Bork, and Stefanie Kandels-Lewis present their research during a podium discussion moderated by Volker Mosbrugger, Director of Senckenberg Research Institute and Natural History Museum.

PHOTO: EMBL/MARIETTA SCHUPP

Diving into Autumn

Participants learn about EMBL's ocean biodiversity research at the Fall Gala

BY MARGAUX PHARES

For one special evening in September, EMBL's Advanced Training Centre was transformed into an underwater grotto on the occasion of EMBL's autumn gala, or Herbstgala. Upon invitation of Iain Mattaj, EMBL's Director-General, 140 participants from the worlds of science, business and politics came together for this benefit event. Among the invited guests were also a group of EMBL Teens – the youngest members of the Friends Programme – who had the opportunity to directly interact with EMBL researchers and supporters. EMBL's ocean biodiversity research was the central theme, thus the scene was set with 'green algae' streaming down from the ceiling high above. The auditorium foyer, bathing in the last of the sun's rays, was illuminated in blue and green light, while participants convened at glowing tables to enjoy an evening of speeches, films and performances.

Much of the action pivoted around the Tara Oceans expedition, a four-year journey around the world that has enabled researchers to learn much more about crucial plankton species in the world's oceans. These hidden depths were explored during a panel discussion featuring EMBL's Peer Bork, Steffi Kandels-Lewis, Eric Karsenti and Rainer Pepperkok, moderated by Volker Mosbrugger, Director-General of Senckenberg. This followed an inspirational speech by Herbert Nitsch, the world free-diving record holder – also known as 'the deepest man on Earth'. Guests were regaled with fine food created by EMBL's head chef Michael Hansen. Entertainment was provided by pianist Rick Coleman and by the Victoria Söntgen Ensemble with a dance performance exclusively created for this event.

The gala, which was organised by EMBL's Office of Resource Development, also featured images from the 'Life in Perspective' exhibition – 3D portraits of plankton from the Tara Oceans samples photographed by EMBL's Sébastien Colin. These were auctioned at the dinner, the proceeds of which will support EMBL ocean biodiversity research in areas ranging from marine model organisms to the oceans microbiome and plankton imaging.

Drivers of evolution hidden in plain sight

A rapid, versatile mechanism that modifies proteins is revealed to be crucial for the evolutionary process

BY MARY TODD BERGMAN

Research led by EMBL-EBI and the University of Washington has shown that the biological diversity needed for evolution can be generated by changes in protein modifications. The findings, published in *Science* in October, provide valuable insights into how different species adapt to different environments and could shed light on how pathogens evolve and become resistant to drugs.

"This study is about understanding how evolution works, which tells you how species adapt to changing environments over many generations," says Pedro Beltrao, a research group leader at EMBL-EBI. "For example, when you compare humans and chimps, they are obviously different, even though a good part of their genetic makeup is more or less the same. Our task is to figure out how diversity is generated, so that we can see in detail how life evolves. That helps us understand how plants and animals adapt and change, and how cancers or bacteria find their way around drugs."

A question of expression

Research into the drivers of genetic diversity has largely focused on gene expression, which controls how much of a given protein will be made, when, and in what tissue. However, the researchers found that a well-known cellular mechanism – one that controls how proteins acquire new functions – also plays a major role.

Proteins are controlled by other proteins by way of 'post-translational modification' (PTM). One type of PTM is phosphorylation: a rapid, versatile protein-regulation mechanism. During evolution PTMs can be acquired via mutations, which allows proteins to gain new functions, turn on or off at different times, and go to different places in the cell. Previous studies comparing proteins in related species have shown very few mutations, so PTMs have not been considered to be a major factor in generating diversity. The collaboration found that only a few mutations are actually required to change these protein-modification sites. In other words, a small number of changes can have a big impact on how proteins and cells work.

IMAGE: EMBL/SPENCER PHILLIPS

An artist's interpretation of the molecular diversity that drives evolution.

"These mutations were hidden in plain sight – we could see them all along, but didn't know they could have such significant consequences," says Beltrao. "We only see it now after many years of developing and refining new experimental methods. Learning more about the role of PTMs in evolution also presents a much more reliable picture of how signalling proteins integrate and relay information inside the cell. This in turn could present exciting new avenues for therapeutic research."

Studer RA, *et al.* (2016) *Science*, published online 14 October. DOI: 10.1126/science.aaf2144

FULL STORY ONLINE:
NEWS.EMBL.DE/?p=8240

Blood, big data and epigenetics

Blood disease research has been taken to a new level with a suite of 47 scientific papers published in *Cell* and other high-profile journals by the International Human Epigenome Consortium (IHEC). To support biomedical research, IHEC and the EU-funded BLUEPRINT project have made the 1000+ associated datasets freely available to all. The work, published in November, is the result of coordinated efforts by scientists in Canada, Japan, Singapore, South Korea, the United States, the United Kingdom, Germany and other EU Member States. EMBL-EBI provided data coordination, analysis and infrastructure, and contributed directly to research findings.

READ MORE IN THE NEXT EDITION OF EMBLETC AND ONLINE: NEWS.EMBL.DE/?p=8505

Turning up the heat on drug side effects

Side-effects of leukaemia drug explained, reveal possibility of repurposing to treat other diseases

BY ADAM GRISTWOOD

By tracking the impact of a widely used leukaemia drug on proteins inside living cells, research led by EMBL and Cellzome has shed light on the molecular causes of the drug's side effects. Published in *Nature Chemical Biology*, the study also indicates that the drug has potential to be repurposed to treat tyrosinemia, a rare genetic disorder that can lead to liver, kidney and neurological problems.

Many drugs used in the treatment of cancer have severe side effects. These occur when the drugs affect not only the target proteins in tumour cells, but also proteins in healthy cells. By identifying proteins that are inadvertently targeted by anti-cancer drugs, scientists aim to learn more about who might be affected, how and why, in order to better inform treatment.

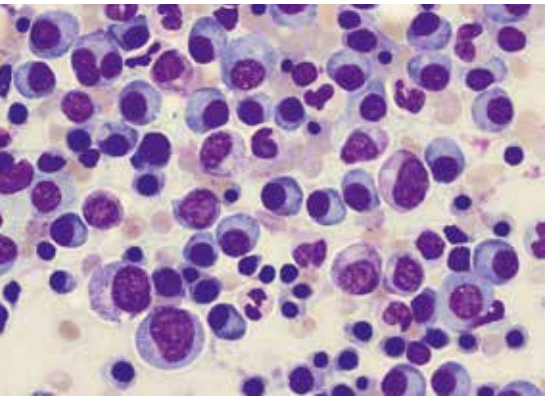


IMAGE: HGH (CC BY 3.0)

Histopathological image of multiple myeloma.

Warming up

Two years ago, at drug discovery company Cellzome, an international team led by Mikhail Savitski developed an elegant method known as thermal proteome profiling, which they believe can provide answers to such puzzles. By heating up cancer cells, the technique enables researchers to compare the 'melting' behaviours of individual proteins before and after the administration of a cancer drug, ultimately revealing which proteins the drug is targeting.

"After we developed this technology I could not stop thinking about ways to develop it and apply it in different settings – it opens up some very exciting research paths," explains Savitski, who joined EMBL as a group leader this year.

Sidetracked

One of these paths emerged out of the blue. The team was developing a refined version of the technology using a drug for multiple myeloma – a type of leukaemia that affects plasma cells. In some patients, the drug, panobinostat, causes a variety of serious side effects, including hyperthyroidism.

In the study, Savitski and colleagues identified an unexpected target of the drug: a protein called phenylalanine hydroxylase (PAH). As its name implies, PAH acts on phenylalanine. Phenylalanine is an amino acid, one of the building blocks proteins are made of, so it is essential for life. But too much phenylalanine can lead to problems including neurological damage and hyperthyroidism. PAH's job in the cell is to convert phenylalanine into another amino acid – tyrosine –, but when this conversion does not happen it can lead to hyperthyroidism. The leukaemia drug inadvertently targets PAH, phenylalanine is not converted to tyrosine as it should be, so it accumulates in a patient's cells. "Our study underscores the importance of monitoring amino acid levels in patients and the need to take caution when applying the drug," says Marcus Bantscheff, head of technology at Cellzome, who co-led the study.

The research, which was supported by colleagues from Utrecht University and the University of Texas Health Science Center, also identifies panobinostat as the first drug capable of inhibiting PAH, opening up potential avenues for repurposing it to tackle other illnesses. "It could provide an opportunity to develop treatments for diseases where PAH plays a big role, such as tyrosinemia," adds Isabelle Becher, the first author of the study. "The study provides an ideal starting point from which one can look to develop a drug that is really specific."

Becher I, *et al. Nature Chemical Biology*, published online 26 September 2016. DOI: 10.1038/nchembio.2185

FULL STORY ONLINE:
NEWS.EMBL.DE/?p=8051

False positive

BY SONIA FURTADO NEVES

Scientists in Theodore Alexandrov's lab at EMBL have developed the first bioinformatics framework for finding metabolites in large datasets from imaging mass spectrometry. The framework and open-source software, published in *Nature Methods*, mimic how people manually analyse such data, but is unbiased, and a million times faster than a human.

FULL ARTICLE ONLINE:
NEWS.EMBL.DE/?p=8484

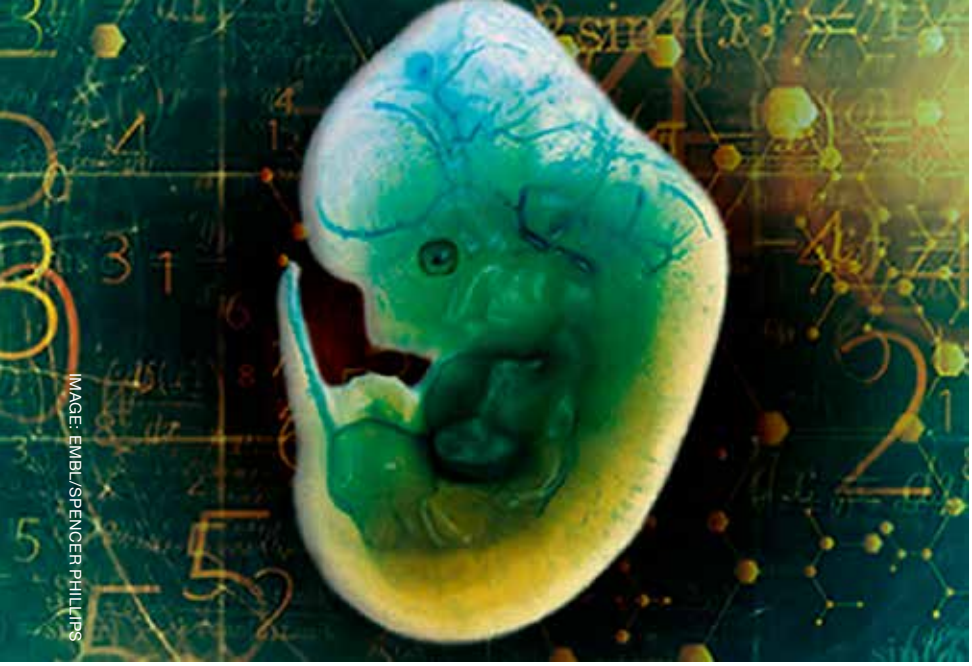


IMAGE: EMBL/SPENCER PHILLIPS

The IMPC's goal is to determine the functions of some 20 000 genes common to mice and humans.

'Essential genes' help focus research

International study identifies 410 genes essential to life in the mouse, and promising candidates for studying human disease

BY MARY TODD BERGMAN

New research from the International Mouse Phenotyping Consortium (IMPC) reveals that roughly a third of all genes in the mouse genome are essential for life. The results of the study, published in *Nature* in September, are an important new resource for studying mammalian development and human disease.

Cataloguing genes and functions

Identifying genes that are essential to life in the mouse provides a window on human disease, particularly in cases where essential genes for mice overlap with genes associated with human disease.

The IMPC's goal is to determine the functions of some 20 000 genes common to mice and humans. This global effort is systematically turning off the protein-coding genes in the mouse genome in order to assess the physiological characteristics associated with each gene. EMBL-EBI, in collaboration with MRC Harwell and the Wellcome Trust Sanger Institute, delivers IMPC informatics. This involves coordinating, analysing and sharing the project's valuable data connecting genotype and phenotype.

Essential for life

The study provides insights into the functions of the project's first 1751 genes, and identifies 410 that are 'embryonic-lethal' – that is, essential for life. The embryonic-lethal knockouts identified corresponded very well with genes from human cancer cell lines previously identified as 'essential to life', and with findings from the ExaC Consortium. "The embryonic-lethal genes we identified have counterparts in humans that are associated with loss of function, which makes them strong candidates for undiagnosed human genetic conditions," explains Steve Murray of the Jackson Laboratory in the US, corresponding author on the paper.

"We worked closely with the biologists and informatics colleagues in the consortium to establish a common language and develop easy-to-use tools," adds Terry Meehan, a principal investigator on the project and IMPC Coordinator at EMBL-EBI. "That makes it easier for everyone to focus on the research, rather than struggling to piece the data together."

Making the most of it

"Science doesn't stand still. We are always working with state-of-the-art technologies to maximise the knowledge we can gain from each mouse, and promoting Replacement, Reduction and Refinement by sharing all the data freely and being transparent in how we analyse it," says Helen Parkinson, head of Molecular Archive Resources at EMBL-EBI. The IMPC incorporates high-resolution 3D imaging and automated, computational analysis of the images.

The consortium shares all of the data and images they generate through an open-source, web-based resource, without embargo. The project's mouse strains are made available through public repositories such as EMMA and KOMP. This enables researchers to mine the data and design their own experiments.

Dickinson ME, *et al. Nature*, published online 14 September. DOI: doi:10.1038/nature19356

FULL STORY ONLINE:
NEWS.EMBL.DE/?p=8140

In 2013, an estimated 1.5 million people died from the disease

IMAGE: JANICE CARR, CENTERS FOR DISEASE CONTROL AND PREVENTION

New drug candidate unleashed for TB

EMBL researchers help to design a lead compound active against four different pathogens

BY MARGAUX PHARES

Due to the alarming spread of totally drug resistant strains of *Mycobacterium tuberculosis* (TB), scientists are seeking new drugs to combat this life-threatening pathogen. Stephen Cusack, Head of EMBL's Grenoble site; and Andrés Palencia, an EMBL alumnus now at the Grenoble Institute for Advanced Biosciences contributed important structural biology expertise to a large consortium of chemists, biochemists and microbiologists led by Anacor Pharmaceuticals (Palo Alto) to help tackle this problem.

Their work resulted in the discovery of a promising new, orally available, anti-TB drug candidate that can reduce the infection in mice with comparable potency to current frontline drugs. Furthermore, the same compound was also shown to be active against three other human pathogens. The results were recently published in three papers in *Antimicrobial Agents and Chemotherapy*.

Four birds with one stone

The researchers demonstrated that benzoxaboroles, a family of small molecules developed by Anacor, have antibacterial or antiparasitic activity against the pathogens behind four widespread and debilitating diseases: TB, malaria, cryptosporidiosis, and toxoplasmosis. These pathogens are very different kinds of organisms, but they all have one feature in common: an enzyme called leucyl-tRNA synthetase, or LeuRS, which is the target of benzoxaboroles.

LeuRS is one of a family of proteins that are essential to protein synthesis in all living cells. Its job is to attach the amino acid leucine to the corresponding leucine-specific transfer RNA ($tRNA^{leu}$) which is used by the ribosome to incorporate leucine into the growing polypeptide chain during protein synthesis. Sometimes LeuRS mistakes leucine for another similar amino acid such as isoleucine, but remarkably the enzyme can correct this error using a second active site, called the editing site.

Benzoxaboroles work by binding to the LeuRS editing site and at the same time attaching themselves to the end of the $tRNA^{leu}$ where leucine would normally bind. Thanks to the boron atom contained in the benzoxaborole, the $tRNA^{leu}$ and LeuRS are held together so tightly that they can no longer function normally. "When you block LeuRS activity you stop protein synthesis and kill the pathogen," Palencia explained.

Complex interactions

To help in the drug development process, Cusack and Palencia used X-ray crystallography and biophysical measurements to show in detail how LeuRS, $tRNA^{leu}$ and benzoxaboroles interact with each other. "Based on the high-resolution 3D structures we determined, Anacor chemists were able to tailor the compounds to better inhibit TB's LeuRS," Palencia said. The compound reported in the publication is as good as TB drugs that are currently in use but, crucially, is also equally active against drug resistant strains. Even better anti-TB benzoxaboroles are in the pipeline and are expected to go into clinical trials soon, the next critical step in the long drug development process. *Cusack and Palencia give their behind the scenes stories: see pages 18-21.*

Palencia A *et al. Antimicrobial Agents and Chemotherapy,* published online 8 August 2016. DOI: 10.1128/AAC.01339-16
Palencia A *et al. Antimicrobial Agents and Chemotherapy*, published online 18 July 2016. DOI: 10.1128/AAC.00873-16

FULL REPORT ONLINE:
NEWS.EMBL.DE/?p=7908

The ‘F’ Word

How the secrets to success can come from failure

ILLUSTRATION: AAD GOUDAPPEL

Cycle of life

Paul Nurse's failed experiment inspired a career that would uncover key mechanisms of cell division

BY ADAM GRISTWOOD

When Paul Nurse was a student in the 1960s, scientists knew that cells divided and made copies of themselves. Yet key questions remained a mystery: What controls these divisions? How is the copying of DNA initiated? What drives cells to divide? Gripped by these puzzles, Nurse, Chair of EMBL's Scientific Advisory Committee and Secretary-General of EMBO, would go on to win a Nobel Prize for identifying crucial mechanisms underlying the cell division process. Yet things could have turned out very differently.

"I had very good grades in school and was offered a place at every university I applied for," says Nurse, who now heads the Francis Crick Institute in London. "However, the offers were conditional on me passing a very elementary French exam, and I failed it six times – it's not like I wasn't trying, but I am completely incompetent at languages."

Against the odds

Struggling with his French re-sits, Nurse left school and spent time working as a technician in a laboratory run by a local Guinness brewery. Each week he quickly completed his work, leaving plenty of time for research projects, which he loved. But he just could not pass French and it took a chance encounter with Birmingham University Professor of Genetics John Jinks to ignite his scientific career. Jinks recognised Nurse's potential and arranged for him to enrol as an undergraduate biology student. "There was a sting in the tail because the University Senate insisted I study French in my first year!" Nurse recalls.

But there were more hurdles to come. "I was initially interested in ecology, but a field trip collecting specimens in freezing waters taught me I was better suited to the warmer environment of the lab," Nurse says. It was here, under the guidance of an eccentric zoology lecturer Jack Cohen, that he undertook a project measuring the respiration rate of dividing fish eggs.

"Cell division is the basis of all growth and development – I was immediately fascinated by it," he recalls. Over the course of the following months, Nurse carefully collected eggs from the University aquarium, placing samples in a sealed chamber. He then measured ambient oxygen levels, painstakingly observing the effects of different inhibitors. "I soon saw that the respiration rate oscillated every fifteen minutes or so, which is also roughly the time needed for the fish eggs to divide," he says. "Strangely this pattern persisted no matter what I did to the system – it seemed incredibly robust."

Yet a week before Nurse was due to hand in the work, a seemingly routine control test left him stunned. "I ran the experiment with no eggs in the chamber and I measured the same, perfect, oscillation," he says. "I repeated the experiment again and again, convinced there must be a mistake. But I eventually realised that rather than measuring the respiration rate of the eggs, all the time I had been monitoring the effects of a thermostat in my apparatus. It was a complete failure from beginning to end."

With his grades at stake and just one week to go before presenting the study, Nurse faced a big problem. "The only thing that I could think of to salvage my degree was a piece of theatre," he recalls. "In my presentation I relived the whole study, from its exciting beginnings to its disastrous ending – and somehow the audience was impressed. One key message was: do controls early on in your study, as soon as it becomes interesting!"

Keep going

"At my low points, I contemplated alternative careers," he says. "But I am very much an experimentalist at heart and I have been lucky over the course of my career to have had very supportive colleagues." Ultimately undeterred, Nurse successfully completed his degree and PhD. As a postdoc, he saw the cell cycle as a way to learn more about what fascinated him most: the nature of life. "The cell is the simplest thing that demonstrates life," he says. "Key to understanding that is knowing how information is managed in the cell to generate order in space and time."

PHOTO: ROSIE HALLAM

Paul Nurse, Chair of EMBL's Scientific Advisory Committee and Secretary-General of EMBO.

Inspired by studies showing how genetics could be used to study the budding yeast cycle, Nurse returned to a research subject that he first encountered working in the Guinness laboratory: brewer's yeast. "I wanted a model organism that would be simple and effective," he recalls. He led work that treated yeast in a way that induced mutations randomly in genes throughout the yeast genome.

Nurse figured that the key to identifying genes controlling cell division in the yeast would come from studying cells that divide particularly slowly (creating bigger cells) or particularly quickly (creating smaller cells). The second category he discovered by chance. He observed some unusually small cells that divided more rapidly before they could grow and identified a mutation in a gene called *cdc2* that appeared to play a role in initiating key stages of the cell division cycle. "Sometimes nature provides the best leads," he says.

After discovering that a *cdc2*-like gene was also in another type of yeast, Nurse wondered if the gene might exist in all organisms – a question he began to tackle at the Imperial Cancer Research Fund labs in 1984. "There were a few eyebrows raised as to what exactly a yeast researcher was doing at a cancer research centre," he says. His team took a human gene library and added it to yeast lacking the *cdc2* gene. Incredibly, after one of the human genes was added to the yeast, it resulted in the cells dividing as normal. It enabled Nurse to go on to draw the astounding conclusion that a fundamental engine driving the cell cycle was the same in all species, a mechanism that had traversed 1 to 1.5 billion years of evolution.

"It was a complete failure from beginning to end"

The work led to the discovery (with friend Tim Hunt) of cellular messenger molecules called cyclin dependent protein kinases – cellular messengers that pass signals and other insights into the nature of the cell cycle, all crucial for understanding health and disease.

"It is important to know the real stories behind science and the failures and successes that are part and parcel of our work to inspire the next generation of scientists," Nurse adds. "There is still a lot we don't know about how cells organise in space and time, but I think we will make real progress in the coming half century because of the methodologies that we have developed in the past five decades. And, of course, as I learned from my fruitless experiments on fish egg respiration, from the countless failures we have made along the way."

Catching the chaperone in the act

How Christian Löw's failed experiment led to an unexpected scientific journey

BY ROSEMARY WILSON

"I probably should have thrown those protein samples away," says EMBL group leader Christian Löw. In 2009, one year into his postdoc, Löw was struggling to make any headway with his research into membrane proteins and he set up yet another crystallisation trial in the vain hope of making that long awaited step forward. "I knew the prepared batch was contaminated with other proteins before we even started," he says. "But we were under so much pressure to get results we went ahead anyway." Predictably, the membrane protein he needed failed to crystallise. Yet Löw had unwittingly shone light on another group of proteins that help chains of amino acids – the building blocks of proteins – fold into a 3D structure.

SlyD show

The story starts over a decade ago when, as an undergraduate, Löw came across a protein known as SlyD. Proteins produced by the cell start off as long chains of amino acids, somewhat like a bead necklace. Only when these chains have been folded into a 3D shape can they do the jobs they are destined to do. For the most part, a chain of amino acids folds into a 3D shape by itself, but for certain arrangements it needs a helping hand. SlyD is a protein of two parts: a chaperone that grabs hold of the chain and pins it in place, so that an enzyme known as prolyl isomerase can catalyse the changes needed. Although well studied, no one had been able to show just how SlyD does this – a problem that has long intrigued Löw, despite it not being the major focus of his research.

Years later, in temporary limbo while his PhD supervisor set up a new lab in Halle (Saale), Löw realised that crystallography could help him learn more about the atomic arrangements of SlyD. Shining X-rays on crystalline samples of the protein, he managed to determine the overall 3D structure of SlyD obtained from the bacterium *Thermus thermophilus*. Yet because protein crystals only capture one snapshot in time, he could not say much about how the protein actually functions. To do so he would have to capture the process at the precise moment the protein binds to the amino acid chain – and crystallise it in the act. "Chaperones such as SlyD only bind to their partners very fleetingly, often for only a few thousandths of a second – it didn't seem possible," Löw explains.

As he started his postdoc, SlyD remained a side project as he wrapped his mind around the challenge of studying membrane proteins. "Membrane proteins are the gateways to the cell and understanding how they let molecules in and out is crucial for working out how we might shuttle drugs into the cell, for example," Löw continues. "It's hard enough to crystallise proteins at the best of times, but membrane proteins are particularly difficult because they have to be extracted from the cell membrane before they can be crystallised. At the time there was a lot of frustration and we certainly did a lot of things wrong, but that's the membrane business!"

Synchrotron surprise

One day after yet another crystallisation trial, Löw was

surprised to see a set of well-formed crystals under the microscope. He knew these were far too forthcoming to be membrane protein crystals, but curiosity got the better of him: he took them to the synchrotron. "That was actually the first time I had been there on my own," he recalls. "I completely fried the few crystals, but nevertheless the data were encouraging." Follow up experiments showed that he had unwittingly managed to crystallise a close relative of SlyD, but this time from the bacterium *E. coli*. "Before we can crystallise a protein, we need to make lots of it," he explains. "We do this by inserting the gene that codes for the protein into *E. coli*, tricking it into producing the protein we need. In our case this didn't work and instead of membrane proteins, we managed to crystallise a contaminant from *E. coli*."

But even this SlyD did not bind long enough with the unfolded amino acid chains to be crystallised. Months later, frustrated with what seemed like another dead end, Löw struck upon an idea. What if he combined the *T. thermophilus* SlyD with amino acids identified for the *E. coli* SlyD? "*Thermus thermophilus* loves extremely hot temperatures, while *E. coli* prefers lower temperatures," he explains. "Typically the higher the temperature the weaker the binding, so I wondered if combining them in this way would hold it together long enough for us to finally manage to crystallise the moment the protein binds to the amino acid chain. And I was right!" he says with a smile.

Ten years of trials, tears and tribulations has now resulted in the publication of a data-rich paper in *BMC Biology*, including structural information and a proposed catalytic mechanism. "By following an unexpected lead, we've contributed significantly to the knowledge about protein folding," says Löw. And as for his membrane research? "We are a lot better at it now than we were eight years ago! Although it is still a challenging field, we have many more tools and methods at our disposal. Failure is such an important part of science: most important is to be able to look at your experiments and, even if it's not going as expected, there could be something interesting there. That is what makes a scientist a scientist. That is science."

Quistgaard EM *et al. BMC Biology*, published online 23 September 2016. DOI:10.1186/s12915-016-0300-3

"I probably should have thrown those protein samples away"

Christian Löw is based at EMBL's Hamburg site.

PHOTO: EMBL/ROSEMARY WILSON

Beyond the papers

Prompted by their discovery of a promising new drug candidate for tuberculosis, Andrés Palencia and Stephen Cusack share what it is like to take fundamental research into a pharmaceutical setting

A journey from bench to clinical trials

OPINION

Andrés Palencia on the work done at EMBL to guide the design of compounds that may help to fight drug-resistant TB and other diseases

Mycobacterium tuberculosis (TB) represents one of the most formidable threats to human health. The bacterium has a hardy outer membrane that protects it from disinfectants and allows it to survive on dry surfaces over long periods. It is also highly infectious: a sneeze from someone infected with TB can release thousands of aerosol droplets containing bacteria, while inhalation of fewer than 10 bacteria is sufficient to cause infection.

The high infectivity of TB has been well known for many years and in the past large hospitals were dedicated solely to isolating TB-infected patients. With the discovery of antibiotics for TB the situation improved and many infections could be treated, but the curve of improvement seems to be reversing. Why?

Drug resistance in the post-antibiotic era

In TB, we find not only multi-drug resistance (MDR), but also super-resistance: strains that are extensively drug-resistant (XDR) are not susceptible to first-line of defense drugs (Rifampin and Linezolid) and to at least one of the second-line drugs; strains that are totally drug resistant (TDR) are even more difficult, if not impossible, to treat. With cases of XDR reported in over 100 countries, new drugs are urgently needed.

Motivated by this need, an interdisciplinary project was established, involving scientists from EMBL in Grenoble (Stephen Cusack and myself), Anacor Pharmaceuticals in Palo Alto, US and others. Anacor and EMBL had previously worked together on a novel antifungal, now approved by the FDA for the treatment of toe infection (onychomycosis), and on the discovery of Gram-negative antibiotics for the treatment of complicated infections in humans, now in clinical studies. These previous compounds, called benzoxaboroles, shared an original mechanism: the inhibition of leucyl-tRNA synthetase (LeuRS), a protein responsible for charging leucine onto transferRNALeu, as required for protein synthesis. (For more on the development of these drugs, see page 20.)

Based on the known antibacterial activity of some benzoxaboroles, new derivatives were synthesized that showed medium potency against TB. High resolution

Andrés Palencia, an EMBL alumnus.

PHOTO: EMBL/ADAM GRISTWOOD

structural analysis of the TB LeuRS bound to one of these compounds gave us clues, at an atomic level, to design new compounds that showed improved activity. These improved compounds had excellent *in vivo* results in mice: they cured TB infections with comparable efficacy to Rifampin and Linezolid. As one would expect for a drug with a new mechanism of action, our compound worked equally well against TB clinical isolates resistant to existing drugs (see page 12).

Benzoxaboroles: one family, many applications

Given the novelty of this inhibition mechanism, we wondered whether the same mechanism could be used to fight other human pathogens, such as *Plasmodium, Toxoplasma* and *Cryptosporidium*, for which new medicines also urgently need to be found. Indeed, we went on to show LeuRS inhibitors that are active against these parasites. While the potency of these compounds is not as good as for TB, these results open the way for studies to improve the activity, and hopefully could lead to new anti-parasitic drugs.

Discovering a novel antibiotic for Gram-negative bacteria was an extremely difficult challenge, but to show that these compounds also have therapeutic potential for the treatment of TB, toxoplasmosis or even malaria, proves just how polyvalent they are. Just consider the different properties of the membranes that a compound has to penetrate before acting on the LeuRS target: it is not an easy task!

So, how is it possible that these compounds work so well against such different pathogens? First, their common target is universal: LeuRS provides an essential function for protein synthesis in all living cells. During the last years, Cusack's group and others have determined the crystal structures of LeuRS from several pathogens, and of the editing domain of the human protein. These revealed structural differences that can be exploited to develop inhibitors specific to a pathogen and that do not act on human protein, thus avoiding dangerous side-effects. Secondly, benzoxaboroles are small in size and easy to modify with different chemical substitutions; they also have good drug-like properties, an overall good oral bioavailability and low toxicity. Together, these properties make them very attractive for drug discovery.

This project has been extremely motivating for me: working with scientists from very different but complementary disciplines has favoured an exchange of ideas that was quite inspiring. Antimicrobial development is a long and very difficult path and tackling the problem from different angles was probably the key to our success. Working in such a big consortium also made possible getting promising compounds from bench to clinical trials in a relatively short time.

It makes me so happy to see our structures guiding the development of new compounds, some of which I hope can become medicines for the treatment of several infectious diseases.

Andrés Palencia is continuing this research on anti-parasitic drugs at the Institute for Advanced Biosciences in Grenoble, France.

Palencia A *et al. Antimicrobial Agents and Chemotherapy*, published online 8 August 2016. DOI: 10.1128/AAC.01339-16

Stephen Cusack, Head of EMBL's site in Grenoble.

PHOTO: ROYAL SOCIETY

2006, a year

OPINION

Stephen Cusack, Head of EMBL's site in Grenoble, looks back on the early days of his collaboration with Anacor developing anti-infectives targeting leucyl-tRNA synthetase

It all started at the 21st International tRNA Workshop in Bangalore in December 2005 where I first met Dickon Alley, Head of Discovery Biology at Anacor Pharmaceuticals in Palo Alto.

Anacor was founded to discover, develop and commercialise novel small-molecule therapeutics derived from its boron chemistry platform. Anacor scientists had screened a library of benzoxaborole compounds and shown that one of them (AN2690) was a potent and broad spectrum anti-fungal, whose target they showed to be the fungal leucyl-tRNA synthetase (LeuRS).

For many years, my lab had been determining crystal structures to understand how bacterial LeuRS works, including its editing function. Hence the meeting with Dickon in Bangalore, facilitated by Susan Martinis, from the University of Illinois, another biochemist working on LeuRS editing with whom we were already collaborating. We were all excited at the idea that structural biology might help understand how AN2690 functions.

Things moved fast and 2006 turned out to be an incredibly exciting year of discovery, the fruits of a highly interactive collaboration between the Anacor chemists and biochemists and my group. 100 mg of AN2690 was shipped to Grenoble in February 2006. On 21 March 2006 at 12.13pm I emailed Anacor:

'Dear All, Champagne all round! Anya [Yaremchuk] and I got the data yesterday. We have a beautiful 2 Å structure with the compound and AMP! It reacts with AMP to make a post-transfer substrate-like compound (transition state?) in the editing site with the AMP mimicking the terminal adenosine 76 of tRNA. So I guess you guessed right about the mechanism!' *Stephen*

# of champagne

Dickon replied:

'Congratulations that is excellent news!!! It was such good news the chemists productivity dropped dramatically this morning as they were thinking about all the possible chemical mechanisms that could go on in the editing active site.'

Then at 16:22 pm the same day I sent the following mail:

'Dear Dickon, I have just analysed the data we collected yesterday on the tRNA complex crystals soaked with the compound. These data are only at 3.5 Å... but the compound is clearly there covalently attached to the ribose in the editing site!!!! (more champagne)'.

These first structures, done in collaboration with my colleagues Anya Yaremchuk and Michael Tukalo, although of the bacterial LeuRS, not the fungal enzyme, still told us the essentials about how the compound inhibits leucyl-tRNA synthetase.

In parallel, my student Elena Seiradake was working on the editing domain from the fungal pathogen *Candida albicans* (which is significantly different from the bacterial one, although the mechanism of action does not change) and, with the help of Weimin Mao from Anacor, quickly made progress. On the 17th October 2006 I emailed Anacor:

'Dear Dickon, For the third time ... champagne (you owe me a lot of bottles!). Crystals of *Candida* editing domain diffract to better than 2 Å resolution (even though they are only 10 microns thick) and we have a dataset at 2.2 Å.' *Stephen*

The bubbly reply came back on the 18th October 2006:

'Dear Stephen, Excellent news! We will have to make it a Jeroboam or Mathusalem of Californian sparkling wine. The last couple days I went to a couple of sparkling wine vineyards, Chandon and Tattinger. There is also Freixenet and Mumm vineyards here as well. What is your preference? Fantastic.' *Dickon*

Later on 21st November 2006, another exchange:

'Dear Dickon, As of today, the Candida editing domain with AN2690-AMP is solved!' *Stephen*

'Dear Stephen, Wow!!!!!! and Congratulations, this is excellent news!!!! This will help us get better antifungal compounds as we are at the moment still stuck with AN2690 as our best antifungal compound. Sounds like we will need an entire vat or pipeline of champagne to celebrate at this rate!!!!!' *Dickon*

Meanwhile, my postdoc Thibaut Crépin succeeded in obtaining crystals of the complete *E. coli* LeuRS-tRNALeu complex that diffracted to exceptionally high resolution (2 Å). In November 2006 I emailed again:

'Dear Dickon, This should have the whole company jumping up and down! Basically Audrey [Zhou] got it right!' *Stephen*

A manuscript entitled 'An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site' was published in June 2007 in *Science*. AN2690 received FDA approval in 2013 and is now on the market as Kerydin® (tavaborole), a topical treatment of onychomycosis (toenail fungus). Lots more crystal structures done by Thibaut and then Andrés Palencia, another postdoc in my lab, were crucial in guiding development of new benzoxaboroles specifically tailored to target Gram-negative bacteria and *M. tuberculosis*. The latter was also shown to be active against the apicomplexan parasites *Plasmodium* and *Toxoplasma* (see page 12).

However nothing quite matched the excitement and fun that we had that first year!

FULL STORY ONLINE:
NEWS.EMBL.DE/?p=7871

The forelimb of a mouse embryo, showing muscle fibres in red and tendons in green.

IMAGE: M.P. COLASANTO (CC BY 4.0)

What would it take to regrow an arm?

Exploring what it would take to regrow a lost limb, and what we might learn along the way

BY SONIA FURTADO NEVES

If you were to attempt to regrow an arm, there would be two ways to go about it, says James Sharpe. You could either coax the body into regenerating the limb, or you could produce an arm in the lab and graft it on. Of course, neither option is as straightforward as it may sound.

Sharpe is Coordinator of the Systems Biology Programme at the Centre for Genomic Regulation (CRG) in Barcelona, where his lab tries to understand precisely how limbs are formed. "We know quite a bit more about limb development than about some other systems or organs," says Sharpe. Unlike the heart or the brain, limbs are not essential for life. From a scientist's standpoint, this makes them ideal: while they are still just tiny buds of tissue, barely 1mm across, you can interfere with them without destroying their 'life-support system' – the rest of the embryo. So as early as the 1940s scientists were opening chicken eggs and studying how a chick's wing is formed. Like us, chickens are vertebrates, so a lot of what was learnt in those early studies probably holds true for humans. Over the years, thanks to advances in genetics and microscopy, our knowledge of how limbs form has grown in leaps and bounds.

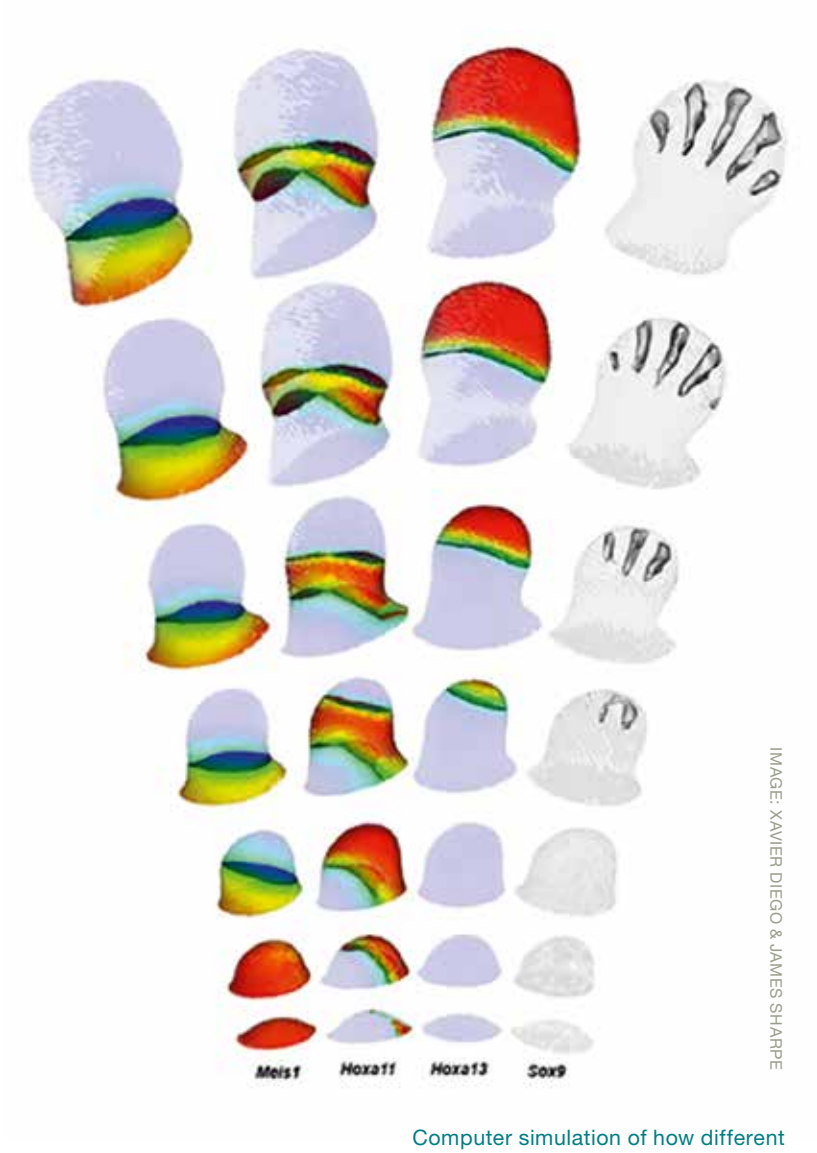


IMAGE: XAVIER DIEGO & JAMES SHARPE

Computer simulation of how different genes shape the limb bud into upper arm, forearm, hand and fingers over a two day period during development.

Scientists now know many of the molecules that sculpt a mass of embryonic cells into a functioning arm, hand and fingers. They have uncovered gradients, where a particular molecule is found in high concentrations near the body, and diffuses out so that the further away from the body a cell is, the less it is exposed to that molecule. Like markers by the side of the road, these gradients tell cells how far along the arm they are, so that cells know when to stop growing and start making a hand. In the hand, Sharpe and others have found an interplay of 'activating' and 'repressing' molecules that seems to define the strips of cells that will become fingers, and those that will be chiselled away to create the spaces in between. "We have a lot of information, but we're coming to the conclusion that a lot of our stories about how this system works, based on that knowledge, are probably dramatically simplistic," Sharpe warns. "They make sense, but making sense is not the same thing as being true." Nevertheless, Sharpe is confident that the truth – however convoluted – is within reach. "I think we're in the perfect situation that maybe 10 years from now we will have a really confident view about the complexity of all this," he says.

Getting the arm to grow back

Nadia Rosenthal is similarly excited about the prospects of regenerative medicine. "I think the next decade is going to be very exciting," she says with a smile. "Now that the field is really thinking about what a >>

>> tissue needs to regenerate itself, we're going to come up with ingenious ways to make that happen."

Rosenthal was Head of EMBL's site in Monterotondo from 2001 to 2012, Scientific Head of EMBL Australia from 2010-2015 and is now Scientific Director at The Jackson Laboratory for Mammalian Genetics, US, and Chair in Cardiovascular Science at Imperial College London.

"We know that salamanders can do this, so the question is why can't we?"

Her lab investigates how muscles regenerate. Rosenthal is interested in teasing out the differences and similarities between the skeletal muscles that you show off when you flex your arm and the heart muscle that beats in your chest. As anyone who's pulled a muscle can attest, skeletal muscle can regenerate. The heart, on the other hand, has much less regenerative capacity. Rosenthal and her labs use mice as a proxy for humans, but they also look at animals that *can* grow back an arm: salamanders.

"We know that salamanders and other animals can do this, so the question is why can't we? What are the biological impediments for this in mammals?" she ponders. One difference is that injured salamanders bear no scars. In mammals like us, injury triggers a response by the immune system. If the resulting inflammation doesn't subside in time, cells in that tissue die off, and are replaced with scar. As scar tissue isn't functional muscle, bone or skin, it becomes a barrier, preventing the arm from growing back. This scarring can make it very hard for a patient to fully recover from a heart attack or an injury to the spinal column. Rosenthal and colleagues have found that in salamanders, the chemical signals that immune cells exchange amongst themselves and with the injured tissue are essential for the animal to regenerate parts of its body. But even if we were able to learn the salamander's 'tricks' and somehow co-opt them to prevent or

Nadia Rosenthal, an EMBL alumna, studies how muscles regenerate.

PHOTO: MARIE CHAO

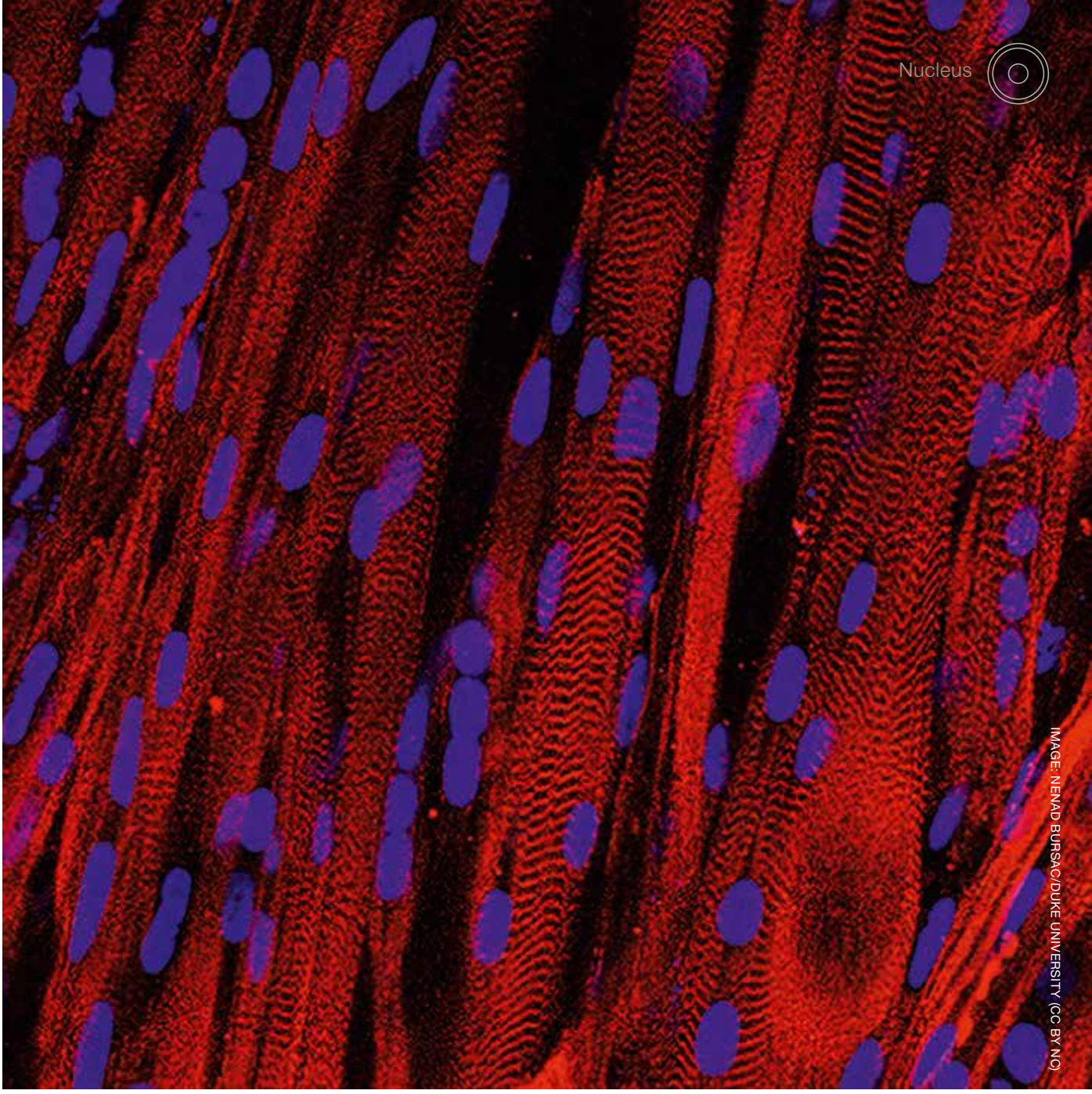


IMAGE: NENAD BURSAC/DUKE UNIVERSITY (CC BY NC)

Lab-grown human muscle bundles, seen under a microscope.

remove scarring in a human patient, that wouldn't be enough for the person's arm to grow back. We'd have to somehow jumpstart growth.

Adding stem cells or other cells with a propensity to build specific types of tissue would be a start, but those cells would require instructions. These could be the 'road sign' and patterning molecules that shape the embryo's arm. But other factors could also be at play. Scientists at MIT, for instance, have recently shown that differences in cells' ability to conduct electricity could also help cells gauge their position. "This would be a much more nuanced way to control things than chemical gradients," says Rosenthal. "And if it turns out to be true, it makes the thought of zapping a tissue to jumpstart growth less sci-fi than you'd think!" >>

>> In any case, both Rosenthal and Sharpe point out that, valuable as the insights from developmental biology are, regrowing an adult arm poses its own challenges. "When you regrow a limb, you have to regrow it out of an organism that has a fully developed immune system. It also has a fully developed vasculature, nervous system... and it's also much bigger than when the limb was beginning to grow in the embryo. So it's just naïve to think that it'll boil down to a simple recapitulation of development," Rosenthal cautions.

To understand how regeneration overcomes the hurdles of adulthood, scientists can probe salamanders and other 'regenerators'. But there are also clues closer to home. Humans may not be able to grow back an arm or a leg, but some of our organs do have remarkable regenerative capacity. "You can basically cut away two thirds of the liver and within two weeks the liver mass has been restored," says Helmuth Gehart, a postdoctoral fellow in Hans Clevers' lab at the Hubrecht Institute in the Netherlands. The liver has several lobes; if a lobe is removed, the remaining lobes grow until they are able to take over all functions of the lost liver tissue. Looking at what drives this regeneration – and what constrains it – could give clues of how to coax other tissues or organs into rebuilding themselves. For the most part, scientists like Gehart, Rosenthal and Sharpe are still at the clue-gathering stage.

Even if one day we manage to master regeneration, growth and development to the point that we can think of making a person's arm grow back, salamander-style, there could still be a practical hurdle. "One would imagine that growing back a whole arm would be quite slow," Sharpe ponders. "What would you do during that time? Would you have to keep the patient in hospital, in isolation, for months?"

Arm in a dish

Considering the challenges in getting a patient's arm to regenerate, would it be easier to grow them an arm in the lab instead? This is one of the approaches that Gehart uses to try to understand how the liver rebuilds itself: getting it to do so – albeit at a much smaller scale – in a lab dish. He is among a growing number of scientists turning to organoids: essentially, balls of cells that act like miniaturised versions of an organ. Gehart is keen to stress that he is not in fact growing livers in a dish. "These organoids have different cell types, and they have all the functions of the organ – they do what the organ normally does – but they have no blood vessels, no nerves, no connective tissue," he explains. Because they have no support structures, cells in these organoids lack important cues that would allow them to arrange themselves into whole organs. So the largest organoids scientists can produce at present are only one or two millimetres in diameter. Can the approach ever get to the stage where we can build a whole arm?

In order to grow an arm in a lab, you'd have to be able to pump blood through it, and, as with getting a person's arm to regenerate, it would

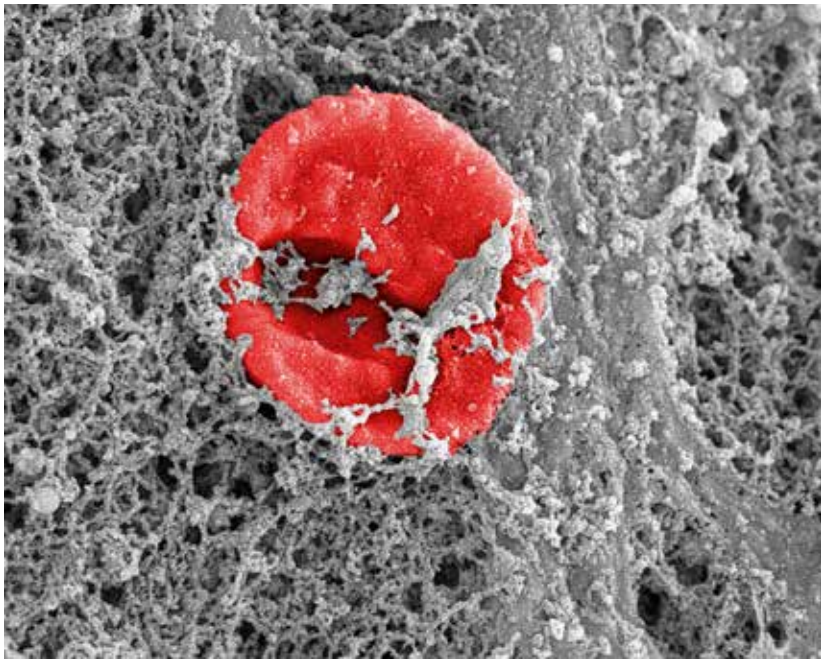


IMAGE: NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES(NIAMS)/NIH (CC BY NC)

Scanning electron microscope image of traumatized muscle tissue, showing a red blood cell (false color) entangled in fibres that are thought to precede bone formation during abnormal wound healing.


PHOTO: CRG

James Sharpe, Coordinator of the Systems Biology Programme at CRG, studies how limbs are formed.

probably help if you really knew the drivers of arm development. But aside from that, says Sharpe, you'd face a spatial challenge. "An arm has a certain proportion of muscle cells, bone, tendon, skin, etc. But if you just mixed the right number of cells together in a flask at random, most of the possible configurations are not an arm! So an exciting challenge for us in my lab," he says, "is how do tissues organise themselves, geometrically?" In an effort to find out, Sharpe's lab in Barcelona uses a combination of experiments, imaging and computer models. "These systems are beautifully, fascinatingly complicated, so computer modelling is absolutely essential, because humans are not very good at thinking of thousands of cells, in 3D space, changing over time."

Beneficial baby steps

"I don't know of anyone who is trying to grow an arm in a lab," says Sharpe. Considering all the biological challenges, and given the advances in prosthetics, it's possible that by the time we are in a position to regrow a 'natural' arm, artificial ones may have supplanted the 'real thing'. Or the two fields may merge, offering future patients bionic arms. Ethical considerations will also come into play, not least in the context of how we view disability.

"We learn as much from what doesn't work as what does"

For now, progress will likely come in incremental steps. Scientists are beginning to be able to build relatively simple tissues like skin, for example. And researchers have recently been able to grow heart cells that can beat, by seeding them onto a flexible scaffold, which allows the cells to stretch and create the beating movement they'd have in the heart.

Building from that, says Sharpe, it seems quite plausible that as the field matures, it will become possible to build more complex arrangements – perhaps combinations of bone and muscle, for instance – that could be transplanted back into the body. "Ironically, these 'little steps' may even be more beneficial than being able to build a whole arm," he points out, "because a lot of the damage that humans have to put up with isn't as dramatic as losing an arm; it's parts of an organ dying off or getting damaged for all kinds of reasons."

Some of those baby steps are already helping patients. Doctors can already treat burn victims, for instance, with skin grafts grown from the patient's own cells. These grafts are not yet perfect. They don't have hairs or sweat glands, although promising work in mice indicates that may come soon. And even these imperfect skin grafts can serve as a scaffold for the patient's own skin to grow back on.

Clinical trials are testing similar approaches for patching patients' knees with cartilage grown from their own cells. And just this year, two clinical trials reported encouraging results of patients who were able to see again after receiving transplants of cornea grown in the lab – either from their own cells or from cells of donors. >>

>> As scientists in these fields look to other areas of engineering for inspiration, entirely new approaches can emerge. "I just spoke to someone at a conference who has developed microparticles that could be delivered to the right place in the body and release factors that would stimulate regeneration," says Rosenthal. "You could imagine that that sort of control would allow for a lot more refinement in the way we deliver drugs, too."

Not all promises will be fulfilled, but they'll all bring new insights, says Rosenthal: "We learn as much from what doesn't work as we do from what does." And some of that knowledge can also be harnessed to stop unwanted growth. "Many of the aspects that we study in regenerative medicine have a lot of applications in cancer, of all things," says Rosenthal. Many of the parameters that she and others aim to stimulate for regeneration need to be reined in to treat the uncontrolled growth that is cancer.

Best of both worlds

So will we ever be able to regrow an arm? Going back to Sharpe's options of getting the body to regrow or creating an arm in the lab, Sharpe, Rosenthal and Gehart all agree that if we ever find a solution, it's more likely to be something in between: growing components in the lab, and grafting them on to the body with the right stimulants to form a functional arm. And they all predict it won't happen any time soon. "There's not going to be a eureka moment when someone grows back the legs on a Paralympic athlete," says Rosenthal, "I think it's going to be much more gradual."

"I absolutely don't think it's complete science fiction," says Gehart, "but we clearly need a better understanding." As that understanding grows, more and more people may receive a helping hand – at least figuratively speaking.

MORE ONLINE:
EMBL-CRG PARTNERSHIP FOR RESEARCH IN SYSTEMS BIOLOGY: WWW.EMBL.DE/RESEARCH/PARTNERSHIPS/REMOTE/CRG

EMBL-HUBRECHT INSTITUTE PARTNERSHIP FOR STEM CELL AND TISSUE BIOLOGY: WWW.EMBL.DE/RESEARCH/PARTNERSHIPS/REMOTE/HUBRECHT

Salamanders and newts like this California newt can regrow their limbs.

PHOTO: CONNOR LONG (CC BY SA 3.0)

Design for life

EMBL's senior graphic designer Petra Riedinger retires after 40 years producing posters, graphics, artwork and more

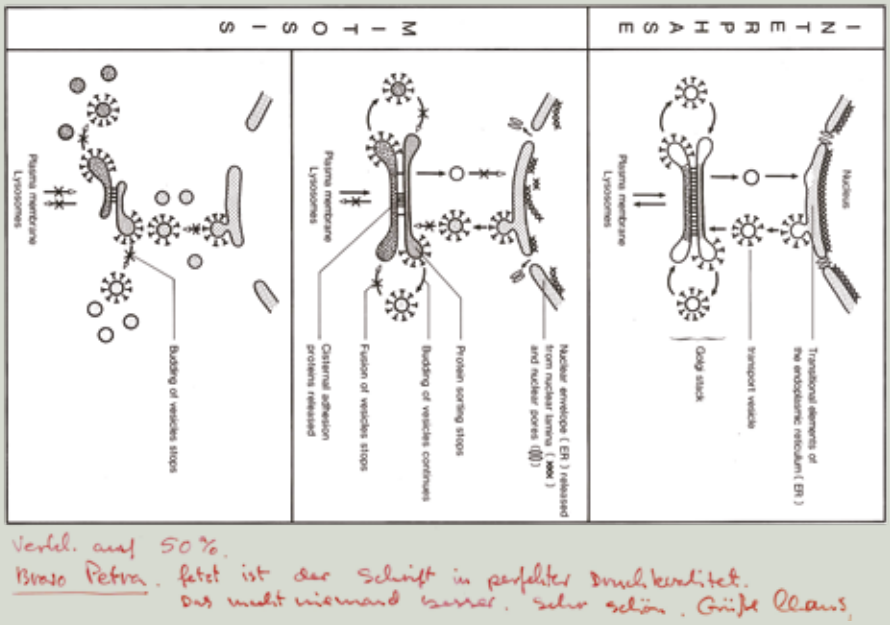
BY ADAM GRISTWOOD

Four decades ago, a newly qualified technical illustrator called Petra Riedinger paid a spontaneous visit to EMBL. Intrigued by the buzz around the development of a new intergovernmental research institution in Heidelberg, near her hometown, she believed she could help researchers at EMBL to visualise their science and bring data to life. She was hired on the spot, beginning a story of graphics, artwork, illustrations, posters, maps, cards and more that has spanned nearly the entire history of EMBL to date. "I remember the special atmosphere at EMBL that day, which remains the same today – you can smell it and feel it," says Riedinger. "People at EMBL are very open and willing to share and collaborate, there is lots of freedom and there are opportunities to develop. It is a very special place."

Early days

At the time Riedinger joined, the idea of having a graphics expert at a scientific institution was almost unheard of – but her impact on the >>

Petra Riedinger in her studio in 1977.



Verkl. auf 50 %.
Bravo Petra. Fotot ist der Schrift in perfekter Druckqualität.
Das macht niemand besser. Sehr schön. Grüße Claus

A hand drawn graphic, complete with appreciative complements from Claus Christensen, the first head of EMBL's Photolab.

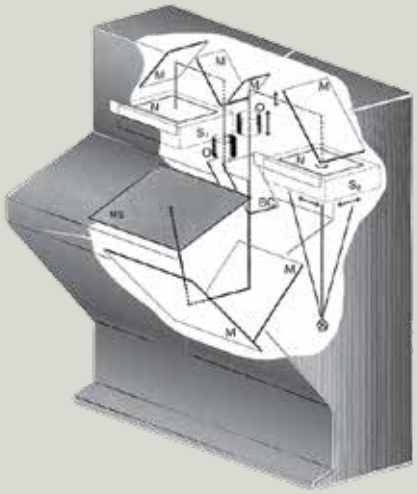
IMAGE: EMBL/PETRA RIEDINGER

>> laboratory was immediate. "I was very excited to join EMBL because I wanted to learn more about the great research happening here and saw many ways that I could apply my skills," she explains. "I joined before the days that computers were commonly used in graphic design and my early work was painstakingly hand drawn, often after detailed talks with scientists. Corrections and edits to images had to be carefully scratched off the paper – we could only do this two or three times before damaging it, so there was not much margin for error."

Riedinger began life at EMBL in an office in downtown Heidelberg as the finishing touches were made to the laboratory's headquarters. But as soon as it was ready, she set up in her studio next door to EMBL's electronic workshop. "It was amazing to see the institute being built, brick by brick," she recalls. "At the time we were like a small community. EMBL has grown tremendously in size and stature since: there are new buildings, new sites, more people and it has been an incredible journey."

Taking inspiration from her colleagues, Riedinger developed her own techniques. "Using a curve template from the electronic workshop was my own personal revolution," she explains. "It made diagrams and curves much easier to draw: I believe I was the first to adopt this method – and perhaps the only one who ever used it!" she explains.

As the lab grew, Riedinger frequently became involved in other projects, providing graphics for hundreds of scientific papers as well as a multitude of other projects. "There is an entire shelf of documents destined for EMBL's archive, while my portfolio has filled hundreds of pages, I will continue working on it into my retirement!" she says.



Hand drawn in ink, a 1983 technical design for a prototype device to optically compare electrophoresis gels.

Graphic depicting the developing fruit fly embryo for EMBL's 1998 Annual Report.

Riedinger's work has featured on the covers of a range of well-known scientific journals.

IMAGES: EMBL/PETRA RIEDINGER

Design specialist

The rise of computers, Photoshop and colour printing gave even more ways for Riedinger to express her creativity, and her work was in high demand. This meant a difficult decision. "I decided to move away from technical illustration and specialise in graphic design," she explains. "Graphics can tell a vital part of the science story: you see the visual and you want to read on. They can simplify something very complex and help specialists and non-specialists alike to understand it."

Petra Riedinger in her office at EMBL in Heidelberg

PHOTO: EMBL/MARIETTA SCHUPP

Riedinger designed the EMBO Gold Medal, a design which is still used today.

Illustration for a 2008 EMBO Workshop on Evolutionary and Environmental Genomics of Yeasts, hosted at EMBL in Heidelberg.

IMAGES: EMBL/PETRA RIEDINGER

Riedinger's favourite project was a graphical analogy of a growing fruit fly embryo for EMBL's Annual Report in 1998. "The laboratory did not have a digital camera at the time, and to make the graphic I brought in an old pair of trousers and imaged the zip under a scanner," she recalls. "It's was very popular and many other biologists have requested versions of it for their own work."

Riedinger's artwork sometimes held a hidden personal connection. "Together with Volker Wiersdorf, I designed an image used on the cover of the *Journal of Cell Science* using wooden spools from my mother's old sewing machine," she says. "I digitally modified the engraving on the spools and group leader Peter Becker sent it to the journal to accompany a paper." Her work has also featured on the cover of high profile journals such as *Nature*, in this case visualising a network for work carried out at EMBL spinoff company Cellzome.

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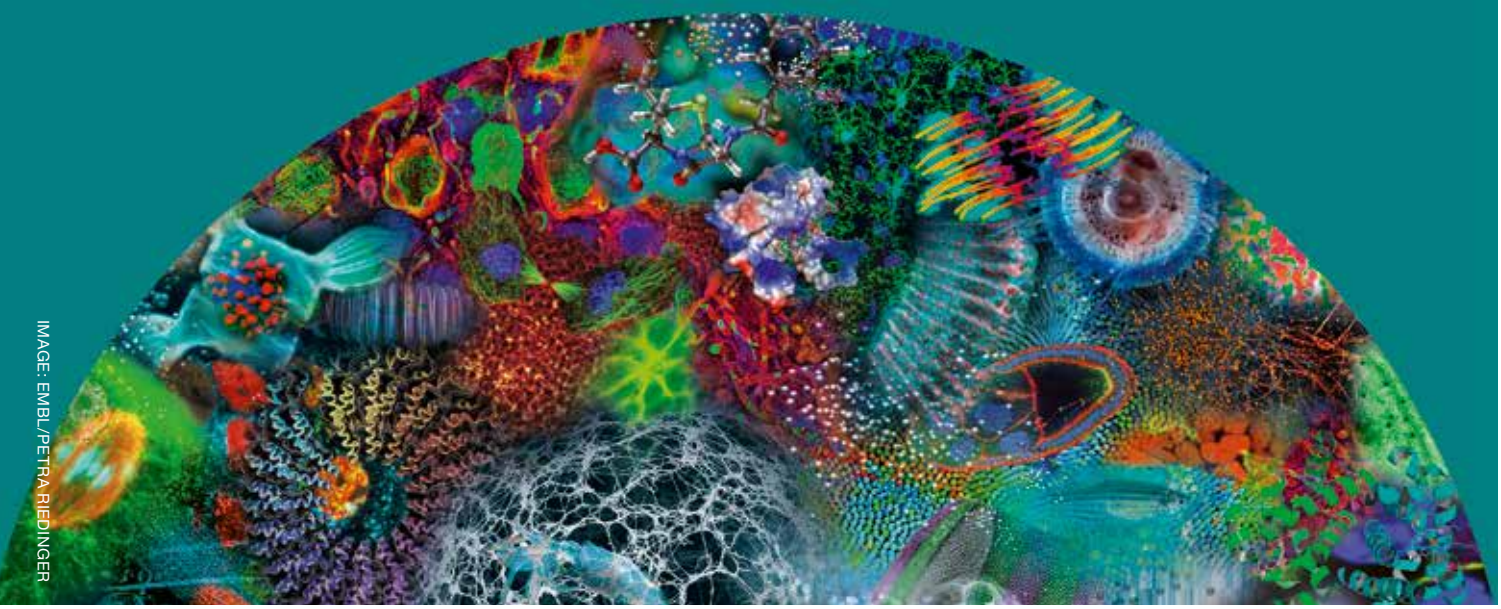

IMAGE: EMBL/PETRA RIEDINGER

EMBL Exhibition stand graphic combining images from all EMBL units to showcase EMBL's special collaborative spirit.

>> She also reflects on what was perhaps her most difficult brief: drawing Charles Darwin smiling. "For a conference poster, group leader Michael Knop requested an image of a relaxed looking Charles Darwin, socialising with a glass of wine – and somehow cloning and yeast had to be involved! I searched everywhere for an image of the famous naturalist smiling, but he always appears very serious," she recalls. "There was only one thing I could do – draw him myself."

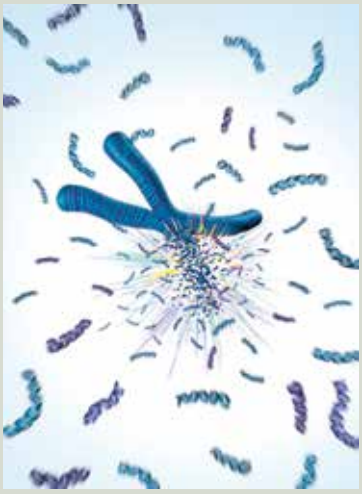

IMAGE: EMBL/PETRA RIEDINGER

Illustration of an inherited mutation in the TP53 gene, which likely causes chromosome 'explosions' linked to cancer.

World famous

Riedinger's work has also helped to spread the word of EMBL's science through the global media. "My daughter was once visiting India and she stumbled upon one of my graphics on the front page of a national newspaper profiling a study by group leader Mathias Treier," she says. Another graphic that is frequently used by news organisations is an illustration of an 'exploding' chromosome, used to depict work by group leader Jan Korbel and colleagues that found a link between the inherited mutation and a particularly aggressive form of childhood brain cancer. "EMBL's research is of interest and relevance the world over, and its been a privilege to work with the many inspiring people at the institute – including Nobel and Leibniz prize winners," Riedinger adds. "It's been a real honour."

She reflects on the diversity of science she has helped to visualise over the years. "Oftentimes the work carried out here by scientists is not in textbooks, it is completely new and I would make time to work with the scientists until we were both absolutely happy with the final product," she says. "There is an incredible openness at EMBL: I always felt free to ask questions, and there are many ways to learn more about the latest research, such as the annual Lab Day when people from all EMBL sites come together to share their ideas."

Working under four EMBL Directors-General, Riedinger has seen first-hand almost the entire history of EMBL and is excited for its future. But as she moves into retirement she assures us that she is not going far. "One of the great things about EMBL is that alumni are always welcome," she says. "Even when I become a pensioner, I will firmly remain part of the EMBL community. I wouldn't want it any other way: EMBL is a special world."

During her time at EMBL, Riedinger applied her talents to support the work of many teams, groups and individuals across the laboratory including in science, administration and communications. She is one of a small group of people at EMBL who witnessed the very beginnings of EMBL and she has been a valued member of staff ever since. On behalf of the whole of EMBL, we wish her all the best for the future and look forward to learning about her retirement adventures.

Cultures

PHOTO: STEFAN GÜNTHER/LIFE IN PERSPECTIVE

How a team of scientists and artists at EMBL transformed microscopy data into stunning 3D images

BY MARGAUX PHARES

Capturing life

Shattering starfish nuclei. Cells collapsing like fabric. Protein puzzles with thousands of pieces. These moments of microscopy are commonplace in the lab, but for one team of scientists at EMBL they offer an artistic perspective on the biological sciences. 'Life in Perspective', a visualisation of 3D microscopy as lenticular images, was recently displayed at the Heidelberg city library. Going from microscope to capturing the perfect picture was not without experimentation. From collecting data to timing snapshots of chemical reactions, the scientists and co-creators of the art exhibition share some of their challenges, how they took them on and what 'Life in Perspective' means for communicating science beyond the lab.

The germ of an idea

"Initially this project began because Stefan [Günther] and I just wanted to look at our research data in a different way," explains Gustavo de Medeiros, a postdoc in the Hufnagel group at EMBL in Heidelberg. But soon the ambition of the pair of scientists grew. "We realised it did not make sense to just keep this up in the lab – we wanted the public to see science communication as art. We envisioned a huge, interactive exhibition, where people could touch and see and discuss the art and science."

At first, it was not easy. "Organising something like this was completely new for us, as well as for EMBL," de Medeiros continues. "I think because we had so many ideas at once it was tough convincing people to support us at the beginning. But we kept going."

A few key supporters helped to get the ball rolling. "Stefan and Gustavo approached me for advice and help getting to administrative contacts," says Manuela Beck, a graphic designer working at EMBL. Joran Deschamps, a PhD student at EMBL, also joined the team. Not only did he work with Günther and de Medeiros on the science, but he also pushed the project to remain artistic in focus. With the support and guidance from EMBL Director Matthias Hentze, the team decided to focus on one

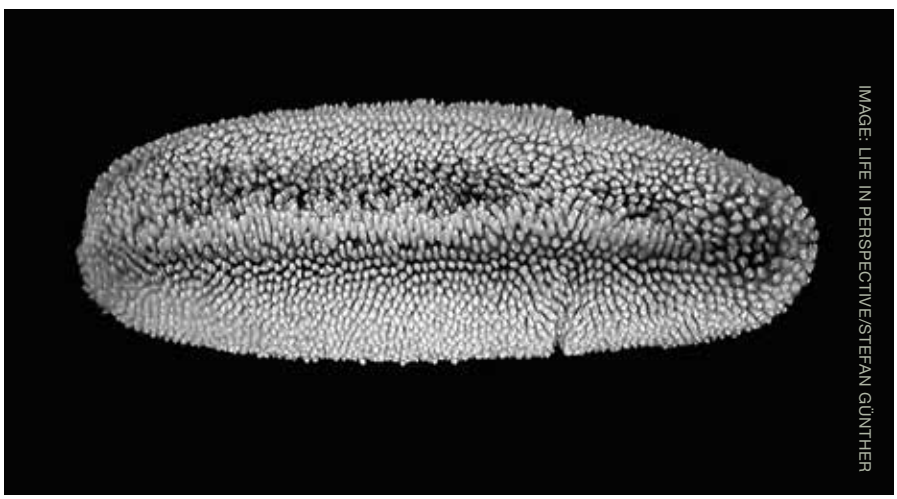

IMAGE: LIFE IN PERSPECTIVE/STEFAN GÜNTHER

in perspective

PHOTO: COURTESY OF URS HOFFMAN-ROHRER

technique – lenticular images – and showcased six images for the 2015 Annual Reception at EMBL. This exposure piqued more people's interest in the project and prompted numerous labs to contribute.

"We put out an open call for data to create more prints," de Medeiros says. "We were surprised to find that some data is stored but remains unused. It just sits on a shelf!"

Once the data was provided it had to be processed. "For me it was very beneficial to work together with scientists and to realise that there is not a big difference between art and science when doing creative work," says Beck. "This exhibition is a good opportunity for scientists and non-scientists to be fascinated by the beauty of a microscopic organism. Although in the beginning, you don't even need to know what it is – it could be anything! The part of it I find the most fascinating is that you're implicitly part of it. These pictures are like open doors to see what's inside your body, or what's at the bottom of the ocean that's invisible to our eyes."

Bug data

The first challenge to making data look good visually was to make the final image look like something our brain would expect. "To represent a 3D volume from a stack of 2D slices was difficult to understand – how do you project volumes in such a way that the brain thinks they are in 3D?" de Medeiros says. In traditional projections, all of the 2D slices would be collapsed onto one plane. To our brain, this looks weird, since we cannot perceive depth in this way. To overcome this obstacle, de Medeiros and his colleagues used a >>

>>technique to make our brain think the image has perspective.

And then there is the sheer amount of data to work with, as Günther demonstrates. His image follows a fruit fly embryo in development, from the point of fertilisation up to gastrulation, or the stage when the single layer of cells that initially form the embryo folds inward. During this timeframe, one nucleus turns into hundreds, and they migrate to the surface of the embryo. The cells keep dividing until they reach about 6000 in number. Günther was then faced with a formidable challenge: visualising this stage of development in a quality that could track every single one of these thousands of cells.

"With light sheet microscopy, the method that we used, we generated a lot of images," he says. "A single time point consists of 200 images in order to record the depth. The entire video we recorded of the fly developing was over 24 hours long and consisted of 2 terabytes of data, which is four times the size of a normal computer hard drive! In the end, we only show about 30 minutes of the video."

Reworking data

Jan Kosinski, of Martin Beck's group at EMBL Heidelberg, was part of a team that pieced together the structure of a nuclear pore. They first used electron tomography to get a rough idea of what the nuclear pore complex looked like. They then identified the structures of the component proteins, previously found using methods such as X-ray crystallography, to piece together the final structure.

"This is how we solved the puzzle, so to speak – having a template and a thousand pieces, and fitting them together using software we designed," Kosinski explains. "Imaging the nuclear pore was a project more than five years in the making: When I joined the project, it still took one year to generate the first initial shape, and another year to fit the pieces in it. I'm proudest of making the automated program that takes these pieces and puts them all in place. And of course, that we solved the biggest protein structure in the cell. It is mind-blowing!"

The yellow and red proteins on the outer ring of the pore form a repeating unit. With scientific publications, according to Kosinski, similar proteins such as these are shaded in similar colours. But for the exhibition, Kosinski coloured the proteins in the nuclear pore differently from how he did it for a report published in *Science*. "In both scientific publications and this art exhibition," he says, "colour choice is arbitrary. But for 'Life in Perspective', Stefan and Gustavo preferred to use colour to increase the perception of depth in the pore." The deeper you move into the channel, the more blue proteins you see; the farther out you go, the more red ones you see.

Exploding opportunities

Unlike Kosinski, who used existing data for 'Life in Perspective' , postdoc Natalia Wesolowska in Péter Lénárt's lab had to collect new data so that she could generate an image with sufficient resolution for the large lenticular prints. Her image of a starfish oocyte, or egg cell, shows its nucleus about to burst open so the oocyte can pass on half of its chromosomes to its daughter cell as it becomes a mature egg. A protein called actin floods the nucleus and forms a shell that helps the nuclear membrane to shatter. But first, the oocytes need to receive a hormonal signal that says, "It's time to divide" – something Wesolowska can signal to the oocytes in the lab. After that, it's time to quickly prepare the cells for imaging with confocal microscopy.

How the nuclear pore complex was coloured for 'Life in Perspective' (left) compared to how the image was coloured for a report published in *Science* (right).

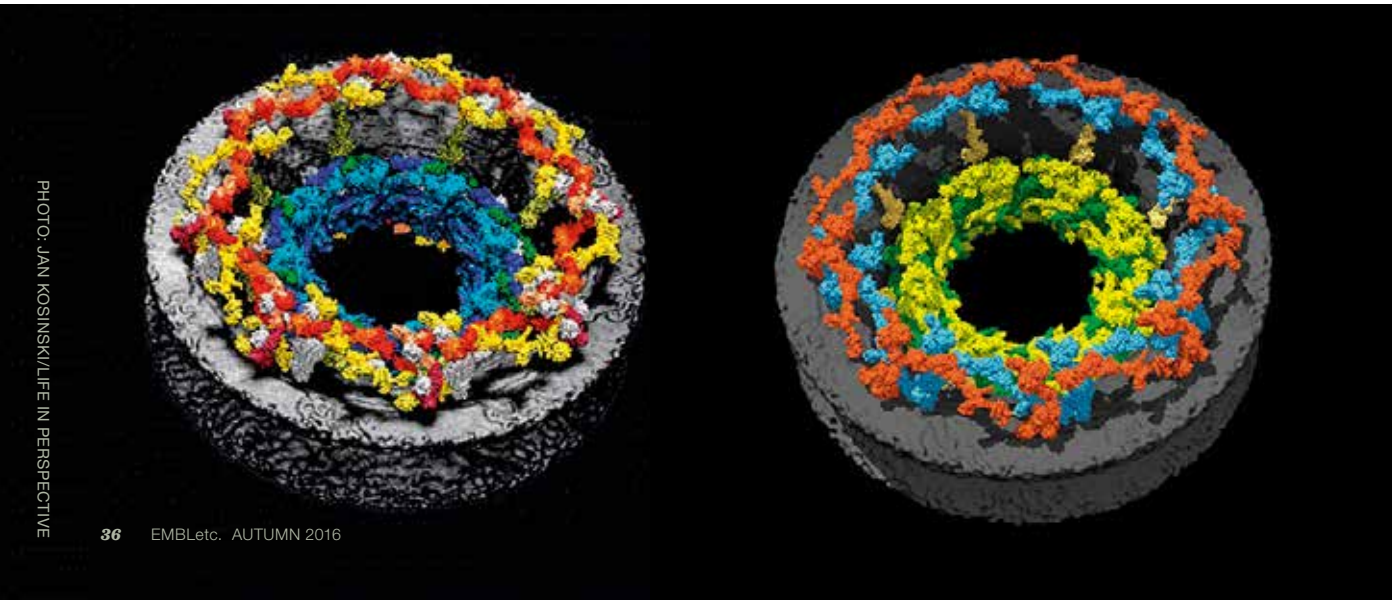

PHOTO: JAN KOSINSKI/LIFE IN PERSPECTIVE

PHOTO: LIFE IN PERSPECTIVE

Gustavo de Medeiros explains the physics of lenticular prints on a guided tour of the exhibition in the Heidelberg city library.

"In order to prepare the cells for imaging, we have to capture them in that particular moment of time – when actin has gone into the nucleus – and then make them visible with antibody staining," she explains. "Whenever you use fixatives, you worry about destroying certain structures in the cell and actin is particularly sensitive in this regard. Part of the difficulty of this project was finding a way to fix the actin and make sure it looks the way it normally does in a cell. We had to tweak what chemicals we used, so it's just right."

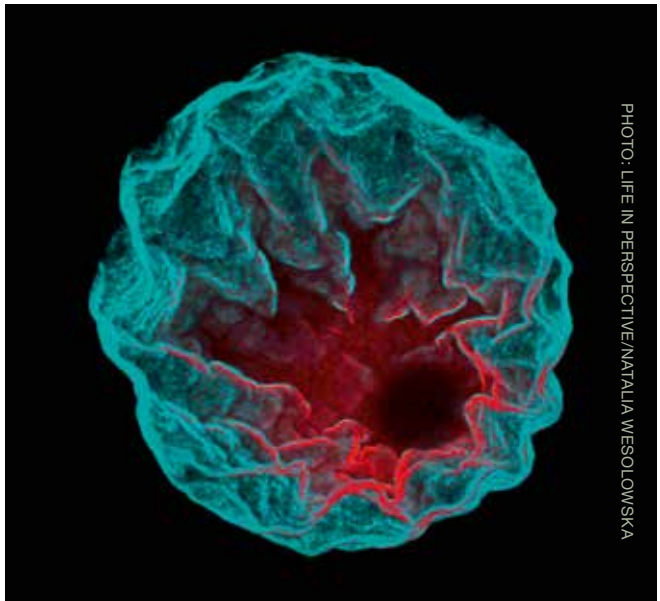

PHOTO: LIFE IN PERSPECTIVE/NATALIA WESOLOWSKA

The time window in which to fix the oocytes is also quite small. "After I introduce the hormone, which signals the cell to divide, it usually takes about 15 to 20 minutes before I see the nucleus start to look crumpled – like a deflated balloon. And I then know that the actin-flooding step has just happened. One of the difficulties of my project is that this step only lasts a minute and I only wanted to capture that moment." Once Wesolowska determined the precise timing for a fresh collection of oocytes, she was ready to spike a new batch with hormone, this time around for fixation.

Life in Perspective featured as part of the OFF//FOTO festival at Heidelberg's City Library.

"I want to help my people find and follow their own paths"

Pathways Welcome: Alba Diz-Muñoz

PHOTO: EMBL/HUGO NEVES

New group leader combines physics and biology to answer the 'hows' of cell movement

BY SONIA FURTADO-NEVES

The Diz-Muñoz group plans to explore how mechanical properties affect the movement of immune cells or cells in a zebrafish embryo. Working at the interface between mechanics and biology, they will investigate how cell behaviour and signalling cascades inside the cell are influenced by factors like the forces the cell is subjected to, or the ones it generates.

Name one tool you can't do without.

I'd say the tool that got me into this business, and is the reason I'm still in it, is the microscope. I went into biology because it's beautiful and intriguing. In my PhD I worked with zebrafish embryos, and realized that developmental processes are just stunning! You wonder "How can this happen reproducibly every time? How do the cells know what they are doing, where they're going, and when?" The 'how' is the question that drives me.

What is your philosophy for running your lab?

Well, I am aware that building a lab depends a lot on the people you hire, and how those personalities fit together. My philosophy is that we're individuals, but we work as a team, and try and help each other to answer very hard questions. So I'm here as a member of that team, which means I provide an infrastructure and a space where we can develop ideas and projects together.

What will you be looking for as you build your group?

People who are curious and motivated. I think that a motivated and intelligent person can learn anything.

How have you felt about your transition from postdoc to group leader?

For me it's been a change in perspective. As a PhD student and postdoc, I was the one deciding what I wanted and when to do it. Now as a group leader, things are different, because the focus has shifted to the interests and time of my people. I want to help my people find and follow their own paths.

Do you have any advice for someone thinking of making that move?

Go for it! I applied for this job early in my postdoc, thinking 'I'm gonna give it a shot, see what happens, and learn from the experience.'

My advice is to try early, interview and get some practice. If it doesn't work, then next time you will do better. And if you have good ideas and you can justify why you're the person for the job, you might get it!

FULL INTERVIEW ONLINE:
NEWS.EMBL.DE/?p=7260

"Working in very interdisciplinary environments has always been the best constellation for doing great science"

Welcome: Mikhail Savitski

New head of Proteomics Core Facility also runs stability proteomics lab

BY MARGAUX PHARES

PHOTO: EMBL/MARIETTA SCHUPP

For Mikhail Savitski, running a research group and a core facility is "a fantastic challenge." The cross-pollination between them informs his research which is based on mass-spectrometry. His group is working on a technology that measures the stability of proteins, setting the stage for more effective drug treatments as well as addressing open questions in molecular biology.

What got you interested in science in the first place?

Back then it was physics and mathematics that I was mainly interested in. I come from a scientific family. My mother has a PhD in physics, and her parents worked in science. From a very young age, when I lived in Russia, my grandmother would tell me mathematical riddles. Because she always had the same type of riddles, I think at age five I saw the pattern and I told her, "I think I understand all of mathematics!"

How did you come to EMBL?

After I got my PhD from Uppsala University, I saw an advertisement from Cellzome, an EMBL spin-off company. I had no intention of going into industry at all, but I applied for it because they were doing fantastic science in my area – proteomics – and it was located on the EMBL campus in Heidelberg. I had read a lot about EMBL and I was happy to be closer to it.

What are your research interests?

I work in a new area called fold-change stability proteomics, a method of assessing the stability of proteins in living cells. While at Cellzome, I worked on developing a new technology that turns out to be a very powerful tool for detecting protein-drug interactions inside living cells. In drug studies it is very difficult to ascertain two things: Whether or not a drug actually enters a cell and binds to the protein it is supposed to, and what other proteins this drug binds to. Many drugs, such as those used to treat cancer, can share a lot of undesired off-targets. Meaning that not only do they bind to the protein of interest – which would suppress the disease – but they also interact with other proteins. Sometimes this leads to negative side effects, but it could also sometimes lead to beneficial effects. The technology that we developed enables us to answer these questions. Currently, in collaboration with Wolfgang Huber, Martin Beck, and Jan Korbel we are working on further developing this technology and applying it to fundamental questions in molecular biology.

For more on Savitski's work, turn to page 10.

FULL INTERVIEW ONLINE:
NEWS.EMBL.DE/?p=8072

Dealing with the imposter in me

Rosemary Wilson talks about imposter syndrome and how to handle it

PHOTO: EMBL/MARIETTA SCHUPP

I often have a terrible feeling that I do not deserve the recognition I get when I write a good story or take a great photo. It feels as if everyone has made a mistake and will suddenly wake up to the truth that I don't know what I'm doing and expose me for the fraud that I am. Hello, my name is Rosemary and I suffer from imposter syndrome. Everyone can suffer from these feelings of self-doubt, including women in senior positions. The lack of women in leadership roles in science is a matter for concern, and something that EMBL is actively working to address. Could imposter syndrome in women be part of the problem and if so, what can we do to help ourselves and those around us?

"Could imposter syndrome in women be part of the problem and if so, what can we do to help ourselves, and those around us?"

Together with equality officer Marie Lutz at the Centre for Ultra-Fast Imaging (CUI) on the DESY campus, we decided to open this topic up for debate. As part of a Ladies' Networking Lunch we invited three special guests to share their experiences and tips: Elspeth Garman of the University of Oxford, a guest professor at CUI; Arwen Pearson, professor at the University of Hamburg at CUI; and Katrin Teske-Temperton, career coach at the University of Hamburg.

Rosemary Wilson is a scientific training and outreach officer based in Hamburg and a regular contributor to *EMBLetc.*

Listening to the lively, honest and candid stories from the wonderful women of our panel and audience it became clear to me that I really am my own worst enemy. I will never be cured, but being aware of the ways I slip myself up is a big step towards taming my inner imposter. Here is some advice from our panel that I will be trying to put into practice:

Support networks are important

I have some wonderful colleagues, friends and family members who regularly tell me how much they appreciate and value my work, who push me to push myself, and insist I apply for jobs that I don't believe myself to be suitable for – they all help me to believe in myself a little bit more. This is so valuable and I am truly thankful for it (if not sometimes a little overwhelmed). I love to see people coming through EMBL flourish and go on to do great stuff; I hope I encourage people where I can, but I am sure there is more we can all do to build up support networks to help each other to fulfill our potential. As Pearson said, if your colleagues are doing great stuff, tell them.

Don't belittle yourself

When asked what my job entails I'll say something along the lines of, "Oh, I just write the odd little news article." People who know my work will tell me this is a major understatement. Having been called out several times, I try to stop myself doing this. As Garman said, stop 'doing yourself down'.

Focus your thoughts

Thoughts of self-doubt and reflection are to a certain extent healthy and can help us to develop and acknowledge our boundaries, but we shouldn't let them dominate. Teske-Temperton reminded us that we have the power to do something about that: next time I find myself in a puddle of self-doubt, I will try to refocus and fix on what I know I am good at.

Develop strategies

Teske-Temperton suggests making 'done' lists, not just 'to do' lists; or collecting positive emails and reading them back when you're not feeling too good about yourself. Everyone needs to find what works for them – maybe I'll give these suggestions a whirl, but my friends and colleagues are my pick-me-up.

Garman and Pearson reminded us we can all help to make it easier for others when we see someone struggling by bringing them into the conversation and reinforcing each other's message, be it as part of an expert panel or in a group meeting. Maybe it will also help me to remember that I am quite probably not the only one in that room wrestling with my inner imposter.

Be daring and allow yourself to fail

I know I need to be more daring and push myself out of my comfort zone more. How often have I kicked myself for not voicing my opinion at events, or taking part in a networking event? I'll admit I feel more comfortable on the sidelines cheering others on. But as Garman said, we need to have the courage to try for more, and while we're at it, allow ourselves to fail. When I have pushed myself out there, I've often surprised myself and the experience has taught me something about my strengths or even opened other doors of opportunity. Which leads on nicely to the last point...

Just turn up

I think I will make this my mantra as I consider the next step in my career. After all, what can go wrong? I have plenty of experience under my belt, deep down I know I am good at what I do, I can do this, I will do this. Just turn up.

FULL ARTICLE ONLINE:
NEWS.EMBL.DE/?p=8200

Review: Lab Girl

"I found her blend of scientific precision and literary prowess fascinating"

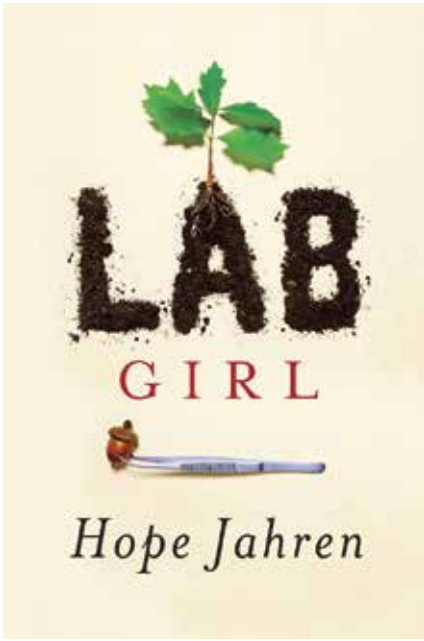

PHOTO: COURTESY OF JAHREN LAB

Hope Jahren's autobiography educates and delights

BY ROSEMARY WILSON

First and foremost, *Lab Girl* is a love story. It is an ode to science and the people in the life of biogeochemist Hope Jahren. The book details her career in science and the people who support her on this journey. It is a genuine and beautifully written story.

Early on we see Jahren studying Chaucer with her mother at the kitchen table. Just as science would become a key part of her life, this early exposure to literature helped shape her talent for writing. Throughout the book, these two important parts of her life are cleverly combined to produce one great read. I found her blend of scientific precision and literary prowess fascinating, and as I know from my own writing, that's no easy feat.

Taking root

Interspersed with Jahren's own journey is the story of the beloved trees that she has spent her life studying – the miracle that is a seed becoming a shoot before growing tall and strong to bear fruit. Having pursued my own PhD in botany, these educational inserts and research updates felt like familiar friends, reminding me of seminars, field work and research papers from a previous life. Interesting and fascinating in their own right, these chapters mirror Jahren's own development.

Jahren's journey begins in Minnesota, where as a child she plays under the benches in her father's science lab in a local community college. It is here that she falls in love with science. Later, after starting a degree in English Literature, Jahren finds her calling in science, where she feels at home and accepted for what she is. From there, her career has many elements that scientists, and especially female scientists, will relate to. The constant worry about money, for instance, and how to pay the salary of her loyal and trusted sidekick, Bill. Or being shunned at conferences as the strange female scientist who won't conform. Not to mention the regular moves across country, each time building a new lab from scratch. However, despite the hardships, the uncertain future and at times near poverty, Jahren never

once doubts that she has taken the right path.

The sense of dedication, determination and vocation that Jahren embodies in her story – that is what it is to be a scientist. I still remember the exhilaration at finally getting a breakthrough in the lab, but unlike Jahren these thrilling moments weren't enough for me to overcome the funding concerns, the pressure to publish and the need to continually uproot myself that comes with pursuing a career in science. I chose a different path, and I admire Jahren and others like her all the more for it.

Jahren is open and candid about her career decisions and brutally honest about her personal struggles and journeys of self-discovery. Her detailed descriptions of her mental health issues, for instance, touch on a sore subject in science, and I hope her voice helps to break down this taboo. The story of her horrific pregnancy was painful to read, as was her obvious disappointment at the lack of support she felt she received from her university at the time. I have never had to endure these horrors but her struggle to find her identity and her final acceptance of herself as a mother bought tears to my eyes.

I laughed, I cried, I loved this book. Yes, part of that is because I love science and plants, and because I can relate to Jahren's journey of self-discovery as a scientist, woman and mother. But it's also a damn good read and I would recommend it to anyone. Thank you for sharing, Hope Jahren.

Awards & honours

Duncan Odom of the Cancer Research UK Cambridge Institute and Paul Flicek from EMBL-EBI have been jointly awarded a prestigious Wellcome Trust Investigator Award to study the regulatory potential of repeat elements in the evolution of tissue-specific transcription. The collaborators will integrate experimental and computational analyses of the function and activity of newborn and ancient repeat sequences in four tissue types in ten mammalian species.

Sebastian Hauke, a PhD student in the Schultz Group at EMBL Heidelberg, was one of three young scientists to win the Rainer Rudolph Stiftung Award this year for his thesis in the field of protein biochemistry and biotechnology. Hauke established a specific protein labelling strategy, based on small, bright and photoactivatable fluorophore conjugates for dual-colour photoactivation and super-resolution imaging inside live mammalian cells. The award was presented to Hauke this October in Halle, Germany.

Maria Leptin, Director of EMBO and group leader at EMBL in Heidelberg, has been elected as a member of the German National Academy of Sciences Leopoldina. Founded in 1652, the Leopoldina is one of the oldest academies of science in the world. It is dedicated to the advancement of science for the benefit of humankind and to the goal of shaping a better future. With some 1500 members, the Leopoldina brings together outstanding scientists from Germany, Austria, Switzerland and many other countries.

Alumni

For the future

PHOTO: EMBL

This edition, we interview this year's John Kendrew and Lennart Philipson Award winners Jop Kind and Ernst Stelzer, learn about the Szilárd Library's past from the occasion of its reopening and share with you next year's events which take us to Australia, Norway, the USA and beyond – please mark your diaries! The alumni community is growing fast with almost 7500 EMBL alumni, as well as almost 500 former members of EMBL Council, the EMBL Scientific Advisory Committee and former staff of EMBO, EMBLEM and EMBL Ventures. We thank you all for your continued support and wish you a happy start to 2017.

Mehrnoosh Rayner
Head of Alumni Relations

For a full list of 2017 alumni events, see the back page of this edition.

Szilárd Library: an

Mary Holmes, who headed the EMBL library in Heidelberg from 1974 to 1998, speaks to EMBL's current senior librarian

BY IOANNA YDRAIOU

How and why was the Library founded?
John Kendrew, EMBL's first Director-General, wanted a library from the outset. After we worked together in Cambridge, he approached me in 1974: "I don't want a computerised library," he reassured me – he wanted something very old-fashioned. The first year I worked for free, in my spare time; it was exciting to build up a library from the first pencil.

PHOTO: EMBL/MARIETTA SCHUPP

Mary Holmes was a special guest at a recent event unveiling a refurbishment of the Szilárd Library.

PHOTO: EMBL/MARIETTA SCHUPP

Inauguration of the Szilárd Library in the late 1970s, led by John Kendrew.

open book

What's the story behind the name?
To recognise Leo Szilárd, Kendrew hoped to put his name to the campus access road, but the city said it must be named after a Heidelberg scientist (Meyerhofstraße is named for Otto Meyerhof, a scientist from the Max-Planck Institute for Medical Research). Instead, Kendrew named the library in Szilárd's honour. I've heard a lot about Szilárd and would have loved to meet him. He died in 1964, but his wife did visit the library and was very appreciative of the gesture.

Starting from scratch must have been quite a challenge...
I'd never worked in a scientific library, so I visited the World Health Organisation in Geneva and the Biozentrum in Basel for inspiration. Initially, we subscribed to 30 journals, but we had no library in which to put them! I asked the then Head of Administration, "What happens when the journals arrive?" He answered: "We'll buy you two cupboards". As the collection grew, the library moved and expanded from one small room, to two, then three. In 1977, the great day came to move up to the current site.

And it kept evolving...
Fortunately, because there weren't an enormous number of scientists initially, we could do things quite slowly. Until the 1990s, we had a card catalogue, and typed daily notices of journal deliveries. As we got more journals and books, I asked: "So, what about computers?" Kendrew and then Lennart Philipson refused. When we finally started online searching, only librarians could access the digital catalogue – scientists came directly to us, which must have been quite frustrating for them.

What was the highlight of your time as a librarian?
I still miss much about EMBL, the people especially. I particularly enjoyed developing the book collection myself, especially the 'history and philosophy of science' section – the people who borrowed extensively from this category were often my favourites!

Thinking in 3D

Ernst Stelzer earns 2016 Lennart Philipson award for advances in light sheet microscopy

BY MARGAUX PHARES

For Ernst Stelzer, coming back to EMBL's Heidelberg campus "is like coming back to an old friend." He arrived in the '1980s' as a physicist, and the innovative technologies developed by his teams have paved the way for biologists to further understand life at the microscopic level, and in unprecedented detail – from how neurons communicate with one another, to monitoring the beating heart of a fish. In recognition of his contributions, Stelzer was awarded this year's Lennart Philipson award by the EMBL Alumni Association.

"The University of Frankfurt, where I am now based, may have been my alma mater," Stelzer says, "but let's face it: I spent 28 years here at EMBL." Among the first group of PhD students, Stelzer began at EMBL's Heidelberg site in 1983 working on confocal fluorescence microscopy. The atmosphere at EMBL was quite different back then. For one thing, the lab did not possess a single fluorescence microscope. Even then, "in those days, it was not yet thought of as a quantitative tool or measuring device," Stelzer says. "Microscopy was more thought of as a way to just visualise something."

Back to basics

By 1993, together with his postdoc Stefan Hell, Stelzer had developed 4Pi microscopy. During the same year he and his PhD student Steffen Lindek patented and built confocal theta microscopes, a project that later involved James Swoger. By 1998 the team started to build something called a tetrahedral microscope, a machine that improved resolution using four lenses. Every calculation and equation they did over the years, though, brought them closer and closer to a striking revelation. The team realised that they could build a machine that would let them see life as never before. They set out in search of spare parts around the lab – an unused lens, a laser tucked away in a closet, a motor abandoned by a former postdoc. From these, they constructed an early version of a remarkable machine, one of the first implementations of light-sheet based fluorescence microscopy.

The difference between traditional microscopy techniques and the machine Stelzer built can be illustrated using the example of imaging a developing fruit fly embryo. Previous microscopes would shine light evenly on the fly egg. And because its yolk is opaque, light would scatter and make it very difficult to see inside – let alone visualise it in 3D. Additionally, the

amount of light used in the system can expose the specimen to up to 1000 times more energy than we typically receive from the sun. "You would not want to go to the beach in that!" Stelzer jokes.

The new microscope overcame both of these obstacles. First, rather than repeatedly illuminating the entire fly – and frying it to a crisp – their microscope shone light through the egg in very thin slices, or planes. "Imaging in 3D is different than 2D," Stelzer says. "We don't just look in one direction. We look at eight different directions in order to get a whole view of the specimen." Scientists can then put these slices together using a computer and digitally recreate the specimen in 3D. And since less light energy is being used to image the egg at a time, the fly can survive imaging for days at a time. Selective plane illumination microscopy, or SPIM, was born.

To boldly go...

The next challenge was to convince other biologists. "People seemed hesitant to try something so new at the time," Stelzer remembers. But EMBL alumnus Jochen Wittbrodt, who was working with medaka fish, stepped up to the challenge. They brought on other students, including Sebastian Enders, Jan Huisken and Philipp Keller. Together, they did something no scientist had done before: see the inside of a live, intact fruit fly embryo, and image it in 3D.

The results were astounding. Through thousands of images put together like a detailed flipbook, the team could clearly see and trace the organs as they developed inside the fly embryo – the pinching off of thorax and abdomen, the banding of rounded segments, the growth of the eyes. The whole period of imaging lasted seventeen hours. And what's more, the fly survived intact and was able to complete embryogenesis. Without delay, Stelzer and Steffen Lindek wrote a patent for SPIM and the team got to work on a prototype.

By the early 2000s what began as a side project became a full-time focus. The team had constructed a monolithic microscope carved out of a single block of aluminium. Later versions were built in increments with increasingly advanced lenses – and they even turned to German car manufacturers for other parts. "The motors that we ordered from one company were not even in the catalogue yet!" Stelzer remembers.

Applications of light-sheet based fluorescence microscopy have come a long way since this adventurous group of scientists were hacking parts together to think in 3D. Researchers can now use it to probe into deep tissue, such as in plants and zebrafish, as well as better understand diseases that affect humans, such as type 1 diabetes and congenital disorders. "You take on a different attitude toward your specimen when thinking in 3D," Stelzer says. "Life is not flat – cells don't grow between a glass slide and cover slip. Cells grow on cells! The seeds of light-sheet based fluorescence microscopy were sown at EMBL – and thanks to the efforts of biologists, physicists, engineers and many other professionals, its applications are now being developed and used around the world."

"Life is not flat – cells don't grow between a glass slide and cover slip. Cells grow on cells!"

PHOTO: COURTESY OF ERNST STELZER

Chromatin Cartographer

Jop Kind, this year's John Kendrew Award winner, reflects on the imaginative questions that led him to the prize

BY MARGAUX PHARES

PHOTO: EMBL

EMBL alumnus Jop Kind's research focuses on the role of DNA organisation in genome stability, cell development and disease. Kind's work has paved the way for the development of powerful technologies to map chromatin, or balled-up DNA, in single cells, earning him this year's John Kendrew Award.

Chromatin was understood as a way to package and condense lots of genetic material into a tiny space. In the early 2000s, though, scientists started to understand that the way the two metres of chromatin is wrapped inside a nucleus could itself impact gene expression. Kind was gripped by this new understanding and was determined to research it more.

During his master's internship at the Netherlands Cancer Institute, Kind came across a poster in the department of cell biology: an announcement of an EMBL conference. But he remembers most

"You need to be in constant reflection – especially when the big picture lies in single cells"

the stunning image of a castle on the poster, the Heidelberger Schloss. "I was very much into German writers and philosophers and poets from the Romantic period," Kind remembers. "So this picture, of this castle – it really moved me." He began searching for a lab at EMBL where he could pursue his PhD.

Hot in Heidelberg

Only a few laboratories at EMBL were working with chromatin at the time Kind saw the poster. But he joined Asifa Ahktar's lab, which was studying the similarities and differences in the underlying mechanisms of gene expression between male and female fruit flies. Kind entered as a biochemist. At EMBL, he picked up skills in fly genetics, genomics, and bioinformatics, all in pursuit of his biggest question: How does this wrapping of DNA play a role in gene expression?

It wasn't always easy getting to an answer. One particularly daunting challenge took place in a summer at the beginning of his PhD. It was extremely hot: up to 40°C on some days. Kind and his colleagues were based in temporary lab containers. "We were all in shorts and flip flops," he says with a smile. "It definitely was not ideal." The heat made their experiments a big mess: "We couldn't grow bacteria because it was warmer than 37°C. They were in heat shock all the time!" But he kept going.

"One of my favourite parts of being at EMBL was the collaborative atmosphere," Kind says. "Whenever you had an idea, you could just knock on somebody's door and talk about it. We worked really intensely. But then when we went out in Heidelberg, it was also really intense!"

By the end of his PhD, Kind demonstrated one of the first links between gene expression and spatial organisation of chromatin. It had to do not only with how the DNA was wrapped, but also its location within the nucleus. He was specifically interested in the 35 percent of DNA that was touching the interior of the nuclear membrane, or lamina. What Kind found would challenge the way scientists think about cell division and tumour growth.

Spinning yarns

For his postdoc, Kind joined Bas van Steensel's group at the Netherlands Cancer Institute, who had developed a technique to study spatial organisation of chromatin. But what Kind wanted to do was track nuclear organisation in single cells over time, and so he fine-tuned this technique to figure out which parts of DNA touch the lamina in two methods. The first marks the DNA, the second pinpoints its identity.

Kind can explain the complexity of his lab's work with just a hollowed-out tennis ball, red yarn, and green paint. The tennis ball, he explains, is like the nucleus. Normally the nucleus is packed with DNA, or yarn. But in order to figure out where the yarn touches the ball, Kind paints the inside of the ball. The green paint represents a sort of ink that recognises DNA and permanently stamps it. After unravelling the yarn, Kind can see exactly where it touched the 'nucleus' the contrasting green paint spots. In the lab, this 'stained' DNA can be visualised on a chromosome map.

But here is where it gets even more exciting: This molecular stamp not only sticks to mother cells, but it is also passed on to daughter cells. Kind predicted that the layout of DNA would be faithfully inherited through different generations. To his surprise, this was not the case. The DNA layout differed between individual cells of the same genetic makeup – the mother cells and daughter cells. In other words, the green paint spots were in different places among the same strands of yarn.

His work has unravelled even more questions to answer. Among them: What does this mean for the growth of specialised cells? Or tumour cells, which have a chaotic growth and gradual disappearance of nuclear structure over time? Why would one cell decide to give its genome, damaged or not, to the next generation?

Now a Junior Group Leader at the Hubrecht Institute, Kind predicts the next step will be in deciphering relationships between DNA packing and its effects on the regulation of gene activities and DNA repair. Kind remains focused. "When you are in the lab all the time, it's easy to go into tunnel vision and veer into different directions than you were originally going," he says. "For that, it's important to zoom out. You need to be in constant reflection – especially when the big picture lies in single cells."

EMBL in pictures

Recent snapshots of life at EMBL

PHOTO: EMBL

The ATC in Heidelberg looked beautiful for the Herbst Gala, see page 8 for more.

PHOTO: ROBERT SLOWLEY

Sarah Morgan and a visitor at the EMBL-EBI Open Day 2016.

PHOTO: EMBL/ISABELLE KLING

Moving in. Jamie Hackett's lab in Monterotondo slowly takes shape.

PHOTO: EMBL

In October, alumni and staff met to discuss their research and to network in Barcelona, Spain. The next alumni event in Spain will be held in 2018 in Madrid. Lola Ledesma and José María Almendral (pictured) will be organising it.

PHOTO: EMBL/ROSEMARY WILSON

Fabio Dall explains the structure of a ribosome using a 3D printed protein at Hamburg's First Day of Science, hosted at Universitätsklinikum Hamburg-Eppendorf.

PHOTO: EMBL/ISABELLE KLING

A scientist-to-be using loops to try to fish protein crystals out of a plate at the EPN campus in Grenoble. EMBL and our campus neighbours spent a Saturday explaining molecular biology and protein crystallography to visitors as part of Fête de la Science, a major science festival in France.

Explaining structural biology at the European Learning Laboratory for the Life Sciences workshop at EMBL Hamburg.

PHOTO: EMBL/ROSEMARY WILSON

Events

February
14

La Sapienza University, Rome
EMBL-Sapienza Lecture: Peter Dayan, Gatsby Computational Neuroscience Unit, Sainsbury Wellcome Centre

March
6-10

EMBL Heidelberg
EMBL Course: STED and RESOLFT based Live-Cell Super-Resolution Fluorescence Microscopy

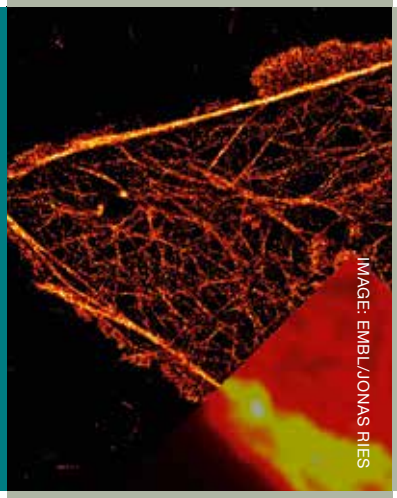

IMAGE: EMBL/JONAS RIES

April
2-8

EMBL Heidelberg
EMBO Practical Course: Mechanisms of Actin-Dependent Force Generation

May
3-6

EMBL Heidelberg
EMBO Conference: Chromatin and Epigenetics

May
11-13

EMBL Heidelberg
EMBO | EMBL Symposium: Metabolism in Time and Space: Emerging Links to Cellular and Developmental Programs

IMAGE: EMBO/SANDRA KRAHL

May
14-17

EMBL Heidelberg
EMBO | EMBL Symposium: Neural Circuits in the Past, Present and Future

Upcoming meetings
Alumni

27 January
Alumni board meeting, EMBL Monterotondo

24 March
Pensioners' Annual Coffee, EMBL Heidelberg

5 May
EMBL in Italy, TIGEM Naples (tbc)

22 May
EMBL in the UK, Oxford University

9 June
EMBL in Australia, Garvan Institute of Medical Research

21 July
Alumni board meeting, EMBL Heidelberg

21 July
Alumni Awards @ Lab Day, EMBL Heidelberg

29 September
EMBL in Norway, Oslo University

3-5 November
EMBL in the USA, Beauport Hotel, Gloucester, MA

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