The European Molecular Biology Laboratory Magazine

Issue 98 Winter 2021/22

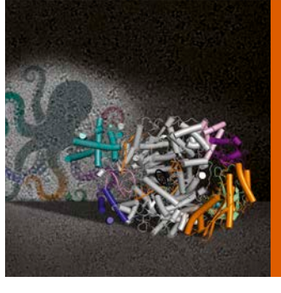
EMBL etc.

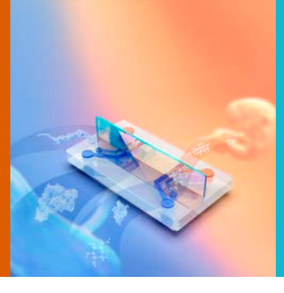
One Health

Contents

Nucleus

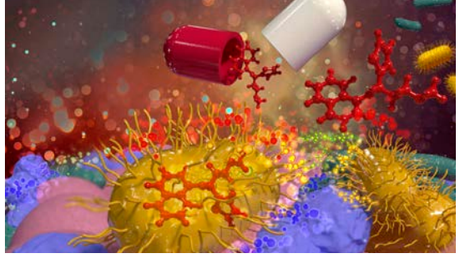
Feature stories





Synapse

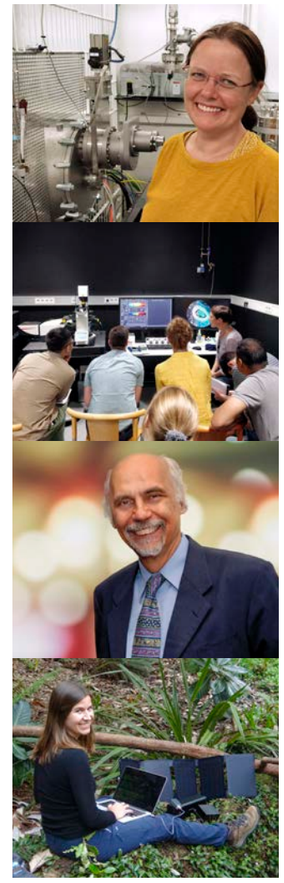
News stories



Cultures

EMBL community stories

Alumni



Editor's note

PHOTO: STUART INGHAM/EMBL

As we began work on this issue of *EMBLetc.*, I was reminded of a fairly well-known allegory. It centres around blind people encountering an elephant for the first time. Each one has touched a very different part of the animal, yet confidently exclaims their certainty in the elephant's shape. The person holding the tail thinks the elephant is like a rope. The one studying the torso thinks the animal is like a wall. And yet another tentatively touches the trunk and says the elephant is like a thick snake. The moral, of course, is that individual perspective often doesn't provide a full picture. But even this allegory falls short. Because what is left out of the story is that the elephant is a product of its environment.

Today's most pressing issues – climate change, food security, antimicrobial resistance, diseases that move between humans and other species – all require not just a multitude of perspectives to achieve understanding and find solutions, but also an appreciation for their interconnectedness.

The concept of One Health, conceived a decade ago, addresses this need for wider awareness. It says that scientists should work in a multidisciplinary fashion as well as factor in our relationship to other species and our environment. The health of – the planet, humans, and other species – is all inextricably linked. One part of this trio cannot be healthy, if other parts are sick.

Global in scope, One Health sets out to design and implement programmes, policies, legislation, and multidisciplinary research to deliver the best possible public health outcomes. And EMBL plays an important role.

In December, EMBL's annual Science & Society conference will address One Health and its myriad issues, such as antimicrobial resistance, zoonotic disease, and harnessing the potential of One Health research. The conference will give researchers the opportunity to consider new networks and collaborations that incorporate partners like NGOs, industry, and government.

To me, the forward-thinking nature of this conference epitomises EMBL. As one of EMBL's science communicators, I get to report on how EMBL and collaborators make discoveries, how their world-class technology enables this work, and how an enterprising training approach builds a pipeline of stellar researchers.

This *EMBLetc.* issue mirrors this, and the bulk of the magazine's stories spotlight science that explores the nexus of human, animal, and planetary health known as One Health. It includes pieces about food security aided by EMBL-EBI's genomics, structural biologists helping to develop an antiviral against Lasso fever, researchers reapplying an approach for studying antibodies to better understand nanoplastics, a PhD programme that is evolving to meet future science needs, plus interviews with speakers from both the upcoming Science & Society conference and EMBL's SARS-CoV-2 conference.

EMBL's next research programme, *Molecules to Ecosystems*, begins in 2022, and will add a molecular biology lens to better understand One Health. This issue richly shows EMBL's critical role in advancing what we know about and consequently can do to improve our One Health.

Ivy Kupec
Editor

Publisher
European Molecular Biology Laboratory

Managing editor
Ivy Kupec

Publication coordinator
Haipeng Zhou

Editors
Mehrnoosh Rayner
Tom Furnival-Adams

Design
Designyard

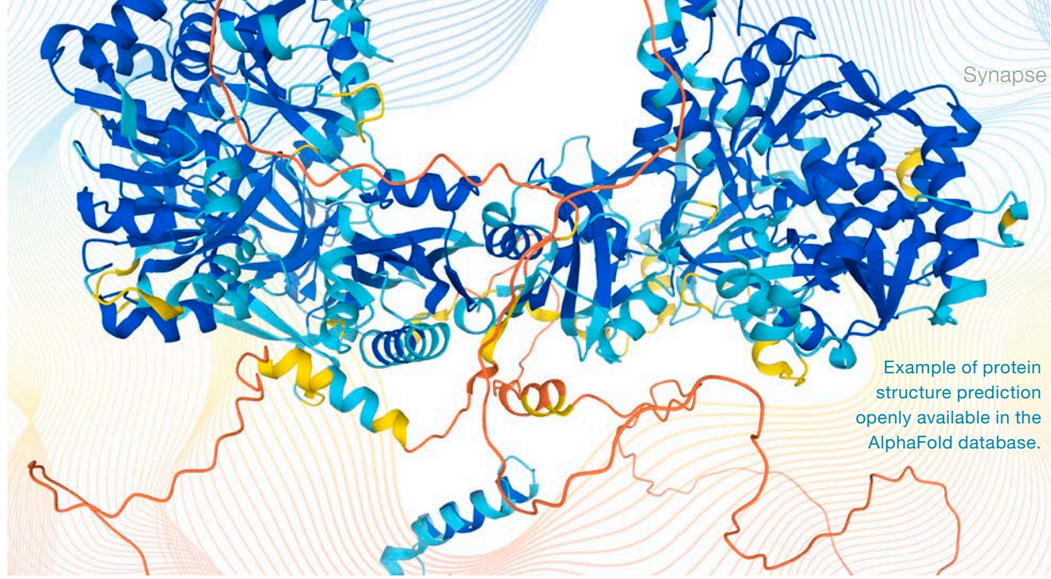
Art direction
Tabea Rauscher

Illustration/design
Karen Arnott
Holly Joynes
Aleksandra Krolik (cover)
Isabel Romero Calvo
Rayne Zaayman-Gallant

Printed by
ColorDruck Solutions

Contact
news@embl.de

embl.org/news



SOURCE IMAGE: ALPHAFOLD. DESIGN CREDIT: KAREN ARNOTT/EMBL

Most complete database of predicted protein structures

DeepMind and EMBL release more than 350,000 protein structure predictions to scientific community

BY VICKY HATCH

EMBL has partnered with DeepMind to make the most complete and accurate database yet of the human proteome – all ~20,000 proteins expressed by the human genome – freely and openly available to the scientific community. The AlphaFold Protein Structure Database offers a treasure trove of data that could unlock future advances and herald a new era for AI-enabled biology.

AlphaFold, DeepMind's AI system that can predict a protein's shape computationally from its amino acid sequence, was last year recognised as a solution to the 50-year-old grand challenge of the protein-folding problem. It is already helping scientists to achieve in months what previously took years.

The new database builds on AlphaFold's sophisticated algorithmic innovations and EMBL-EBI's decades of experience in sharing the world's biological data, as well as many contributions from the international scientific community.

In addition to the human proteome, the database launches with ~350,000 structures including 20 biologically significant organisms such as *E.coli*, fruit fly, mouse, zebrafish, the malaria parasite, and tuberculosis bacteria. Over the coming months, its coverage will be expanded to almost every sequenced protein known to science, with over 100 million structures.

"Our goal at DeepMind has always been to build AI and then use it as a tool to help accelerate the pace of scientific discovery itself, thereby advancing our understanding of the world around us," said DeepMind Founder and CEO Demis Hassabis. "We believe this represents the most significant contribution AI has made to advancing scientific knowledge to date, and is a great illustration of the sorts of benefits AI can bring to society."

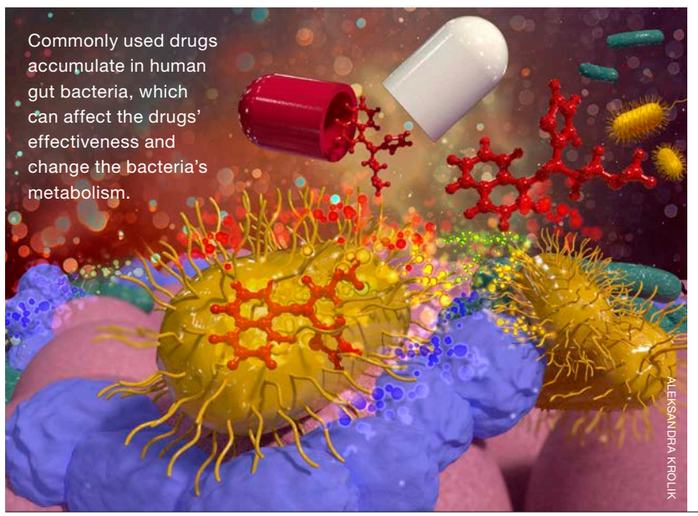
"The AlphaFold database is a perfect example of the virtuous circle of open science," said EMBL Director General Edith Heard. "AlphaFold was trained using data from public resources built by the scientific community, so it makes sense for its predictions to be public. I believe that AlphaFold is truly a revolution for the life sciences, just as genomics was several decades ago, and I am very proud that EMBL has been able to help DeepMind in enabling open access to this remarkable resource."

Tunyasuvunakool K, *et al. Nature*, 22 July 2021.
DOI: 10.1038/s41586-021-03828-1

Jumper J, *et al. Nature*, 15 July 2021.
DOI: 10.1038/s41586-021-03819-2

New insights into gut microbiome

EMBL scientists offer new findings to better understand the gut's influence on the rest of our body



Commonly used drugs accumulate in human gut bacteria, which can affect the drugs' effectiveness and change the bacteria's metabolism.

With a complex community of trillions of microbes constantly interacting with each other, the gut microbiome has increasingly become an important area of interest for molecular biologists as its impact continues to be far-ranging. Recent EMBL research has provided new insights into underlying molecular mechanisms that range from evolution of bacteria in the human gut to drug–microbiome and host–pathogen interactions.

Gut microbiome changes over time

EMBL's Bork group and international collaborators investigated the evolution of bacteria in the human gut microbiome, asking how these microbes persist throughout our lifetime and how they spread geographically.

The results of this study will help inform development of tailored probiotics, which are live bacteria found in particular foods or supplements, as well as dietary or medical interventions, to treat gut disease and maintain a healthy gut microbiome.

Drug accumulation in gut bacteria

Another new study has found that common medications can accumulate in gut bacteria, altering bacterial function and potentially reducing drug effectiveness. These interactions could improve understanding of individual differences in drug effectiveness and side-effects.

The study involved researchers from EMBL's Patil, Typas, Bork, Zimmermann, Hennig, Schultz, and Beck groups as well as the Savitski team, its Genomics, Proteomics, and Metabolomics core facilities, along with other collaborators.

Salmonella's survival strategies

One of the most common foodborne pathogens, *Salmonella enterica* is known for causing diarrhea, fever, and stomach cramps. It has learned to hijack our body's own systems, turning them into a comfortable home where *Salmonella* can survive and thrive.

A team of scientists led by EMBL group leader Nassos Typas uncovered new details of these survival strategies. The researchers analysed protein interactions in *Salmonella*-infected cells and identified diverse molecular machineries and cellular trafficking networks that support the pathogen's growth and reproduction.

SARS-CoV-2 and the gut

EMBL scientists from the Alexandrov and Steinmetz groups, together with collaborators, transformed human intestinal cells into 'mini guts' to follow the infection process. Their study indicates the potential for infection to be harboured in a host's intestines and reveals intricacies in the immune response to SARS-CoV-2.

These findings may shed light on the pathogenesis of SARS-CoV-2 infection in the gut, and indicate why the gut should be considered to fully understand how COVID-19 develops and spreads.

Hildebrand F, *et al. Cell Host & Microbe*, 9 June 2021. DOI: 10.1016/j.chom.2021.05.008

Klünemann M, Andrejev S, Blasche S, Mateus A, *et al. Nature*, 8 September 2021. DOI: 10.1038/s41586-021-03891-8

Walch P, Selkrig J, *et al. Cell Host & Microbe*, 07 July 2021. DOI: 10.1016/j.chom.2021.06.004

Triana S, *et al. Molecular Systems Biology*, 27 April 2021. DOI: 10.15252/msb.202110232

Exploring ways to protect the planet against pandemics

Upcoming EMBL SARS-CoV-2 conference looks to the future

BY IVY KUPEC

It's been two years since the first COVID-19 cases in China, and yet the pandemic continues.

On 10 December, EMBL will assemble global experts for, SARS-CoV-2 – Two Years On: Science Meets the Challenge. Researchers from multiple fields will present the latest developments in SARS-CoV-2 molecular biology and epidemiology, public health strategies, and approaches to protecting the global population against the virus. Specific topics include zoonotic disease, new medications, vaccine development and its equitable worldwide distribution, and pandemic preparedness. (Page 12 features a preview interview with Sarah Barclay from Imperial College who will speak on zoonosis at the conference.)

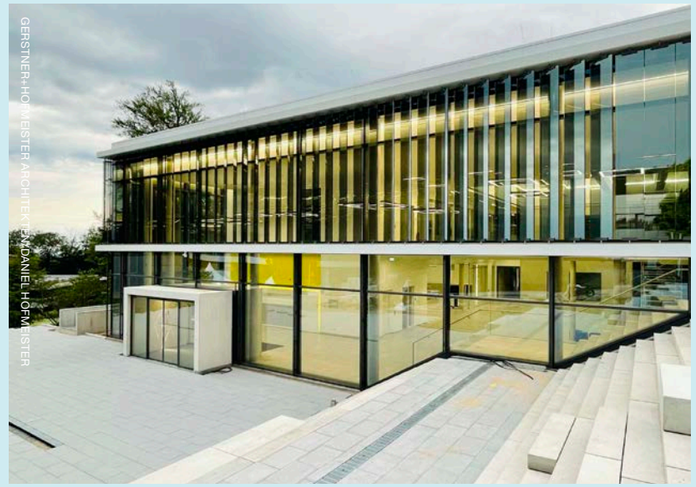
"Open science needs to be at the core of any new national or international measures we enact to monitor and combat emerging viral threats," said Head of EMBL Grenoble Stephen Cusack.

"We should be investing now and not trying to catch up later on," said EMBL Director General Edith Heard, "That means providing tools and infrastructure that allow for smart collaboration and ensuring the next generation of scientists is working in robust, multidisciplinary research settings."

MORE ABOUT THE CONFERENCE:
s.embl.org/eid21-01

EMBL Imaging Centre welcomes first users

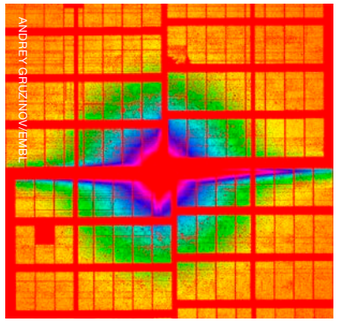
The EMBL Imaging Centre is having its first open call for users this autumn. Here's one of the most recent photos of the completed facility. Its opening is an important moment for the European science community. The Imaging Centre will offer the most advanced high-resolution electron and light microscopy technologies, including academically developed methods that are not yet commercially available. Likewise, it will build on EMBL's decades-long history of world-class service provision for life science research.



A governance and advisory structure for the centre has been established to ensure the highest possible scientific and technical standards, and it will provide independent external advice on technology strategy as well as project prioritisation of the new service unit.

Information on user access and technical capabilities is available from the EMBL Imaging Centre web pages (embl.org/imaging-centre).

SAXS at European XFEL helps study coronavirus proteins



ANDREY GRUZINOV/EMBL

Scattering pattern of a protein during the SAXS experiment using XFEL. The pattern is formed by X-rays from the XFEL beam, which scatter when they hit the sample. They are captured by a detector consisting of multiple panels, visible as rectangular tiles in the image.

A new tool to investigate how antibodies bind to the virus proteins will help to develop medical strategies

BY DOROTA BADOWSKA

A collaboration led by researchers from EMBL Hamburg's Svergun Group used small-angle X-ray scattering (SAXS) at the European XFEL to obtain data on samples containing coronavirus spike proteins and antibodies that can bind them. This is the first time that an X-ray laser was used to collect a SAXS curve of a protein. The results from this experiment could improve our understanding of the immune response to coronavirus and help to develop medical strategies to overcome COVID-19.

SAXS is a powerful technique, which has proven to be extremely useful in investigating macromolecular structures such as proteins in native form under physiological conditions. This gives a measure of the shape and size of a protein and how it changes, for example, when antibodies bind.

The experiment involved research teams from the European XFEL, EMBL Hamburg, CFEL, DESY and the Max Planck Institute for the Structure and Dynamics of Matter. With this pilot experiment, the teams managed to demonstrate the possibility of ultrafast time-resolved SAXS on biological samples at the XFEL's beam.

What lies beneath: the building blocks of life

Analysis of more than two million images sheds light on distribution of nitrogen-fixers in oceans

BY EDWARD PRIOR

As one of the major building blocks of life, nitrogen cannot be assimilated by most organisms without nitrogen fixers – microbes that 'fix' atmospheric nitrogen into more usable forms. Nitrogen fixers on land have been studied in detail, but those in the ocean are much less well understood due to limited observations.

A recent collaborative venture explored the global distribution of marine nitrogen fixers. Using data collected by the Tara Ocean expedition – plankton samples of all sizes, as well as corresponding data on the environment these were found in – the researchers employed machine learning prediction tools to analyse over two million images in combination with DNA sequencing data. EMBL's Advanced Light Microscopy Facility played a central role in the project, enabling the acquisition of these high-resolution images.

This work has also proved that integrative analyses of molecular and imaging data can lead to more accurate explorations of ocean microbes. Such explorations provide valuable information relating to factors such as climate, and how ecosystems are being affected by the impact of human activity.

ELODIE BERNOLLIN/TARA OCEAN FOUNDATION

In this study, scientists worked from more than two million images of plankton samples, generated by the Tara Ocean expedition across the main oceanic regions from 2009 to 2013.

Pierella Karlusich JJ, *et al. Nature Communications*, 06 July 2021. DOI: 10.1038/s41467-021-24299-y

ALEKSANDRA KROLIK/EMBL

Nucleus

Communicating risks in public health

After decades spent considering ways to incentivise action on global health issues, Chris Dye thinks a deeper understanding of how people judge risks and costs may hold the key

BY EDWARD PRIOR

Chris Dye will speak at EMBL's Science & Society Conference, One Health: Integrating Human, Animal and Environmental Health. He provided some thoughts about his public health experiences as an epidemiologist and a World Health Organization (WHO) Director of Strategy.

Chris Dye, an epidemiologist and professor who served as the WHO Director of Strategy, is fascinated by how humans assess risk and what influences their decisions, and the opportunities to then mitigate or solve complex and interconnected global health challenges.

Every day, we each subconsciously calculate risks and benefits. An early morning run, or an extra slice of bacon? Wait at the pedestrian crossing, or dash across the road? Accept a new medical treatment, or take our chances?

From 2014 to 2018, Dye was Director of Strategy at the WHO, serving as science advisor to the Director General.

While these personal decisions are familiar, the calculations that underpin them – the cost of action versus risk of inaction – are also well-known to policymakers, who must grapple with emerging and potentially major global challenges.

CHRIS DYE/WHO

The path to studying people's assessment of risk

Dye set out to be an ecologist but was quickly drawn into the world of public health. A PhD involving mosquitos ultimately led to an interest in public health and epidemiology.

His career has since spanned the full spectrum of public health. From collecting sand flies in South America, to advising government ministers and the WHO Director-General, Dye has spent decades grappling with human health at a population level. He's witnessed first-hand the complex calculations that leaders make in relation to future threats.

"If we look at any kind of choice, be it around hazards like pandemics and climate change, chronic diseases, or choices around investment in health or sanitation systems – we have to think about how we can persuade people to act," Dye said. "And that comes down to understanding and manipulating risks people perceive."

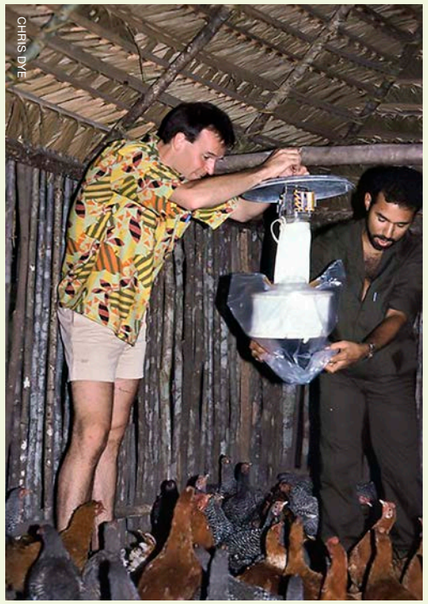
Dye frames this potential 'manipulation of risk' in terms of thought processes he believes are common to all situations in which costs and benefits are weighed.

"Essentially, it's an economics question... time, effort, willpower, information," he said. "If we can just adjust that balance of costs and benefits, making benefits seem greater and costs smaller, we're more likely to invest in prevention. Fundamentally, we must get people to value the future more... in the present."

Challenging the disparities in public health decision-making

The internal function – or dysfunction – of global health systems also shaped Dye's early career. It was while studying leishmaniasis that he first understood disparity in public health policymaking.

In parts of South America, sand flies transmit leishmaniasis to animals and humans, causing fever, weight loss, disability, and death. Despite infecting more than 1.5 million people annually, and killing 20,000 to 30,000 people a year, leishmaniasis is part of a group of diseases referred to as neglected tropical diseases.



CHRIS DYE

In 1991, Chris Dye was using light traps to catch sand fly vectors of leishmaniasis on Marajo Island, Brazil.

ALEKSANDRA KROLIK/EMBL

In later years, however, public health experts presented a possible way to make progress. "The inspired idea was this... no one was interested in these 15 to 20 diseases separately (but) together in one named package they form a very significant hazard, and one that was much harder to ignore. Many of those neglected diseases – like trachoma, like schistosomiasis, like river blindness – have greatly benefited."

By grouping diseases like this, public health experts essentially mimicked an approach insurance brokers use, pooling risks across groups of people. Dye argues this technique offers a way forward to deal with significant global health challenges.

Finding the right path forward

Much of Dye's work has embraced the concepts of One Health, and the way it brings together diseases in humans, diseases in animals, and the environment. Dye stresses a real need for cooperation among disciplines.

"The word 'multidisciplinary' is very frequently used," he said. "In my experience, much less frequently is it given practical and useful meaning."

"We have to think about how we can persuade people to act. And that comes down to understanding and manipulating risks people perceive."

Dye is positive about the potential of applying new thinking to the challenges ahead, and believes the successes achieved around vaccine development during the COVID-19 pandemic can be repeated elsewhere.

"Many of the big problems we face are indeed soluble, provided we are willing to engage properly with the argument," he said. "One of the things I've learnt across the years is the value of understanding, instead of presupposing. That understanding should be a starting point for analysis – it sets the scene for conducting evaluations that are most likely to deliver practical solutions, for One Health and more widely."

EMBL'S SCIENCE AND SOCIETY PROGRAMME:
s.embl.org/science-and-society


ALEKSANDRA KROLIK/EMBL

Catching up with Wendy Barclay

Professor Barclay shares research insights ahead of presentation at EMBL conference on SARS-CoV-2

BY EDWARD PRIOR

Wendy Barclay, a virologist and expert in the spread of respiratory viruses, started her scientific career working on the common cold and then moved on to study influenza viruses. We caught up ahead of her appearance at the EMBL conference SARS-CoV-2 – Two Years On: Science Meets the Challenge.

Wendy Barclay has studied how viruses cross from animals to humans and cause pandemics.

What is your laboratory's current focus?
We're looking at the evolution of SARS-CoV-2 since it emerged in humans and seeing where it is headed. When the virus first emerged, it was 'good enough' to infect humans and transmit among us. As it circulated more in the human population, it evolved to become even more transmissible, and transmission became the driving selection – the primary factor for people getting infected. But that might be changing.


IMPERIAL COLLEGE LONDON

As more people around the world become infected and recover, or receive a vaccine, I think a different selective force will begin to act – antigenic force, meaning the strength of the interaction between antibody and antigen. So, the spread of the virus will be steered by how well antibodies disable viral proteins, rather than just transmissibility. We think the virus will evolve to escape control by the immune response that people are creating through vaccination and direct infection. But at the same time the virus has to remain fit and transmissible. We're looking at the effect of mutations on the spike protein to see how they balance immune escape with maintaining transmissibility.

You've worked to improve how science is communicated. How good has messaging been during the pandemic? Does the use of unproven 'alternative' treatments reflect a failure of communication?
Overall, many more science voices have entered the public domain, and that's very good. The pandemic has been such a huge event that it's not surprising that some level of misunderstanding in the public domain, as well as miscommunication, still exists. We live in an era where even regular, established media are sometimes not as trusted as the information available on social networks. That presents a real challenge – I certainly don't see this as a fault of scientists. I think they have really stepped up during the pandemic. Talking to the media is incredibly time-consuming. During the swine flu pandemic, I had some days going from studio to studio, doing one interview after another. All of that comes on top of research work. People have been working incredibly hard.

The pandemic and our response to it has brought in new scientific approaches and technologies. Which will have lasting impacts?
One of the lasting changes will be around vaccines and vaccine development. Our ability to produce vaccines so quickly – and use new types of vaccines like the mRNA vaccines – will be a lasting legacy. It will also help us with the inevitable future pandemics that we face. And these kinds of modern vaccines will also help us with other diseases. I've worked on flu for most of my career, and I suspect some of this new vaccine technology will be employed now for flu vaccines. It will be used not only for pandemic flu but also for seasonal flu. When we update seasonal flu vaccines, we'll be able to use more synthetic-style vaccines than in the past.

Looking ahead, what technologies could make the biggest difference to your work?
One of the biggest is next-generation sequencing. The ability to sequence a whole genome of a virus so quickly, to deep sequence it and understand the diversity of the sequence within the virus population, and then watch how the virus evolves as it replicates in humans or animals, that's incredible. When I did my PhD, I remember running old-fashioned sequencing gels to sequence a single polio virus. It would take an entire thesis and three years of work. Now we can do it in three hours!

"Our ability to produce vaccines so quickly – and use new types of vaccines like the mRNA vaccines – will be a lasting legacy."

Professor Wendy Barclay will speak on zoonotic disease at the EMBL conference SARS-CoV-2 – Two Years On: Science Meets the Challenge, held virtually on 10 December 2021. Registration is open till 2 December.

MORE ABOUT THE CONFERENCE:
s.embl.org/eid21-01

Can data help feed a hungry world?

How genomics, open data, and multidisciplinary science can improve agriculture

BY OANA STROE

Feeding a growing population in a changing world requires new technologies, collaboration, and a whole lot of data. The need is clear and urgent: in 2020, 2.37 billion people did not have access to enough safe, nutritious food.

Scientists around the world are working to solve this problem in a number of ways, for example improving crop yields or producing disease-resistant, drought-protected crops. Much of the data and insights they generate find their way into EMBL-EBI data resources – openly and freely available libraries of molecular data for all plant and animal species. And these are the data that sit at the heart of finding solutions for feeding the world.

Genomics – an essential tool

"New technologies are enabling researchers to measure traits, or phenotypes, of plant and animal species that global food supplies rely on, and connect them to underlying genomic regions," explained Sarah Dyer, Ensembl Plants Team Leader at EMBL-EBI.

(Image at centre) Bioinformatics and genomics – essential tools for global food security.

"Linking genes to desirable traits – such as high yields for a plant, or disease resistance for farmed animals – could be a gamechanger for agriculture. However, such traits are often polygenic in nature, meaning they can't be traced back to a single gene, which makes the work of linking genotype to phenotype very complex."

Linking gene to trait

EMBL-EBI is involved in a series of international collaborations working to improve the fundamental understanding of genome to phenome research, with the aim of helping farmers and breeders to make food production more robust and sustainable. These include FAANG, a coordinated initiative to understand genome-to-phenome links in farmed animals, as well as more specialised projects such as BoVReg, which focuses on cattle; GENE SWitCH, working on pigs and chickens; AQUA-FAANG focused on farmed fish, and Designing Future Wheat (DFW) for wheat.

"Plant and animal genomics can help us produce more healthy food using fewer natural resources, while also improving animal welfare and conserving biodiversity," said Peter Harrison, Genome Analysis Team Leader at EMBL-EBI.

Adapt to changing climates

"As a warming climate and extreme weather become the norm, we need to futureproof food production. This means using our understanding of genomics to speed up the selection for desirable traits. For example, dairy cattle often produce less milk due to heat-induced stress, when temperatures get too hot. Using genome-wide DNA markers that predict tolerance to heat stress, cows can be bred to be more resilient to the increasingly hot temperatures of our climate," said Harrison.

"But understanding the genotype of desirable traits is no easy feat," continued Harrison. "It takes experts in bioinformatics, molecular genetics, animal breeding, reproduction physiology, and animal welfare to understand this complex puzzle. We also need robust data infrastructure, analysis tools, and standardisation. This way, data produced in different parts of the world is of a comparable standard. For example, data from Europe can be combined with data from Australia or the Americas, and can be analysed to reveal new insights. This is why coordinated international efforts for standardisation of genomic data, such as FAANG, are so important."

Equip against disease

"Plant genomes are often very large and sometimes polyploid, meaning they have multiple copies of identical or similar chromosome sets, so they can be difficult to work with," explained Dyer. "But new genome sequencing technologies are helping us overcome these issues and we're now seeing high quality genomes for different varieties of the same plant species."

For example, Ensembl Plants now offers 14 wheat genomes from the 10+ Wheat Genomes and DFW projects, which makes it easy to identify variations specific to each variety. And these datasets are important because they can help producers increase the diversity of their crop.

We know that monocropping is a high-risk strategy – you can lose your entire crop if they're affected by a disease or pest – whereas diversity can make a crop stronger. Genomics reveals that diversity.

Understand pests and pollinators

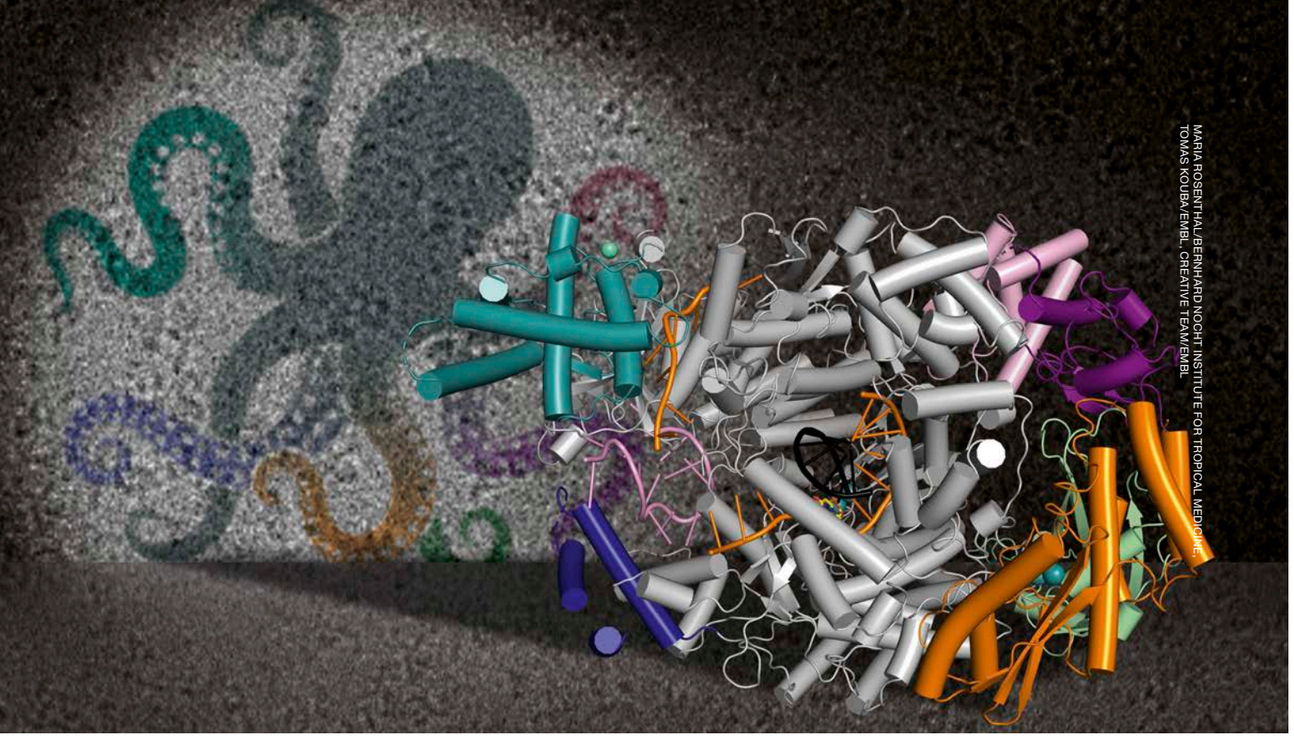
"We mustn't forget about the unseen heroes and villains of plant production: the pollinators and the pests," continued Dyer. "Taking a genomic approach can inform the design of strategies to deal with pests while protecting pollinators. Ensembl Metazoa is a great place to explore these genomes."

To make your plants more resilient to pests, researchers need to understand the genomics of the plant and pest alike. One recent example was a project that sequenced the genomes of a set of whiteflies, tiny insects, no larger than 1mm in length, that regularly cause billions of dollars' worth of damage to cassava, cotton, tomatoes, or bean crops in the developing world. As a result, the genomes of six species of African Cassava whitefly are now available in Ensembl Metazoa for scientists and breeders to better understand these insect pests.

These examples are only the beginning of what genomics can do for agriculture. Just as genomics helps us understand human health, it is also a lens for understanding the plants, animals, and insects that global food production depends on. But new discoveries will depend on pooling knowledge from many sources, which is why public data resources like Ensembl are critical.

"We mustn't forget about the unseen heroes and villains of plant production: the pollinators and the pests."

– Sarah Dyer, Ensembl Plants Team Leader at EMBL-EBI



MARIA ROSENTHAL/BERNHARD NOCHT INSTITUTE FOR TROPICAL MEDICINE; TOMAS KOUBA/EMBL; CREATIVE TEAM/EMBL

(Opposite) The Lassa's virus polymerase casts the shadow of an octopus in images with its many moving components.

Wrangling an octopus-like viral replication machine

EMBL structural biology is part of an international collaboration addressing zoonotic disease caused by Lassa virus

BY MYLÈNE ANDRÉ

Endemic in Western African countries, Lassa virus is transmitted to humans through food or household items that are contaminated with the urine or faeces of *Mastomys* rats. Even though many people who become infected with Lassa virus are asymptomatic, one in five infections results in severe haemorrhagic disease, attacking vital organs like the liver, spleen, and kidneys.

The World Health Organization (WHO) lists Lassa fever as a significant public health threat with high epidemic potential and no effective countermeasures. Lassa fever has no vaccine and only one drug – a broad-spectrum antiviral called ribavirin, which has limited efficacy.

Even though researchers are working on a vaccine, an effective antiviral is needed to reduce the number of severe cases and deaths. This is where structural biology can help.

Sharing expertise

To understand the intricate mechanism of viral replication, structural biologists focus on a key component: the viral polymerase. In an infected cell, this enzyme replicates the virus's genetic information. The genome copies are then packaged into new virions, which escape the cell and can infect a new host. Determining the polymerase structure helps researchers understand how a virus replicates, giving them important insight into how to design drugs that can stop the infection.

Stephen Cusack, Head of EMBL Grenoble, focuses his group's research on the polymerases of several human pathogenic viruses, particularly influenza virus. Because influenza and Lassa viruses are from the same family – both segmented negative-strand RNA viruses – Cusack's group started collaborating on Lassa virus several years ago with Maria Rosenthal and Stephan Günther from the Bernhard Nocht Institute for Tropical Medicine (BNITM) in Hamburg.

"Stephen Cusack was at the forefront of research on influenza and ahead of the field with respect to bunyaviruses and arenaviruses," said Günther, the head of the virology department at BNITM. "We thought it was excellent synergy because he already had a lot of technological knowledge we could transfer to the Lassa polymerase."

The Lassa polymerase has characteristics that complicate the process of determining its structure, which Rosenthal, a BNITM structural biologist and group leader, had tried to obtain for several years. "After a long testing of other systems, I went to Grenoble to test the system developed by Imre Berger (an EMBL Grenoble alumnus), and applied by the Cusack group to influenza. We got very good expression of the protein," Rosenthal said.

The polymerase also has a peculiar architecture with a core and flexible outer components. "We call the Lassa virus polymerase an 'octopus' because it's like it has arms floating around, which makes it very hard to catch in one position," said Tomas Kouba, a postdoc in the Cusack Group.

Macromolecular crystallography – an imaging technique commonly used in structural biology – couldn't be used to observe the Lassa polymerase, because the protein moved too much to capture all the arms. Cryo-electron microscopy (cryo-EM) offered the solution as it enables snapshots of the protein to be taken in different functional states.

"We applied to Lassa the techniques that Kouba and Joanna Wandzik (a former EMBL PhD student) developed to visualise influenza polymerase in action," Cusack explained. "We used cryo-EM facilities both in Grenoble and at the Centre for Structural Systems Biology (CSSB) at the University of Hamburg."

Promising structures

This collaboration between researchers from EMBL Grenoble, BNITM, and Kay Grünewald's lab at the CSSB provides details on nine structures of the Lassa viral polymerase in different functional configurations.

"When you observe this 'octopus', you also want to see how it behaves, how it moves its arms to eat or catch something," explained Kouba, one of the paper's three principal authors.

"The power of cryo-EM is that you take millions of pictures of the protein. Then you can sort them into several boxes: one box with an arm up, and then one box with the arm down," Rosenthal added. "In the end, you have more highly resolved images of octopus arms in a variety of positions, so you can model them."

These studies provide crucial insights into the Lassa virus, which has only four different viral proteins – very few compared to other viruses, such as herpes or SARS-CoV-2, which have dozens of components. The proteins make up for their small number by assuming multiple functions, like a Swiss Army knife. The researchers could, for example, visualise polymerase activity and propose how to block viral replication.

One Health: preparedness

The collaboration also explores other segmented negative-strand RNA viruses on WHO's priority list. These include pathogens causing certain insect-borne viral diseases whose geographical spread may be affected by climate change.

Formerly located mostly in tropical areas, these viruses are extending their range. This is already the case for tick-borne Crimean-Congo haemorrhagic fever virus, which has spread into southern Europe, or mosquito-borne Rift Valley fever, which is expected to spread.

Even though these viruses differ significantly in many respects, their polymerases are closely related, and identifying similarities between them could help develop a broad-spectrum antiviral to tackle them all.

"Structural biology is important to understand what we are actually looking at," Rosenthal said. "How could you win a fight if you don't really know who you're fighting? If we know how these viruses work, then we have more ideas on how to tackle them."

From creating new antimicrobials to combating Alzheimer's disease

Structural biology provides insights into the diverse functions of fibrous protein in humans, amphibians, and bacteria

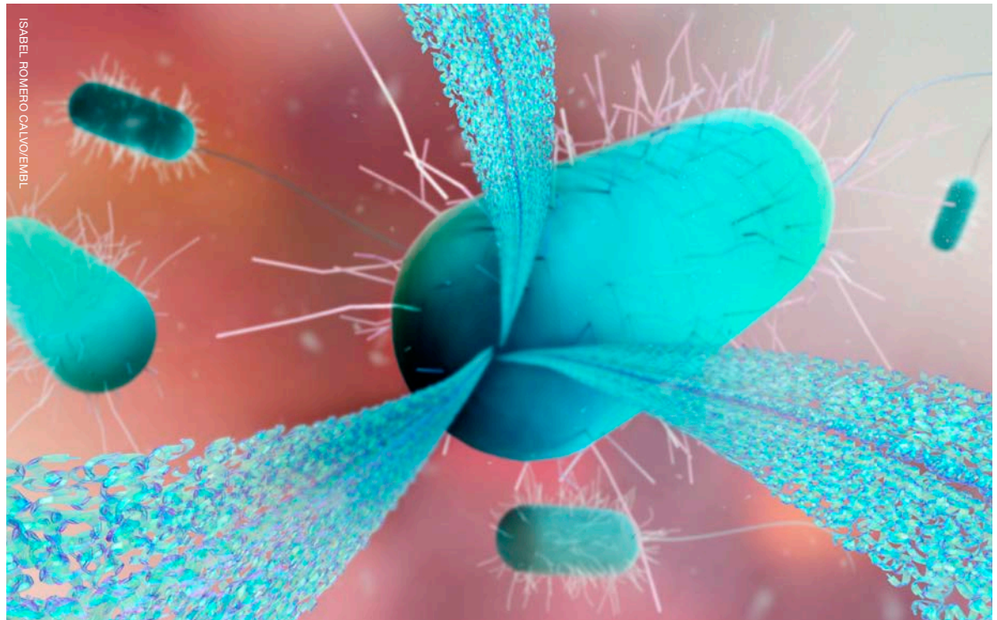
BY DOROTA BADOWSKA

What do Alzheimer's disease, dental cavities, and a blocked sink drain have in common? They can all involve nanometre-sized bacterial protein fibres that can form molecular constructions as strong as steel.

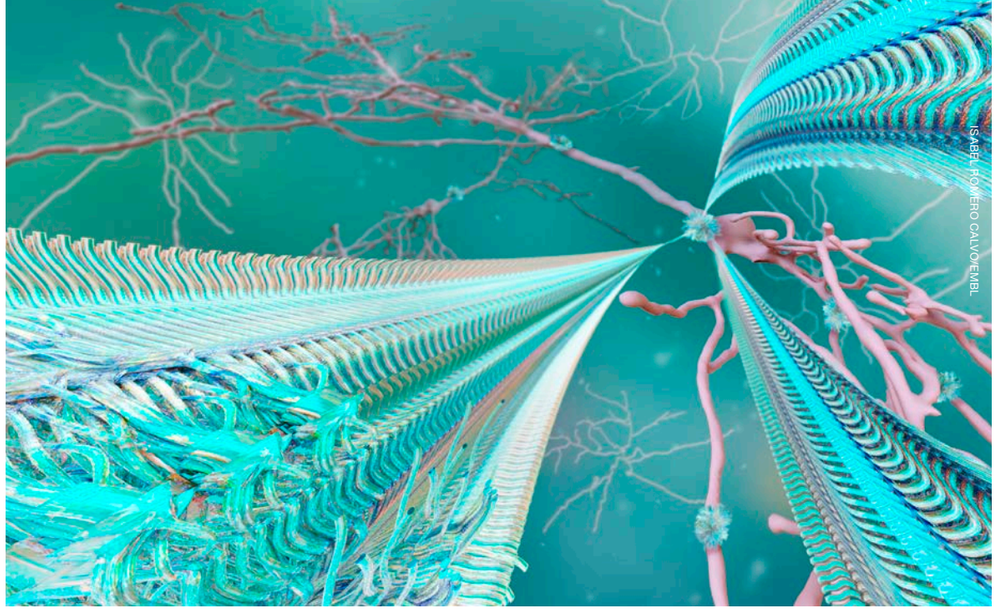
These fibres form a scaffold that stabilises extremely sturdy layers of bacteria on various surfaces, such as human teeth, a catheter, and even the inside of the sink drain. The fibres can probably also form in the human body during infection, killing immune cells and making bacterial infections more aggressive.

The Landau Group at EMBL Hamburg and at Technion – Israel Institute of Technology discovered the structural basis of these bacterial fibres' stability and activity. The findings present new ways to develop therapeutic strategies that treat infections not by killing the bacteria but by disrupting the fibres that serve as their 'weapons'. The aim is to stop bacteria from doing harm while the host fights the infection on its own.

This approach offers a major advantage: in contrast to antibiotics, anti-fibre drugs might be less prone to antibiotic resistance, which



Scientific illustration showing nanometre-sized bacterial protein fibres (PDB 6S6M), which assemble into molecular constructions that stabilise sturdy layers of bacteria on various surfaces, including in the human body.



Scientific illustration showing human neuronal amyloids (PDB 2M4J), which form structures similar to those made by bacterial fibrils.

the World Health Organization considers one of the top 10 global public health threats. If it is not tackled, antibiotic resistance could lead to diseases such as tuberculosis and pneumonia becoming completely untreatable. In many countries, certain antibiotics are already ineffective in more than half of patients, and the number of drug-resistant bacterial species is growing. This research could help to find an urgently needed alternative to antibiotics.

Certain proteins have a fascinating ability to spontaneously self-assemble into supramolecular fibres, thereby gaining new properties. With the use of structural biology techniques, the Landau Group analysed the atomic structure of fibres secreted by certain bacteria in the gut and in many foods. They saw that these structures have striking similarities to a group of human proteins called amyloids, which also form supramolecular structures. Many amyloids, for instance amyloid-beta and alpha-synuclein, are linked to disease. They can lump into plaques in the brain and have been found in people with Alzheimer's, Parkinson's, and several other neurodegenerative diseases.

"This connection between bacterial fibres in the gut and human amyloids in the brain could help us find a factor contributing to the propensity for Alzheimer's and Parkinson's diseases," said Group Leader Meytal Landau. "It's possible that certain bacteria present in the gut secrete fibres that are transmitted to the brain and trigger human amyloids to aggregate. This suggests a similar mechanism to mad cow disease, which is caused by eating meat contaminated with infectious proteins called prions."

Interestingly, the same amyloids associated with neurodegeneration also have a protective role in fighting microbial threats. The Landau Group discovered that human and amphibian peptides (small proteins) that are used to combat bacteria also form fibres. These peptides self-assemble into unique fibrous nanostructures, which in the presence of bacteria restructure to become a deadly antimicrobial weapon. Such fibres could serve as a durable, active coating for medical devices or implants, industrial equipment, food packaging, and more.

Landau joined EMBL Hamburg in mid-2019 as visiting group leader. At EMBL, she has access to a synchrotron for crystallographic studies and to cryo-electron microscopes for high-resolution structural studies – tools not available to her group at the Technion in Israel.

"The EMBL beamlines are among the few across Europe suited for crystallographic studies of amyloid fibrils," she explained. "EMBL Hamburg is very attractive because of its integrated facility for structural biology and access to diverse techniques under one roof."

Building a 3D placenta on a chip

A new model could serve as a platform to investigate critical placental barrier phenomena, including defence against bacteria, viruses, and parasites

BY CARLA MANZANAS

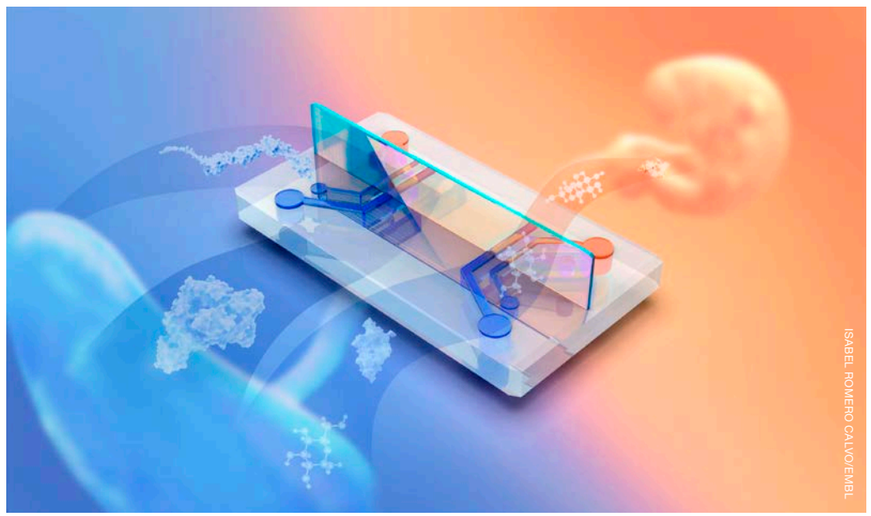
The placenta is a critical organ that develops during pregnancy, supplying oxygen and nutrients from the maternal blood to the fetus. The placental barrier serves as a filter for substances that cross from the mother to the fetus and vice-versa. And those substances can range from viruses, bacteria, or even drugs like ibuprofen or paracetamol.

A dysfunction in such a vital structure can result in health complications for both sides. Pre-eclampsia is one such disease, usually associated with high blood pressure and vascular complications in the later stages of pregnancy.

"Up to eight per cent of pregnant people worldwide suffer from pre-eclampsia. For this reason, we need to build better humanised models in order to understand the causes of this and other placental dysfunctions," stated Kristina Haase, Group Leader at EMBL Barcelona.

Haase and her group will be the first to build a 3D vascularised placenta barrier model on a chip. The chip is a small micro-scale device made from a flexible polymer with a central port wherein cells are grown and spontaneously form vessels inside. Around that port, there are several channels that allow researchers to supply various fluids and molecules of interest to the cells and analyse their development.

"Existing 2D placental models are missing a key component – a perfusable fetal vasculature – so we will build 3D chorionic villi," said Marta Cherubini, the postdoc at Haase Group responsible for developing the model, about how this approach will enable scientists to understand what crosses the placental interface and the fetal bloodstream. "The chorionic villi are terminal branches that look like fingers and this is where the majority of fetal-maternal exchange occurs."



ISABEL ROMERO CALVO/EMBL

A pioneering model to strengthen collaboration

The project, partly funded by the Spanish State Research Agency (Agencia Estatal de Investigación), is a collaborative effort with three main aims.

The first one focuses on creating a robust placental barrier on a chip. To protect the developing fetus during gestation, the placenta builds a continuous layer of specific cells known as trophoblasts, which separate the fetal vasculature from making direct contact with the maternal blood.

The 3D model that Haase and her group are developing is a pioneering one that has never been built before: this will be the first time researchers incorporate several human placental cell types including trophoblasts to generate fetal vessels and the interface layer. In normal conditions, the placental barrier allows for molecules (like sugars) to pass through it without impediments, yet larger proteins and cells from the maternal immune system are blocked. By controlling fluid flow and pressure in the vessels, the scientists will study how changes in mechanical signals influence and regulate the exchange of substances.

Once they fully develop the model, the second aim will be to study how properties of the placental barrier change when inflamed. The exact cause of pre-eclampsia is still unknown, but it is associated with significant inflammation. During gestation, women undergo blood tests to define their risk of pre-eclampsia, so although researchers don't know what causes this complication, they do know several maternal plasma markers related to it. In collaboration with Dr Elena Carreras and Dr Manel Mendoza from Hospital Vall d'Hebron in Barcelona, the Haase group will collect plasma samples from patients from normal and pre-eclamptic pregnancies. They will then inject small amounts of plasma in the previously developed placental barrier on a chip, where they expect impacts on the barrier properties and fetal vascular remodelling.

Last but not least, the third aim is to understand the role of pregnancy-specific glycoproteins (PSGs) in fetal health. PSGs are the most abundant proteins secreted by placental trophoblasts into the maternal blood circulation during pregnancy. They have been linked to the proper development of maternal vessels in the placenta and modulate the immune system during gestation. Scientists have observed low amounts of PSG1 (a specific PSG) in the plasma of pre-eclamptic patients, and this condition is strongly associated with inflammation. In collaboration with Prof. Gabriela Dveksler at the Uniformed Services University of the Health Sciences in the United States, Haase and Cherubini will apply PSG1s on the maternal side of the device to study whether an increase of such proteins improves fetal health in an inflamed environment.

A placental barrier that actually expands knowledge

"A relevant 3D model of a human vascularised placenta will enable scientists to study this complex organ in a controlled and reproducible manner," Cherubini said.

This work will focus on developing a novel *in vitro* tool that could uncover biological processes and functions of common obstetric complications in addition to pre-eclampsia. "A robust human vascularised placenta model would open the door to study the effects of many other external factors such as drugs, Covid-19, or malaria, for instance." stated Haase, envisioning new collaborations with both research institutions and biotech companies.

(Opposite) 3D visualisation of the vascularised placenta barrier model on a chip. The blue channels in the chip represent the maternal side of the placenta and are separated with a membrane from the orange channels, the fetal side of the placenta. This membrane allows for supply of the oxygen and nutrients from mother to fetus, but it is also the door of entry to potentially dangerous molecules or infections. In the image we can also see how some small molecules (like glucose) can cross through the membrane from the maternal to the fetal side of the placenta, while other larger molecules (like albumin) cannot.

Putting *Cryptococcus* in context

EMBL's imaging technology helps researchers gain insights in the fungus' journey from the lung to the brain

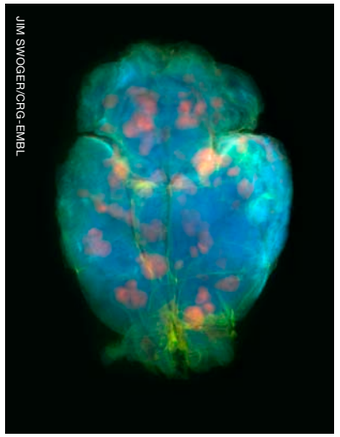
BY CARLA MANZANAS

Found all over the world, the fungi *Cryptococcus* usually doesn't affect healthy individuals. However, it sometimes causes severe meningitis in immunocompromised individuals, like people with HIV. Infection usually occurs when people inhale the fungi, spreading it to the lungs and brain, possibly with fatal consequences.

Greetje Vande Velde, Research Professor at KU Leuven, has studied *Cryptococcus* for almost a decade. How the fungi are able to cross the blood brain barrier is still unknown, and that's why Vande Velde and Jim Swoger, Head of the Mesoscopic Imaging Facility at EMBL Barcelona, started collaborating several years ago.

In 2015, Vande Velde was a postdoc at KU Leuven and Swoger still worked in the Sharpe Lab, at the Centre for Genomic Regulation (CRG) in Barcelona. She spent a research fellowship in the Sharpe lab to visualise mouse organs in 3D with Swoger, using the recently invented techniques Optical Projection Tomography (OPT) and Selective Plane Illumination Microscopy (SPIM).

"Greetje's expertise is in 3D *in vivo* imaging, which allows for live observation of disease spread, but it doesn't allow us to look at cells themselves within the context of organs and tissues," Swoger said. "OPT and SPIM allow us to image complete mouse organs *ex vivo* at high resolution in 3D and help us see the spatial organisation of the *Cryptococci*."



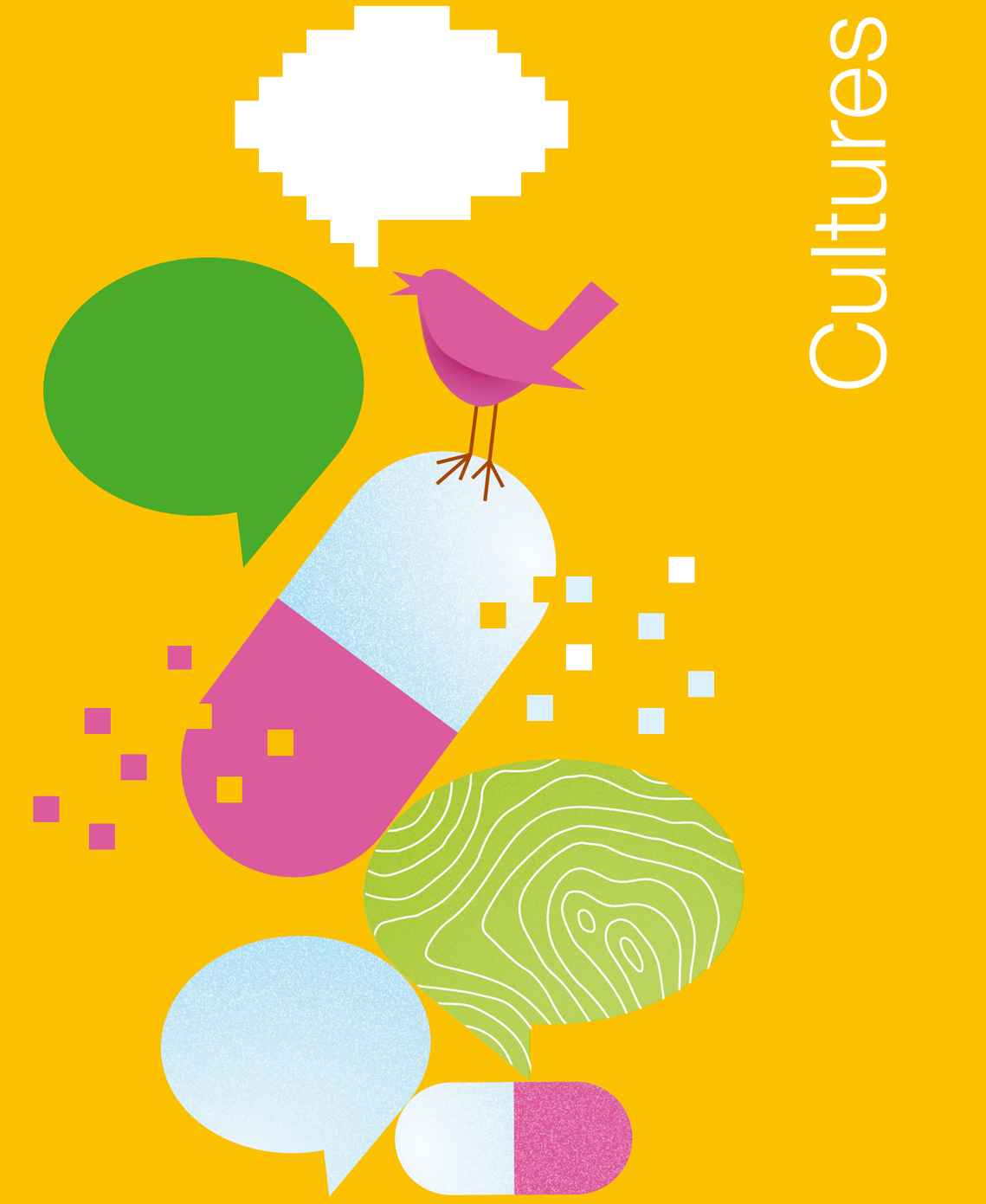
Left: a single OPT projection of a *cryptococci*-infected mouse brain. Fungi-filled lesions are seen in red. Right: an OPT image of a mouse lung, showing vasculature. Two regions of infection can be seen in the lower left.

In 2017, EMBL Barcelona and the Mesoscopic Imaging Facility (MIF) were established, with Jim Swoger as Head of MIF. The project then went a step further by using a combination of the two imaging technologies used at the CRG: OPT plus SPIM. This became the hybrid OPTiSPIM. SPIM provided high resolution, which complemented the imaging speed and multi-modality (fluorescent and absorbing contrasts) of OPT.

Vande Velde and Swoger imaged entire mouse lungs and brains infected with *Cryptococci* to get 3D images at cellular resolution. They could then observe the fungi in the context of entire organs and see how fungal populations were organised in the folds of the brain.

These imaging technologies and the sample preparation protocols allowed the researchers to make novel observations on where and how the fungi assembled – something that hadn't been captured previously. *Cryptococcus* populations were generally organised around the microvasculature of the brain, which is the system of tiny blood vessels like capillaries and venules. Such observations are pivotal to further probing how the fungi enter and infect the brain.

"The collaboration with the MIF helped us achieve important insights towards understanding the disease pathogenesis." Vande Velde said. "There have been cases of apparently healthy individuals with severe cryptococcal infections that challenge our understanding of this disease to this day. We need to tackle this and other infectious diseases without delay."



From antibodies to nanoplastics

EMBL researcher applies structural biology to better understand nanoplastic pollution and find way to solutions

BY IVY KUPEC

When Melissa Graewert took her family to tour the *Tara* research vessel during a 2019 port visit in Hamburg, she had no idea just how much it would impact her own research.

As a structural biologist, Melissa normally analyses the structures of antibodies in the Svergun group at EMBL Hamburg. She visited *Tara* with her four-year-old daughter, who was captivated by how the ship was collecting data for Mission Microplastics, which highlighted the widespread problem of plastics in our oceans.

After the visit, as she peppered Melissa with questions about her research, Melissa's daughter learned – much to her dismay – that her mum's work explored antibodies, not plastics. That's when she got to the point: "Why not plastic?"

Consequently, Melissa herself began to ask, "Why not nanoplastics?"

"The question stayed with me a while," she explained. "I started exploring whether the method we use to study therapeutically relevant antibodies and other biological macromolecules would also be applicable to studying plastics. I realised how little is known about nanoplastics."

It's not uncommon to encounter plastic pollution on beaches around the world, as photographed here by EMBL researcher Melissa Graewert on a recent outing.

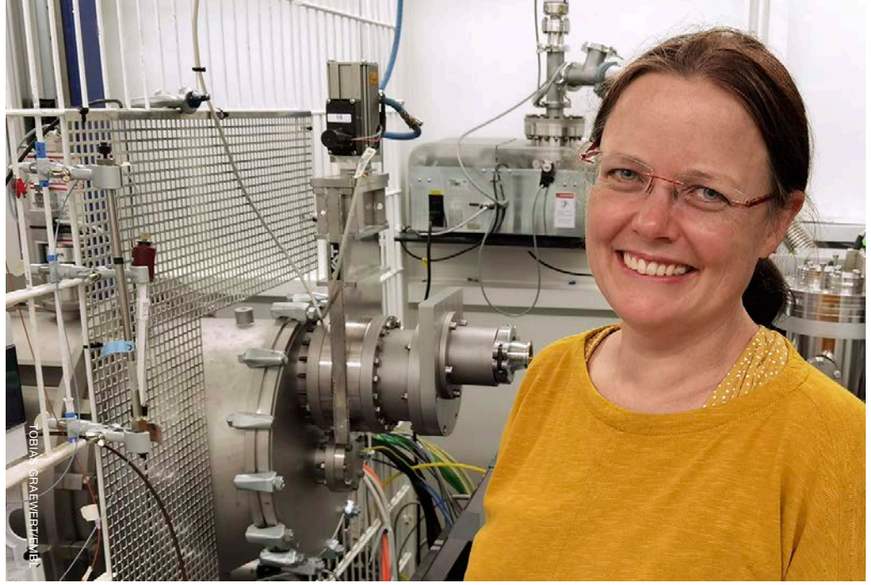
According to the International Union for Conservation of Nature, every year more than 8 million tons of plastic waste wind up in the oceans, breaking down into macro-, micro-, and even nanoplastics, but never quite decomposing. And while plastic contamination is pervasive, its impact is not well understood. Researchers lack effective ways to detect and better understand the structure of these degrading plastic particles, which is necessary to evaluate their impact and develop meaningful solutions.

Structural biology and a synchrotron fill a gap

Until recently, Melissa's work had explored the interactions between proteins, which are the molecular workhorses behind most cellular processes. It's this kind of work that allows researchers to explore ways to manipulate protein interactions and potentially come up with new ways to develop drugs.

At EMBL Hamburg, Melissa had been studying the characteristics of antibodies – their sizes, shapes, surface properties, and stability – with a special X-ray technology known as small-angle X-ray scattering (SAXS), which enables the analysis of protein samples in solution.

Melissa started brainstorming with colleagues, considering the missing information on understanding micro- and nanoplastics and whether their research could assist this new field. Thanks to the group members' varied scientific disciplines,



EMBL's Melissa Graewert and colleagues are taking a structural biologist's approach to better understand nanoplastic particles. Their research will help uncover how plastic infiltration affects our health and food supply, and may lead to novel solutions.

they quickly determined they could combine SAXS with biophysical techniques to close this gap and shed light on the links between particle structure and biological and ecological impacts. With a grant from EMBL's Environmental Research Initiative, supported by Friends of EMBL and other generous donors, they started a pilot project. This is the same kind of approach that EMBL hopes to expand upon in its new programme, *Molecules to Ecosystems*, which begins in 2022 and involves studying organisms in the context of their environment.

"Because we measure samples in solution, SAXS allows for glimpses of nanoplastics in their native state, embedded in water," Melissa explained. "Some studies suggest nanoplastics could bind toxins or pathogens and enable them to spread throughout our bodies. To estimate the potential threat, we're gathering information on nanoplastics' shape and surface properties. This is important to understand how far they can penetrate into tissues and organs of various organisms, including humans."

The team began by creating a reference dataset and making their own nanoplastics from different materials like coffee lids and milk bottle caps to collect baseline measurements with SAXS. Their data will then be compared with results obtained using other techniques. After these baseline measurements, the scientists have begun to move on to real-world samples from rivers, lakes, and oceans, subjecting them to similar analysis.

A plastic slurry is the result of this work, as shown in the milky sample on the right, which is ready to be measured.

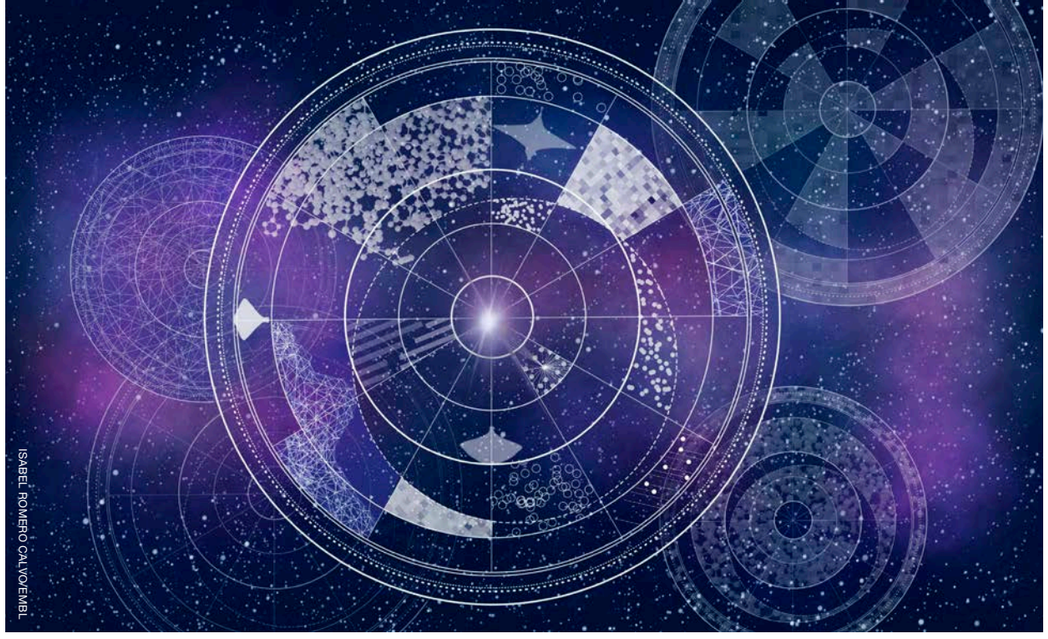
The road to solutions

By characterising nanoplastic structures, EMBL researchers will help uncover what this plastic infiltration means for our health and food supply. It's also about finding solutions.

"There are many promising efforts to produce filters, to deploy 'plastic-consuming' microorganisms, and, of course, to find alternatives to problematic materials," Melissa said. "Luckily, however, reducing plastic waste does not have to wait for these answers. We can all help with that, and we can do that now."

FOR MORE INFORMATION ABOUT THE ENVIRONMENTAL RESEARCH INITIATIVE, CONTACT eri@embl.org OR VISIT: s.embl.org/eri

FOR MORE INFORMATION ABOUT THE FRIENDS OF EMBL, CONTACT friends@embl.de OR VISIT: s.embl.org/friends



(Opposite) An illustrator overlays omics data on a classic star map to convey the navigation towards better understanding how these data fit together.

Charting a multi-omic universe

Machine learning and multidisciplinary collaboration map ‘constellations’ of molecules, which may help customise medical treatments for blood cancer

BY IVY KUPEC

Much like how the earliest astronomers created constellations to make sense of a night sky full of twinkling lights, scientists are mapping the constellations of DNA, proteins, and other molecules in tumours, potentially navigating a way to better customised cancer treatments.

Researchers have long used various kinds of omics technologies to understand the components that biological systems are made of: genomics (sequencing genomes), proteomics (studying the collection of proteins in the tissues of an organism), transcriptomics (studying the RNA), and metabolomics (studying metabolites).

Now, having collected data produced by all these approaches, computational biologists at EMBL have worked closely with biomedical scientists and physicians from the University of Zurich, the University of Heidelberg, the German Cancer Research Centre (DKFZ), and elsewhere to build a machine-learning approach that could help us better understand blood cancer and consequently devise individualised drug treatment plans.

The challenge and opportunity of a ‘model’ disease

Chronic lymphocytic leukaemia is the most common kind of blood cancer in the western world and generally strikes people in their 60s or older. Its impact varies considerably – even at the cellular level. In some people, the disease is quite aggressive; in others, it can be managed by medication, allowing patients to live a long time.

The most effective medication for any given type of cancer is generally not the same for everyone, which has created a puzzle for physicians who may have to guess which drug might work best in each case. Unfortunately, that means subjecting patients, some of whom are already immunocompromised and frail, to treatments with uncertain outcomes that may also have serious side effects.

That said, the high prevalence of this particular leukaemia and the relative ease of obtaining blood samples makes it a suitable testbed for molecular medicine. It is also one of the most studied leukaemias, which means researchers have significant clinical data to build upon.

EMBL Group Leader and Senior Scientist Wolfgang Huber and his collaborators took this opportunity to create a comprehensive multi-omics survey of this disease. Huber compares their approach to using different kinds of telescopes aimed at the same astronomical object – because they operate with different types of light, they provide different types of information about the object, thus giving a more complete picture.

“We had samples from hundreds of patients, allowing us to see the heterogeneity in the molecular landscape,” Huber said. “This allowed us then to map out the constellations of the molecular makeup. The key, however, was to find a ‘North Star’ – a point that looks the same from all different angles we’re looking at it, and enables us to piece the complete picture together.”

Multi-omics constellations lead to novel biomarker ‘North Star’

And, in fact, this astronomers’ approach soon found a common axis line in the otherwise seemingly chaotic molecular universe. By linking data points that trended in the same direction across the multiple omics views, the researchers honed in on a new biomarker that seems to indicate which tumours are more likely to be aggressive.

“We first checked that our algorithm was doing something useful. When we saw that it rediscovered a couple of known things, it gave us confidence that the new effects it found were real,” Huber explained. He noted that the multi-omics data allowed the researchers to see something that was previously hidden in the individual omics datasets.

“When you find something like this in a single dataset, it is often not clear whether it’s worth following up, as it just may be something too convoluted or a fluke in the measurement. But, in our case, because we could see it from different angles, it was more likely to be something of biological consequence,” he added.

A year later, after more detailed experiments by the team of Thorsten Zenz at the University Hospital Zurich, the researchers were sufficiently confident in the meaning of their discovery.

“The next step was boiling down this discovery into a smaller, more practical marker,” Huber said. “Once you know what you are looking for, you can build a specific assay that is rapid and cheap enough to deploy in a clinical setting.”

It is these accomplishments – discovering and then understanding the biological meaning of this biomarker – that were the focus of a recent paper in *Nature Cancer*.

“I think one of the most unique and exciting aspects of this project is that we used a machine-learning method to integrate these omics datasets to identify *new* biology, but in a long-studied and seemingly well-characterised disease,” said Junyan Lu, a machine-learning expert in the Huber Group and the lead author of the paper.

“Currently, much machine learning in biomedical research focuses on mining single omics data, like just genomics or transcriptomics, alone,” he added. “Multi-omics machine learning enabled us to amplify meaningful and clinically related signals among noisy biological data. This is because important biological changes usually affect several molecular layers and are visible in multiple omics datasets.”

Lu performed most of the computational analyses of the omics data, ultimately providing hypotheses for medical collaborators to explore further. “Without the interdisciplinary collaboration with Thorsten Zenz’s group, I would not have had the data from patient samples to work with,” Lu said. “The input from the clinicians and experimental biologists was crucial for interpreting results and refining our hypothesis.”

LEARN MORE DETAILS ABOUT THIS PROJECT:
s.embl.org/multi-omic-universe

New horizons for the EIPP

The EMBL International PhD Programme will evolve its training offers in line with the increasing need for interdisciplinary approaches in life sciences

BY IVY KUPEC

The EMBL International PhD Programme (EIPP) is well known for providing state-of-the-art training to its students. This includes a good balance between theory and practice, close supervision yet creative freedom, a spirit of collaboration, and early independence.

Under the direction of Monika Lachner, Head of Internal Scientific Training and Dean of Graduate Studies, this already well-regarded programme is looking to the future.

"We wanted the additional capacity to push projects that enable innovation in graduate education," Lachner said, highlighting the importance of a newly established program manager position.

Most recently, Fulvio Grigolato joined the programme's two Graduate Officers, Vira Beck and Carolina Garcia Sabate. A physicist by training, Grigolato will contribute to further expanding EIPP's interdisciplinarity and helping it transition with EMBL's next five-year Research Programme.

EMBL has long offered a multidisciplinary approach to science and research. Likewise, EIPP has increasingly encouraged candidates with backgrounds in chemistry, physics, mathematics, molecular medicine, computer sciences, or engineering to apply, so to work closely with biologists answering fundamental questions in life sciences. Currently, approximately 16% of EIPP fellows come from complementary fields.

"Due to their increasing complexity, the scientific questions we face as a society demand increased cooperation among different disciplines," Grigolato said. "A solid interdisciplinary training is the best way to equip future leaders in academia, industry, policymaking, and beyond with the skills required to tackle those questions."


EMBL

The EMBL International PhD Programme is evolving its outreach and training offers, attracting young scientists from a broader pool of backgrounds.

Increasing interdisciplinarity creates new opportunities

Interdisciplinarity is central to EMBL's forthcoming scientific programme, *Molecules to Ecosystems 2022–2026*. The organisation's research will remain firmly rooted in molecular biology, with the goal of gaining better understanding of life in the context of its environment. This requires unveiling not only how living organisms work and function individually, but also how they interact with other organisms and their ecosystems.

EMBL's ambitious approach to life science research creates additional opportunities for complementary disciplines – such as mathematics, engineering, ecology, climatology, and many others – to help investigate living systems and advance understanding of fundamental biological processes. For EIPP, Lachner said, "We have two important challenges: to attract candidates from these backgrounds and then provide the right training."

As such, the programme will increase its visibility at relevant university departments. Furthermore, following the success of EMBL's Lautenschläger Summer School, EIPP will continue developing workshops that inspire undergraduate students to pursue interdisciplinary PhDs in life sciences at EMBL. EIPP will also design and integrate additional customised training modules. Furthermore, the training will reflect the increasingly crucial role that computer and data sciences play in managing and analysing massive amounts of biological data. Information generated by science – molecular biology, in particular – is steadily growing as more advanced experimental techniques provide high-resolution, multidimensional data at unprecedented rates.

The changing science of molecular biology

"Nature doesn't care about the cultural conventions that shape what we consider scientific disciplines," said Anna Erzberger, a physicist and one of EMBL's newest group leaders. "If we want a predictive understanding of the behaviour of proteins, cells, and organisms, and to push the current technological limits of what can be measured, we need expertise from physics, mathematics, computer science, and chemistry."

EIPP fellows note the relevance of interdisciplinary training as well.

"I see EMBL as a great opportunity for collaborations," said Franziska Walterspiel, a chemist and new Deo Group predoctoral fellow. "It will be great to see new partnerships with non-biology departments at universities emerge to strengthen the interdisciplinary aspect of EMBL."

Tim Dullweber, an Erzberger Group predoc, described it like this: "EMBL is a door opener due to its excellent reputation." As a physicist interested in statistical physics and theoretical biophysics, he continued: "The multidisciplinary environment teaches us how to live in between worlds, how to communicate with other physicists as well as hardcore biologists."

EMBL's growing embrace of multidisciplinary work

This same spirit of collaboration and convergence of disciplines is at the heart of many EMBL initiatives — something expected to go beyond EMBL itself to connect with and across member states.

Within the past year, EMBL has signed several memoranda of understanding (MoUs) with a variety of international organisations whose missions complement EMBL's and who offer further enhanced opportunities for collaboration.

Lachner also notes that EMBL's Interdisciplinary Postdoc Programme (EIPOD) continues to be a driving force for collaboration across the organisation. The programme, co-funded by the European Commission under Marie Skłodowska-Curie Actions, supports postdocs who work on self-designed research projects involving two or more EMBL groups. Scientists from other academic institutes, clinics, and industry also participate on EIPOD research projects, thereby fostering collaboration across sectors.

Likewise, recognising its scientific services and core facilities can effectively blend disciplines – especially as EMBL's new Imaging Centre comes online – EMBL initiated a new infrastructure training programme: Career Accelerator for Research Infrastructure Scientists (ARISE). It will attract scientists aspiring to develop and lead infrastructure services. Applications to ARISE are due in late November for training starting in 2022.

"It's a really exciting time," Lachner said. "I love being in the midst of this kind of change that is rich with innovative ideas to help our PhD programme grow and evolve, which in turn, takes EMBL to this next level as a global leader in science."

Analysis and sorting with flow cytometry

EMBL's flow cytometry facilities support a variety of life sciences research, with new leaders planning to enhance their offerings

BY IVY KUPEC

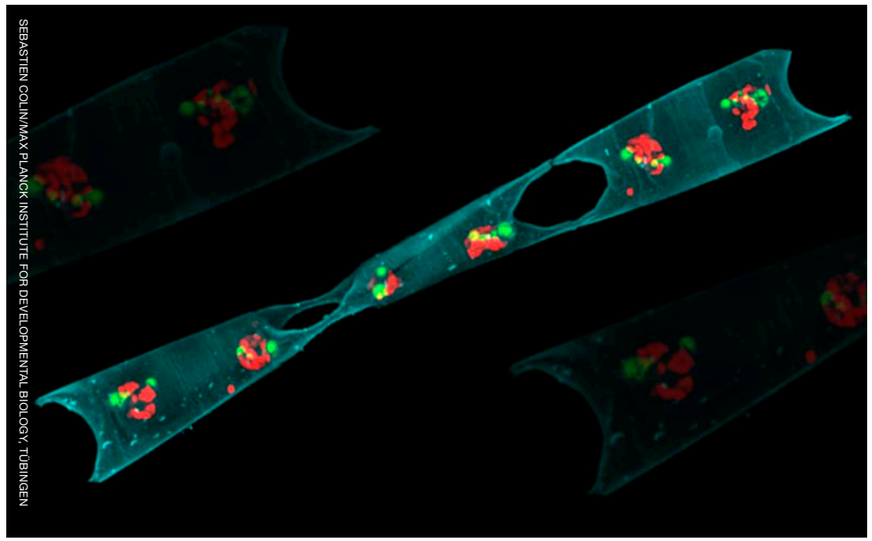
Throughout the planet's oceans reside a modest group of organisms with a fairly monumental task.

These special bacteria, known as diazotrophs, convert atmospheric nitrogen into the biologically usable form that is essential for all organisms to live. As oceans warm and their pH balances change, scientists want to know more about these small organisms that make such a big contribution to our survival as a species. In many instances, the first step of these investigations is done with a flow cytometer.

That is certainly the case for Hugo Berthelot, a postdoc on the Pepperkok Team who is studying the diverse shapes of diazotrophs. He is interested in whether their shape affects how well diazotrophs convert nitrogen or their capacity to withstand climate change in their habitat.

Berthelot is also one of an increasing number of EMBL researchers whose work at the EMBL flow cytometry facilities goes beyond simply analysing and sorting human cells to reflect a broadening One Health perspective.

"We're just at the beginning of understanding the diversity within these cells," Berthelot said. He uses the flow cytometer to sort cells before subjecting them to genomic and other omics analyses – to further understand, for example, where in the cells photosynthesis happens.



Hugo Berthelot, a postdoc on the Pepperkok Team, is studying the diverse shapes of diazotrophs and other cyanobacteria like these *Richelia intracellularis* in symbiosis with *Hemiaulus*. Flow cytometry allows him to sort the various cells for further studies.

The 'fluidity' of a flow cytometer

Cytometers and cell sorters use laser beams to analyse, sort, and separate cells or organisms flowing in a stable stream of fluid.

"Imagine shining a beam of light through a stream of water as droplets pass by," said Diana Ordonez, the head of the Flow Cytometry Core Facility at EMBL Heidelberg.

"The instrument generates droplets containing particles or cells that are excited by the laser beams, measures the emitted light, and then deflects the drop carrying a particle of interest out of the stream and into a collection tube or plate," she explained. "That's what makes it possible to separate out a given particle."

For instance, scientists could separate a population of interest, such as T cells, from a blood sample containing several types of immune cells and use it for downstream analysis.

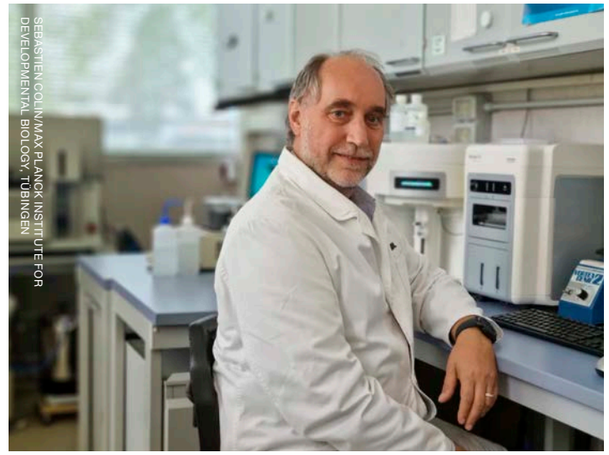
Ordonez and Gerald Pfister, the head of the Flow Cytometry Facility in EMBL Rome's Epigenetics and Neurobiology Unit, agree that if a sample can be suspended in a liquid, a flow cytometer can analyse it.

"The most classic example is when you have blood tested. Cell populations in your blood are identified and quantified using a flow cytometer," Pfister said. "But flow cytometers are used for looking at a variety of things – algae cells, ciliates (protozoans with hairy edges known as cilia), bacteria in water samples, even in food quality control systems to assess bacteria in milk or yeast cells in beer."

Flow cytometry and building bridges

Ordonez, who has worked at EMBL Heidelberg's flow cytometry facility since 2015, took the helm in February.

Pfister came to EMBL Rome's facility in June after more than 20 years in different roles in industry and academia around the world, from Austria and Brazil to Belgium to Qatar. In Qatar, he spearheaded the development of a flow cytometer core lab. In all his roles, he has been mindful of end-user service as well as public outreach.



Gerald Pfister heads up the Flow Cytometry Facility at EMBL Rome.

"My hope is to be actively involved in projects here," Pfister said. "At this point, I have a lot of tips and ideas, so I can really contribute as people plan projects."

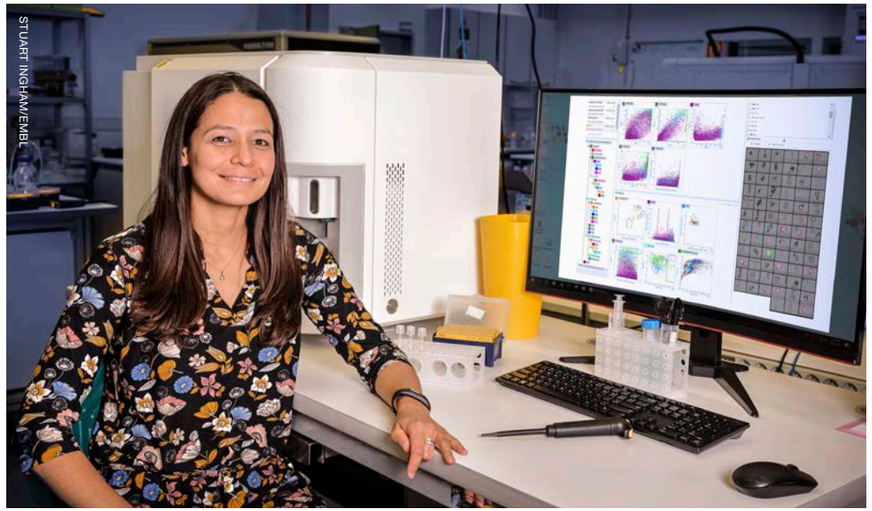
Ordonez also has a long history with flow cytometry. Before coming to EMBL, she used flow cytometry at the Centre d'immunologie de Marseille-Luminy to study a variety of immune cells – T cells, B cells, dendritic cells, natural killer cells, monocytes, and progenitor cells – in mice. Her goal was to establish a reliable model to analyse the role that a specific kind of white blood cell has in the immune response.

She then moved to EMBL, principally because – like Pfister – she enjoys training, advising, and assisting other researchers in flow cytometry. It's this attitude that is a guiding force for both scientists as they share their plans for the future.

Looking ahead

As EMBL embarks on its next five-year research programme, EMBL's flow cytometry facilities are looking at ways to adapt to an increasingly multidisciplinary environment, and one that will begin exploring living systems in their natural context.

"I have a PhD in freshwater biology, so I am looking forward to this challenge," Pfister said. "This opens up opportunities to collaborate with different research teams, not just on bio-medicine or related to medical conditions." >>


STUART INGHAM/EMBL

Diana Ordonez has worked at EMBL Heidelberg's flow cytometry facility since 2015 but began her leadership role there in February.

The two EMBL facilities have flow cytometers and cell sorters with slightly different capabilities. Ordonez and Pfister perform most of the flow cytometry work themselves, advising individual researchers on their given projects, developing optimal flow applications, and troubleshooting their experimental setup.

Training helps to expand the pool of hands-on users and allows others to learn how flow cytometry can be used in their own varied research projects. From data analysis workshops to practical courses in flow cytometry and cell sorting presented in cooperation with the German Cancer Research Center (DFKZ), EMBL's flow cytometry training is offered to the international science community and is always in high demand. It's why Ordonez is looking for creative ways to expand it.

Teamwork makes the flow cytometry work...better

Collaborations with other EMBL core facilities have been part of that creative management approach in the past, so they will likely play a role in the future. Ordonez is quick to note the convenient location of the Genomics Core Facility (GeneCore), which is right across the hall doing gene sequencing – a logical follow-up to flow cytometry for epigenetics and genetics researchers.

Over the years, the challenging scientific needs of EMBL's flow cytometry customers have made these facilities a good testbed for piloting new technology. In fact, Berthelot's research benefits from exactly this kind of 'beta testing' of a new instrument. He is using detectors to create rapid-fire images and use them in addition to conventional flow cytometry parameters to analyse and separate particles of interest. The images help Berthelot to more easily identify and understand the complexity of organisms present in his samples.

Ordonez and Pfister agree that the two facilities will increasingly find ways to collaborate to enhance their offerings and position themselves better at EMBL.

"I started out studying microbiology because I had this dream to do oil-spill remediation," Ordonez recounted. "Though I ended up studying immunology, we all need to do something for this planet. It just has to be done. All these resources and bright minds here at EMBL can make a difference."

THE FLOW CYTOMETRY CORE FACLITY AT EMBL HEIDELBERG:
s.embl.org/flow-cytometry-heidelberg

THE FLOW CYTOMETRY FACILTY AT EMBL ROME:
s.embl.org/fcf

When 'good' cells go 'bad'

Identifying the molecular differences between healthy and unhealthy cells could be used to switch 'bad' cells to 'good'

BY IVY KUPEC

Theodore Alexandrov is excited. As he begins to speak, there's a kind of fervour about him. He's created a tool that he hopes will change the way we think about medicine.

To cure disease, doctors aim to restore unhealthy cells back to health, re-establishing balance in the organism. But this requires some way of measuring when cells switch between these states – going from 'good' to 'bad' or back again.

Alexandrov has spent the past seven years as a team leader at EMBL Heidelberg, leading the development of a technology that can identify the cellular changes between healthy and unhealthy cells. The result is SpaceM, an open-source method for detecting metabolites – all the small molecules that provide cells with the energy and raw materials they need to function. >>


ISABEL ROMERO CALVO/EMBL

Follow the QR code to a short video explainer of Alexandrov's research.

Lift-off with SpaceM

While not a rocket heading to outer space, SpaceM could help researchers explore new frontiers. The method can identify pivotal changes in a cell’s metabolites, creating a comprehensive molecular profile that pinpoints a cell’s healthfulness.

This information has the potential to transform drug discovery and precision medicine. “To aid drug discovery, we can apply a drug directly to the cells at the point when the cells ‘go bad’ to determine if cells react to the drug treatment,” Alexandrov said. “But also, we create an opportunity for drug development that goes beyond what is done now – to fine-tune drugs so they restore cells’ native, healthy states.”

Pioneered by PhD student Luca Rappez, SpaceM is the result of a joint effort by scientists with expertise in deep learning, cell biology, metabolomics, bioinformatics, and mass spectrometry. The method combines light microscopy and imaging mass spectrometry (a technique that allows scientists to identify and measure the amounts of a cell’s molecular building blocks, including metabolites and lipids).

Measuring the amounts of various molecules indicates a cell’s condition and whether it is healthy – similar to how biomarkers identify low-density lipoprotein (LDL) cholesterol for cardiovascular disease risk, or high-serum creatinine is a marker of kidney impairment.

Alexandrov’s team confirmed the role of these metabolic biomarkers in experiments: feeding excess lipids to a cell under stress, for example, changed its metabolic profile drastically. Interestingly, the biomarkers in these cells strongly resembled those of patients with fatty liver disease. With SpaceM, the scientists could capture and track, step-by-step, the changing metabolic states of single cells.

Their open-source method, which was published in July in *Nature Methods*, can be applied to many different cell types. The Alexandrov team is looking specifically at cells involved in metabolic diseases and prostate cancer.

Restoring metabolic health

“When we talk about metabolic disease, we start with NAFLD and NASH,” Alexandrov said, referring to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). These conditions are caused by fat build-up in the liver and can lead to fibrosis and liver cancer. Common in overweight people or those with diabetes, NASH does not worsen in all patients. However, neither NAFLD nor NASH have approved pharmacological treatments.

In collaboration with Professor Mathias Heikenwalder from the Germany Cancer Research Centre (DKFZ), Alexandrov’s team used SpaceM to examine the metabolic processes in individual liver cells, looking at both NASH cells and neighbouring healthy cells to decipher when cells go ‘bad’.

“The NASH cells actually look healthy, and their phenotype may not have changed from the outside, but on the inside, their metabolic reactions have already been reprogrammed,” Alexandrov explained. “Ultimately, their metabolism is working differently – accumulating more lipids – and this is reflected in the markers.”

The information generated by SpaceM could ultimately help to create therapeutics that fully restore the cells’ correct metabolic programming, and the method has other advantages.

“SpaceM can generate data on a scale hardly possible using other approaches, scanning millions of cells overnight,” Alexandrov said. “It can tell when ‘good’ cells turn ‘bad’ better than microscopy, yet it is cheaper and faster than many alternatives.”

From organoids to medical practice?

Recently, the team started collaborating with researchers at the University of Bern and IBM Research in Zurich to apply SpaceM to personalised therapy for prostate cancer.

Prostate cancer is the second most common cancer in men, and few therapies exist. Dr Marianna Kruithof-de Julio, a research group leader from

Theodore Alexandrov and his team aim to identify specifically when good cells go bad to understand disease better and pinpoint optimal intervention timing.

the university, has established a global network of physicians treating prostate cancer patients. The physicians send cells from their patients to Kruithof-de Julio, who grows them into prostate cancer organoids – 3D clusters of cells resembling prostate tumours. She can then treat the organoids with candidate drugs to test their efficacy.

Previously, the researchers would count how many cells the drugs killed. But that’s not enough, because even a few surviving cells can initiate cancer relapse.

“It would be more beneficial to return all cells to a healthy state,” Alexandrov said, “or at least to know what is going on inside the surviving cells.” He is working with Kruithof-de Julio to determine whether single-cell metabolomics, and SpaceM, can provide this information. If it can, then physicians might be able to use the method to select therapies that offer the least chance of relapse.

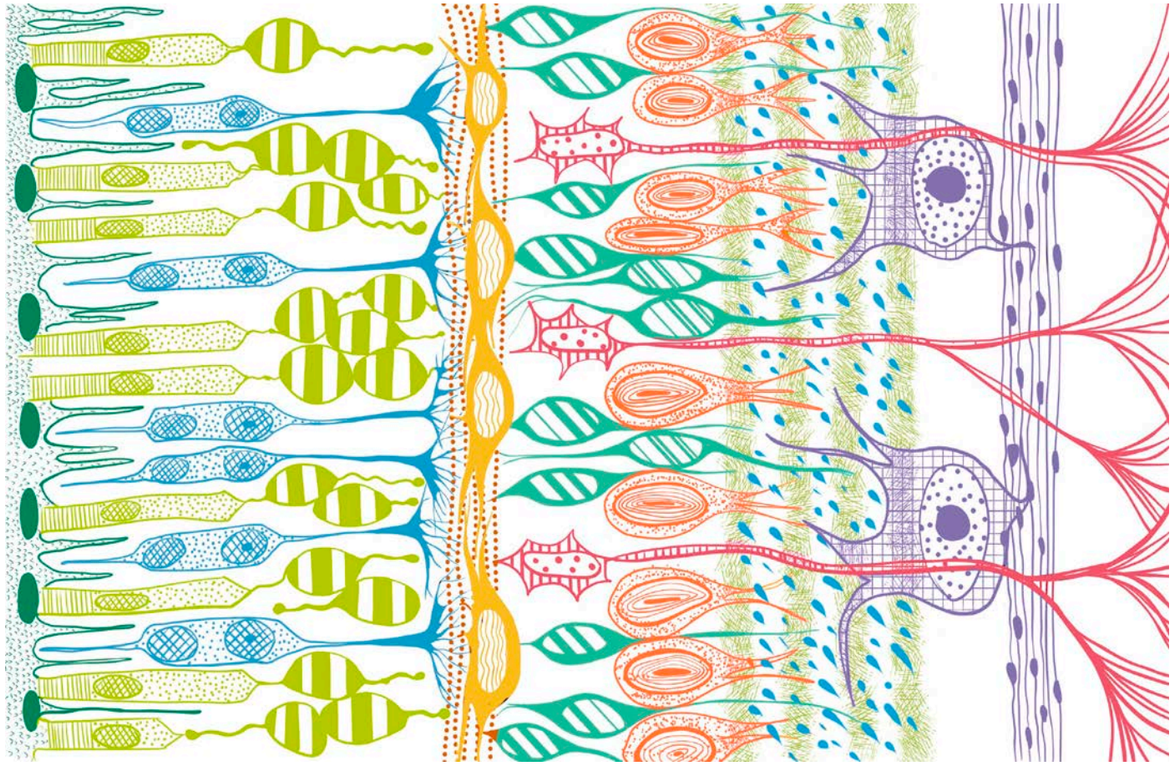
In the future, this approach could also lead to novel therapies that instead of just killing tumour cells would restore them to a metabolic state most similar to that of healthy cells. Alexandrov believes this could potentially add 10–15 years to patients’ lives.

“In this new field, we often walk in darkness where every step requires lots of effort and caution. This is very high-risk, but high-reward,” Alexandrov said. “But if we can succeed at reprogramming cell metabolism to transform ‘bad’ cells to ‘good’, we may change current medicine.”

LEARN MORE ABOUT SPACEM:
s.embl.org/spacem

Vision unveiled: new roles for the retina in visual processing

EMBL scientists have found evidence of an unexpected role for retinal cells in pre-processing visual information; their results provide potential opportunity for future prosthetic visual aids



ISABEL ROMERO CALVO/EMBL

Artistic representation of the complex cell circuit forming the retina. From left: green/blue, photoreceptors; yellow, horizontal cells; dark green, bipolar cells; orange, amacrine cells; purple, retinal ganglion cells.

BY ROSSANA DE LORENZI

Scientists have long known that vision is made possible because our brains decode electrical signals that are sent by the retina. However, recent evidence indicates that retinas may do even more. They too may be deciphering what we actually see.

"Our brain is a predictive machine... It generates a mental model of the outside world based on past evidence and predicts future sensory inputs."

Located at the back of the eye, the retina is a neuronal tissue that receives visual input to the eye and converts it to electrical signals that travel to the brain. Apart from mapping the outside world, the retina extracts visual features, such as colour, contrast, and motion.

The retinal layers contain diverse and specialised sets of cellular components. When light hits the retina, it stimulates photoreceptors, creating an electric signal that is conveyed through other neurons – horizontal, bipolar, and amacrine cells – to the retinal ganglion cells (RGCs).

The RGCs are located on the inner surface of the retina, where they project visual information to the brain via their axons, which make up the optic nerve. These neurons are at the core of the scientists' recent findings.

RGCs have conventionally been considered as a relay, simply integrating incoming visual signals from the eye and conveying them to the brain. However, recent anatomical studies suggest that RGCs may form a more complex network with other retinal neurons through high-speed communication channels.

Scientists in the Asari Group at EMBL Rome found evidence that RGCs can send feedback signals to other retinal cells, and contribute to local computation of visual stimuli by modulating the output signals from the retina. Their results on such a novel gain control mechanism in the retina have been published in the journal *PLOS ONE*.

Building on the team's expertise in computational methods, the scientists developed a biologically inspired mathematical model of the retinal network and derived predictions on how RGCs of the same type modulate each other's activity. They then conducted experiments to confirm those predictions in mouse and salamander retinas.

"Our brain is a predictive machine," said Hiroki Asari. "It generates a mental model of the outside world based on past evidence and predicts future sensory inputs. When the prediction differs from actual sensory inputs, the brain uses the discrepancies (or 'surprises') to update the mental model and adjust our behaviour accordingly. While the brain cortex is commonly assumed to perform such predictive processing, recent evidence suggests that the retina might compute those visual surprises by some unknown mechanisms. We think that the feedback signalling we found at the level of retinal output may play a key role there."

Understanding exactly how this feedback pathway helps retinal function creates a way for researchers to potentially develop future prosthetic devices that could faithfully mimic the retina's visual processing.

The study also shows the benefit of combining experimental and theoretical approaches in neurobiological studies. "Conventionally, scientists run experiments first and then build a model to explain the data," Asari said. "In contrast, we started with a computational model of the retina and derived predictions on the retinal physiology. Then we tested the prediction by performing electrophysiological experiments. This type of theory-driven approach can be applied to other brain areas to better understand their function and is therefore a promising new direction of research."

LEARN MORE DETAILS ABOUT THIS STUDY:
s.embl.org/vision-unveiled

Awards & honours

Jacob Bobonis, a postdoc in the Typas Group, has received the 2021 Nat Sternberg Thesis Prize for his PhD work at EMBL on bacterial retrons, operons producing short satellite DNAs found in many bacterial species. The prize, in tribute to the character and accomplishments of Nat Sternberg, is awarded to a young scientist each year who possesses outstanding qualities that represent Nat Sternberg's skill, insight, rigour, and dedication to science.

Laura Carroll, a postdoc in the Zeller Team, has received the Institut Merieux Young Investigator Award in Antimicrobial Resistance. This award, made by the International Association for Food Protection, recognises outstanding ability and professional promise as a researcher in food microbiology/ food safety.

Charalampos (Babis) Galouzis, a postdoc in the Furlong Group, has received the 2021 best thesis award (Les Grandes Avancées Françaises en Biologie) from the French Academy of Science. This award recognises young scientists who have made some of the most significant scientific discoveries in biology in the year.

Tobias Gerber, a postdoc in the Arendt Group, has been awarded the Otto Hahn Medal by the Max Planck Society. The award recognises young researchers' outstanding scientific achievements, in connection with their doctorate.

Julia Mahamid, Group Leader, has received the German Society for Electron Microscopy's Ernst Ruska Prize 2021, shared with David A. Muller from Cornell University, for advancing the boundaries of cellular electron tomography.

John Marioni, Head of Research at EMBL-EBI, **Alex Bateman**, EMBL-EBI Head of Protein Sequence Resources, and **Takashi Hiiragi**, Group Leader, have been elected to EMBO Membership. It is a lifelong honour that allows elected scientists to serve on EMBO's council and committees, evaluate applications for EMBO funding, and act as mentors to young scientists.

Michael Zimmermann, Group Leader, has been awarded a 2021 FEBS Anniversary Prize of the Gesellschaft für Biochemie und Molekularbiologie for his contributions to better understanding microbial communities in the gut and how they influence our health. The prize, made by the Federation of European Biochemical Societies (FEBS), recognises two researchers each year who are considered part of the upcoming generation of senior scientists for their outstanding achievements in biochemistry, molecular biology, or a related science.

Maria Zimmermann-Kogadeeva, incoming Group Leader, has won the Bayer Foundation Early Excellence in Science Award in the category of Data Science. The foundation presents this international award annually to outstanding young scientists and physicians in the early stages of their academic and clinical research careers.

Alumni

A network that builds bridges


EMBL

We have recently revamped our online presence, and we encourage you to visit the new EMBL alumni website, where you can connect with the community, update your details, see upcoming events, discover valuable alumni resources, and learn how you can make a difference to EMBL and the wider life sciences community. Visit **www.embl.org/alumni**.

Earlier this year, we were delighted to announce Ilaria Piazza (p.42) and Ken Holmes as the recipients of the 2021 John Kendrew and Lennart Philipson awards, respectively. Videos of the talks by Gerd Rosenbaum for Ken Holmes and by Ilaria are available at: s.embl.org/aac2021.

Elsewhere in this issue of *EMBLetc.*, we're proud to showcase the work of Lara Urban (p. 44) and Peter Uetz (p. 46), two alumni whose research bridges the gap between human and environmental health. We're also excited to announce a new lecture series commemorating the legacy of EMBL's third Director General, Fotis Kafatos (p. 41).

Thank you again for being a much-valued member of the EMBL alumni community in 2021. We look forward to growing our special community and seeing and hearing from even more of you in 2022!

Mehrnoosh Rayner
Head of Alumni Relations

We'd like to sincerely thank all alumni who have contributed to EMBL and our community in 2021, from Alumni Association board members and volunteer mentors who have given their time and expertise, to those who have added so much to our events as hosts, contributors, and participants – not to mention the alumni who are supporting EMBL philanthropically by becoming members of the Friends of EMBL programme.

In memory...

…of colleagues and good friends we have lost in the past year. Our thoughts are with them and their loved ones.

Swati Tyagi
d. 23 June 2021, aged 34
Was: Postdoc, Salk Institute for Biological Sciences, San Diego
EMBL: Predoc, Structural and Computational Biology Unit, 2010–2015

John L Telford
d. 27 December 2020, aged 70
Was: Retired
EMBL: Research Technician, Developmental Biology Unit, 1979–1984

Kathryn Anderson
d. 30 November 2020, aged 68
Was: Head of Anderson Lab, Memorial Sloan Kettering Cancer Center, New York
EMBL: Member of the EMBL Scientific Advisory Committee, 2015–2017

Katja Brückner
d. 16 March 2021, aged 54
Was: Professor, University of California, San Francisco
EMBL: Predoc, Developmental Biology Unit, 1994–2000

Jean-Francois Beerblock
d. 6 April 2021, aged 91
Was: Retired
EMBL: Administrative Director, EMBL Heidelberg, 1984–1992

Kevin Leonard
d. 8 May 2021, aged 78
Was: Retired
EMBL: Group Leader, Structural and Computational Biology Unit, 1975–2003

John Tooze
d. 19 May 2021, aged 83
Was: Retired
EMBO: EMBO Executive Secretary, 1974–1994

Jules Hendrix
d. 30 January 2021, aged 80
Was: Retired
EMBL: Group Leader, EMBL Hamburg, 1975–1992

Newly-launched Kafatos Lectures to bring ground-breaking science to the public

New lecture series to bring groundbreaking life sciences to the public

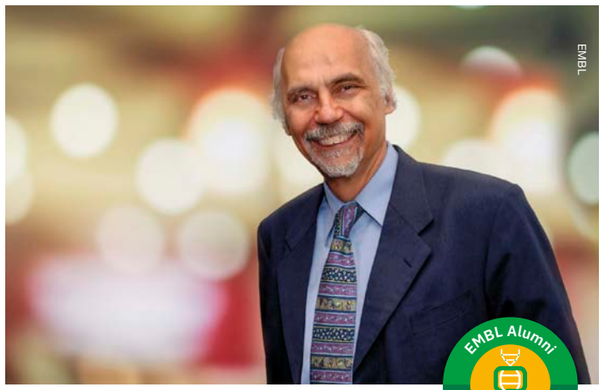
BY TOM FURNIVAL-ADAMS

A prestigious new lecture series commemorating the legacy of former EMBL Director General Fotis Kafatos will help bring groundbreaking life sciences research to people around the world.

The Kafatos Lectures will provide an exciting new global platform for outstanding scientists to share their work with the public through a live, in-person event that is also broadcast online. The annual lecture will be presented by a past or current European Research Council (ERC) grantee.

Speakers will be selected for excellence in public speaking and timeliness of their subject, including its societal impacts. The announcement of the selected speaker will be made at the end of each year. The selection committee includes leading scientists, such as former EMBL Director General Iain Mattaj and former EMBL-EBI Director Dame Janet Thornton.

The inaugural 2022 Kafatos Lecture will mark five years since the death of Kafatos, who was the ERC's founder and first president. Although the lectures will usually be held in the home city of that year's speaker, the 2022 lecture will take place in Kafatos' birth town of Heraklion, Greece. The lecture series is coordinated by the EMBL Alumni Association, which was founded by Kafatos, who was a fervent supporter of outreach and nurturing young scientists.



This new lecture series is named after EMBL's third director general, Fotis Kafatos.

"This award to ERC grantees is the best possible recognition of Fotis Kafatos's extraordinary vision and contributions to European science," said Roberto Di Lauro, an EMBL alumnus, former SAC member and a member of the Kafatos Lecture Selection Committee. "He was the scientist who, more than anybody else, was instrumental in promoting and building the ERC."

Supporting the lecture

EMBL thanks The Bank of Greece, Crete University Press, FORTH, Heraklion Municipality, IMBB, Mathesis and several individuals for their support of the lecture. Thanks to their generosity, €30,000 has already been pledged. To establish the lecture series indefinitely, we encourage other donors to step forward with support to help cover the annual cost of €10,000. To find out more, please contact Mehrnoosh Rayner, Head of Alumni Relations, at alumni@embl.org.

MORE INFORMATION ABOUT THE KAFATOS LECTURE CAN BE FOUND HERE:
s.embl.org/kafatos-lecture

DAVID AUSSERHOFER

Interview with the 2021 John Kendrew Award recipient

EMBL alumna Ilaria Piazza discusses her work, the value of basic research, and why EMBL is unique

BY TOM FURNIVAL-ADAMS

(Above) Ilaria Piazza was awarded EMBL's 2021 John Kendrew Award.

As an EMBL predoc from 2009 to 2014, Piazza explored the structural biology of chromatin proteins with Christian Häring and Martin Beck. She went on to work as a postdoc at ETH Zurich and is now a Group Leader at the Max Delbrück Center for Molecular Medicine. In 2021, EMBL's John Kendrew Award recognised Piazza's groundbreaking work in developing limited proteolysis-coupled mass spectrometry (LiP-SMap) to globally analyse protein–metabolite interactions in their native environment, a technology that is widely used in both basic and translational research. We spoke to her to find out more:

Congratulations on winning the 2021 John Kendrew Award. How do you feel?
I am incredibly honoured. I'm very close to my former EMBL colleagues, and I enjoyed my time there. I found I appreciated EMBL even more when I left, because I realised just how unique it is.

Tell us about your PhD work exploring the regulation of chromatin structure, which is linked to many research areas.
My project with Christian Häring involved figuring out molecular details of a protein complex called condensin. It regulates how much the chromatin – that is, the material where the DNA is stored – is compacted or released during the cell cycle. When cells divide, they must be compressed to reduce volume so that they can be placed in a specific cellular compartment, allowing the cells to divide. The molecular steps by which this happens were unclear. We considered studying the structure of this protein pattern, but most of the structure was not known. At the time, the most common technique for studying such proteins was X-ray crystallography, but it was limited for working with big proteins. After initial failures, I needed a different approach. Other EMBL groups were starting to work on our technique, or developing another technique, cryo-electron microscopy (cryo-EM). So, I reached out to people doing this and others working with mass spectrometry. That helped us figure out which protein subunit was close to another subunit.

Tell us about the highly innovative method called LiP-MS that you developed as a postdoc.
In a nutshell, this approach allows you to take the weight of a protein or portion of a protein, which in turn enables you to figure out the identity of proteins present in a cell – and which ones are present at a higher or lower level. Meanwhile, I heard about a laboratory where these two techniques were used: applying mass spectrometry to study structures, and more specifically, using it to establish whether a protein had a certain structure or not. This is more like getting a fingerprint rather than a high-resolution representation of a protein structure. But it is useful in many different contexts. You can get a full profile of all the present protein structures at the same time. The concept was new at the time and allowed me to follow my main interest while working on a very interesting technology.

How can this method be applied practically?
One obvious application was to use those fingerprints. For example, if you want to make a better drug, you can work on the protein model and figure out how it binds to a given protein and alter the structure. In most cases, we do not know which specific protein is bound by a drug; we just know the drug is effective in treating a certain disease or symptoms. With LiP-MS, you can identify the molecular target within a cell for the drug to bind. We worked on this concept to combine structure profiles of proteins using mass spectrometry to develop a method to detect drug-binding events, for example. Explaining this with drug development clarifies the utility of my work, but cells in natural conditions interact with many other molecules, such as the sugar in sodas or the foods that you consume. Now, my research studies how metabolism regulates chromatin architecture and its impact on gene expression using proteomics, genomics, and metabolomics.

What is the value of fundamental research?
Everything that makes the world in which we live, from cars to vaccines, originally comes from fundamental research that most people would not have found any practical use for at the time. It's a long-term investment and should go hand-in-hand with education. The more we communicate and educate people, the more we show how fundamental research is not only interesting but also important in the long term for society.

What are your thoughts on combining your academic work with translational research projects?
I worked with a start-up company in Zurich called Biognosys, directly transferring my technology from lab to industry. This enabled us to achieve a bigger goal and find practical applications, which are sometimes missing from academic lab work.

What did you learn from your time at EMBL?
Projects assigned to EMBL PhD students are ambitious, so you quickly learn to think independently. Even now, I often repeat to my students: you're probably cleverer than me, and you're definitely faster, because you're younger – I'm past my prime!

Watch the **2021 Alumni Awards ceremony** to see Gerd Rosenbaum give a talk on behalf of the 2021 Lennart Philipson Award recipient, Ken Holmes. (Here at EMBL, we extend our very heartfelt condolences to Ken's family and friends on his passing in early November.)

s.embl.org/aac2021

EMBL alum takes DNA sequencing to the field

A mobile molecular tool is helping us better assess biodiversity impacts in endangered New Zealand species, and around the world

BY LARA URBAN

To preserve planetary health, we first have to understand the well-being of our earth's natural systems. The unprecedented loss of biodiversity has potentially serious consequences for human health, but because so much of nature is uncatalogued, we struggle to quantify this decline.

In my research, I develop mobile DNA approaches to monitor our environments around the world, even in remote and low-resource settings. This research allows me to study freshwater quality, assess the health of critically endangered species such as the iconic New Zealand birds takahē and kākāpō, share vital data with conservationists to directly improve conservation management, monitor biodiversity, and use this knowledge to develop biodiversity credits for threatened ecosystems – all in a rapid, cost-efficient, and localised manner.


1

Endemic to New Zealand, the takahē (*Porphyrio hochstetteri*) (picture 1) is the largest rail in the world and completely flightless. The species was considered extinct due to habitat destruction and introduced predators until a small remnant population was discovered in the Murchison Mountains in 1948. Only ~400 takahē remain, and their genetic diversity is most likely limited.

That's where my research comes in. As an independent research fellow in New Zealand (picture 2), I work with conservationists to promote recovery of this species. We are trying to understand genomic diversity to find its molecular link to fitness traits that boost resilience. This work hinges on the statistical genomics PhD that I completed at EMBL.

As a council member of the European Reference Genome Atlas, I know reference genomes significantly help conservation genomics projects. That's why my team and I created a high-quality reference genome of *P. hochstetteri* based on blood samples from the takahē chick Kohika and her parents.

To perform genomic analyses directly in remote and difficult-to-access habitats, we developed a completely portable DNA sequencing approach that allows for DNA extraction, sequencing, and data analysis *in situ*. I can perform selective DNA sequencing in the field with the pocket-sized nanopore sequencing device MinION, which connects to my laptop (picture 3).


2


3


4


5

PHOTO CREDITS: LARA URBAN AND THE KĀKĀPO AND TAKAHĒ RECOVERY TEAMS, DEPARTMENT OF CONSERVATION, NEW ZEALAND

I used this selective DNA sequencing approach to sequence kākāpō-specific DNA from soil samples, which helped me identify the presence of kākāpō individuals. The kākāpō is a critically endangered flightless parrot native to New Zealand; only ~200 kākāpō survive today (picture 4). My approach will help me estimate important features such as genomic diversity – just from environmental samples! In other research, I study the genomic architecture of disease susceptibility, hatching success, and other phenotypic traits in this endearing bird.

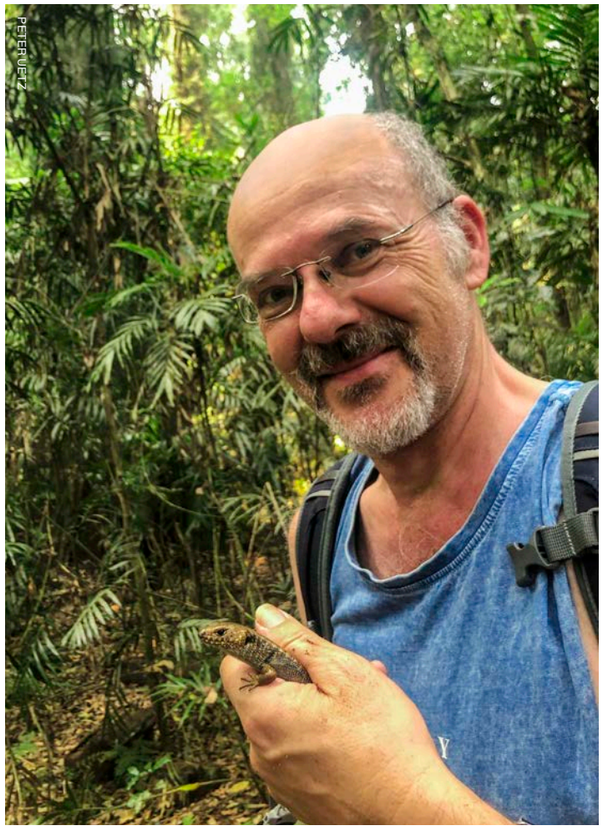
Next year, I will take portable selective DNA sequencing to Whenua Hou, a remote island off the southern coast of New Zealand's south island where most surviving kākāpō live, to better understand a deadly fungal disease that killed many kākāpō chicks (picture 5) during the last breeding season. I have also started establishing this approach for conservation and public health efforts in Rwanda.

"Because so much of nature is uncatalogued, we struggle to quantify [its] decline."

Mobile genomic approaches can help us better understand current and future planetary health. The rapid and cost-efficient *in situ* DNA analysis enables increased access to genomic research for local communities and public health organisations around the world, ultimately democratising its opportunities and benefits.

Addressing the biodiversity crisis with 12,000 reptiles – or one database

An EMBL alumnus reflects on the database he started as a graduate student 25 years ago at EMBL



On a trip to Australia, the author caught skinks, like the Blue-speckled Forest-skink (*Silvascincus murrayi*) shown here.

BY PETER UETZ

When I look back at 1996 and the birth of the EMBL Reptile Database, it feels like the culmination of a few lucky events: the opportunity afforded by the new worldwide web, created in the early '90s; EMBL's relatively new (and enthusiastic) database team; and the lack of biological databases in general.

But that was not enough. As a predoc in Rolf Zeller's group (which studied limb development), I initially thought of starting a database on gene expression patterns, but that was met with little enthusiasm – for good reasons: there was simply not a whole lot of data for a robust database.

After considering a database of protein–protein interactions, I ultimately resorted to an old childhood interest that was indirectly related to my thesis work: reptile taxonomy (the connection to gene expression being the genes involved in limb loss in the evolution of snakes and limbless lizards).

I was not aware of another taxonomic database, so this seemed like a project without much competition. Thure Etzold, on the database team, was very supportive and simply said, "Just give me a floppy disk with the data, and we'll put it online," when I asked him what I had to do. (Yes, people still used floppy disks back then!) A few months later, the EMBL Reptile Database was live – online and even linked to the DNA sequence database, and it was probably one of the first taxonomic databases on the web.

Why a reptile database is useful

As biologists, we want to know what organisms are out there, how things are related, and how they fit into the big picture of life on earth – ranging from molecules to ecosystems. So, we organise that data.

Luckily, while I was establishing the Reptile Database, Frank Bisby in the UK started the Catalogue of Life, a centralised database of *all* species on earth. He soon invited me to take care of the reptile portion of the Catalogue of Life, which was then one of several dozen global species databases.

Today, more than 150 global species databases have accumulated 2 million species (including 12,000 reptiles), and they are increasingly interconnected with many other databases such as natural history collections, image repositories, media databases, and, of course, DNA and other molecular inventories. Millions of people have joined these efforts in citizen science projects such as iNaturalist, which is a user-friendly app for cell phones. The Reptile Database provides the taxonomic backbone for many of these resources, ranging from the US National Center for Biotechnology Information (which maintains GenBank, among other databases) to iNaturalist.

Why you should care

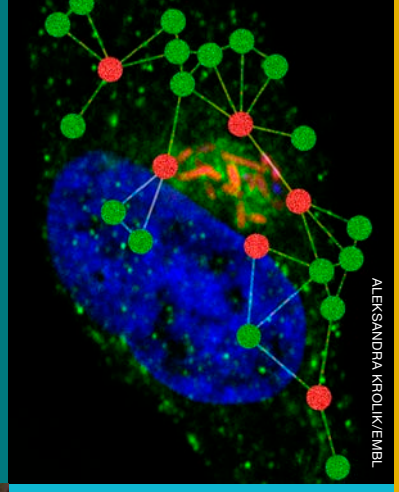
The biodiversity crisis is real. Taxonomic databases record tens of thousands of *new* (!) species every year, and much of this inflation is because we increasingly understand *genetic* diversity. At the same time, the human population increases by 80 million people per year – equal to the population of Germany. The bottom line is human encroachment on nature continues unabated.

We need to document and understand biodiversity as well as conserve it. It's not enough to do the science – we have to fight habitat destruction, deforestation, overpopulation, overconsumption, and bad policies, all of which threaten biodiversity on earth.

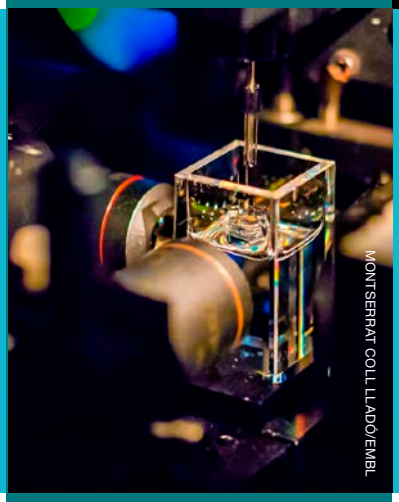
As a nod to the 12,000 reptiles described in databases, the author shares a picture of his own chameleons (*Calumma uetzi*) – a male on the left and a female on the right.

Events

February
22–25
EMBL Heidelberg
EMBO Practical Course:
Integrative Analysis of
Multi-Omics Data


ALEKSANDRA KROLIK/EMBL

March
13–16
EMBL Heidelberg
EMBL Conference:
From 3D Light to 3D Electron
Microscopy

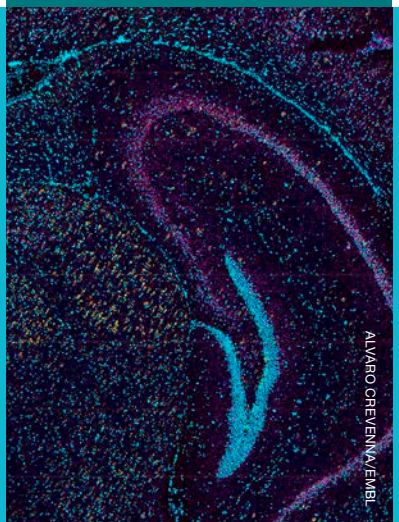

MONTSERRAT COLL LLADÓ/EMBL

April
6–9
EMBL Heidelberg and Virtual
EMBO | EMBL Symposium:
Microbial Infections and Human
Cancer

May
9–11
EMBL Barcelona and Virtual
EMBO Workshop:
Building Networks:
Engineering in Vascular
Biology

May
16–20
Virtual
EMBL Course:
Microscopy Data Analysis:
Machine Learning and the
BioImage Archive

May
15–18
EMBL Heidelberg and Virtual
EMBO | EMBL Symposium:
Mechanobiology in
Development and Disease


ÁLVARO CREVENNA/EMBL

June
20–24
EMBL-EBI
EMBL Course:
Cancer Genomics

Upcoming meetings
Alumni

Monthly
**Coffee with EMBL,
Virtual**

s.embl.org/cwe

18 March
**EMBL Retirees' Afternoon,
Virtual**

26-27 May
**EMBL in Italy,
GSK Vaccines Siena**

30 May
**EMBL in the UK,
University of Dundee**

8 July
**EMBL World Alumni Day,
EMBL Heidelberg and Virtual**

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