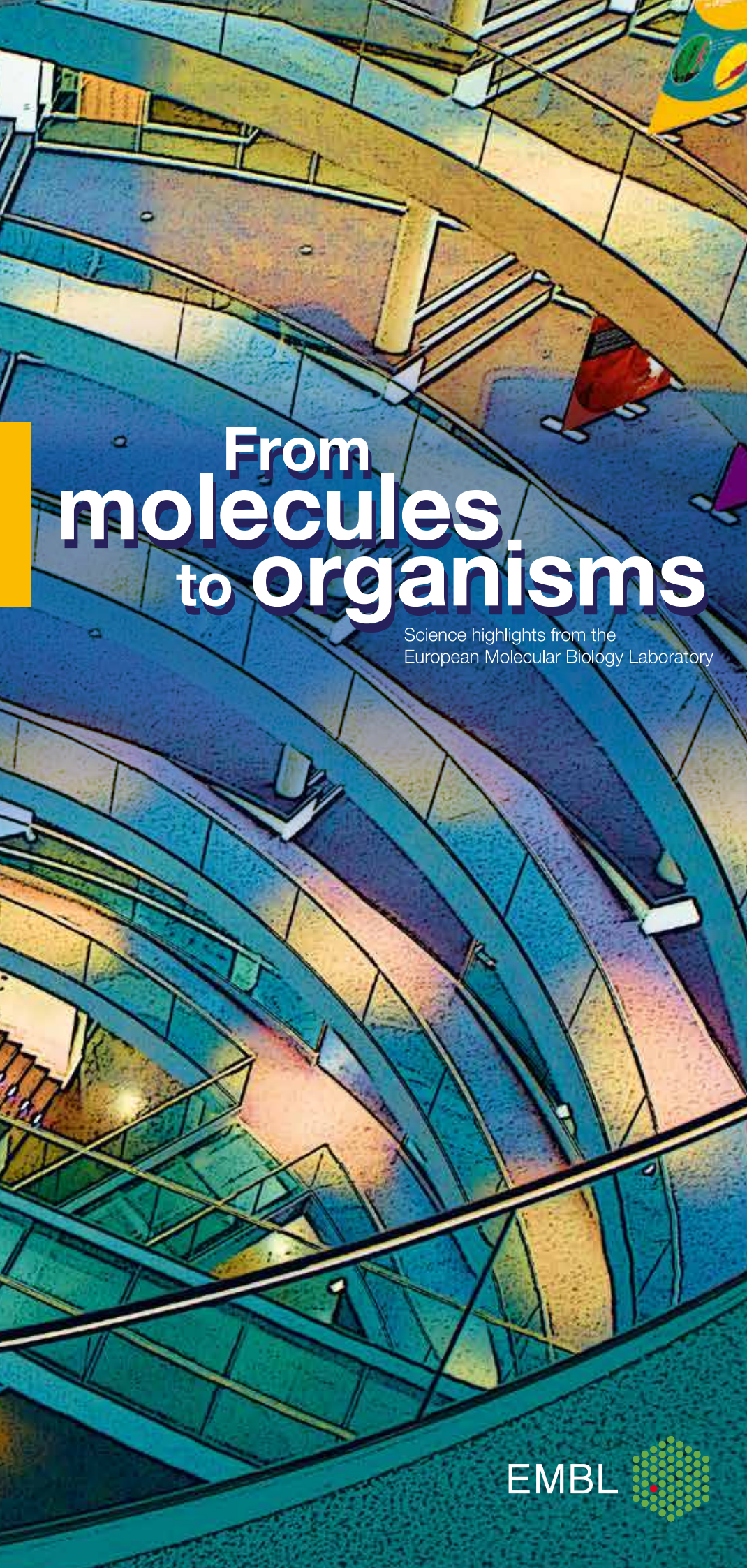


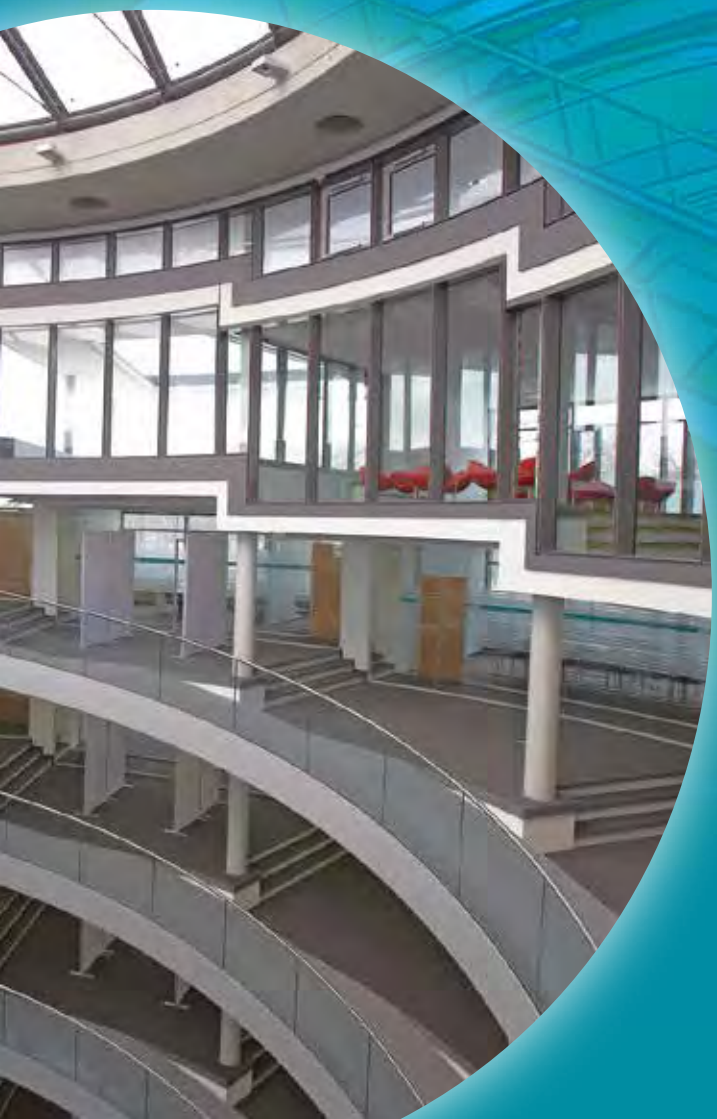
From molecules to organisms

Science highlights from the
European Molecular Biology Laboratory

EMBL

From molecules to organisms

is a permanent exhibition at the EMBL Advanced Training Centre in Heidelberg, Germany. It presents snapshots of EMBL science, inviting you to explore the wide spectrum of life science research carried out in Europe's leading laboratory for molecular biology.



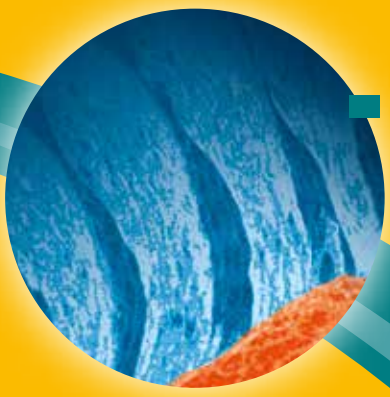
The EMBL Office of Information and Public Affairs would like to thank all those who helped to produce this exhibition. Special thanks go to the EMBL Photolab and the scientists who provided scientific images and artwork.

We thank the following people for granting us permission to use their images: Andrew Carnie, Janice Haney Carr, Stephen Curry, Tiago Ferreira, James Gathany, Carsten Janke, Douglas Jordan, Darryl Leja and André-Pierre Olivier.

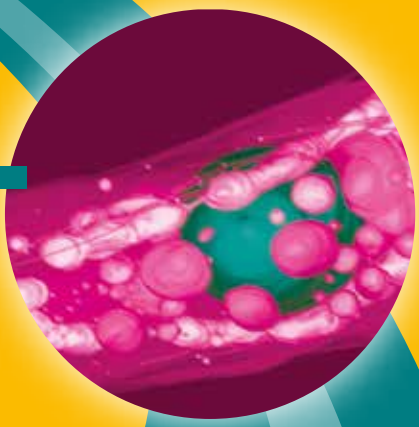
What can animals teach us about human diseases?

From molecules to organisms

How do computers help us to understand living organisms?



How does one cell give rise to an entire organism?



How can we learn about cells and what's inside them?

What are the nuts and bolts of life?

How do we unravel the molecule of life?

As Europe's leading laboratory for research in molecular biology, our mission is to be at the forefront of life sciences research, technology development and transfer, and to provide outstanding training and services to the scientific community in the member states.

What makes EMBL

When they move on, EMBL alumni take the expertise and contacts they gain here back to our member states, along with the EMBL spirit.

In the course of their research, our scientists develop new methods and instruments in their fields. At EMBL we actively seek to facilitate and accelerate the transfer of such innovative technology from basic research to industry, allowing society to benefit from it.

Italy
Germany
France
Denmark
Norway
Croatia
Greece
Australia
Belgium
Portugal
United Kingdom
Iceland

Research at EMBL spans tiny molecules to entire organisms, including aspects of human health, and has a strong emphasis on interdisciplinarity and collaboration. This is reflected in a growing network of partnerships between EMBL and universities and research institutes worldwide.

We believe that excellent basic research requires continuous training and exchange with other experts. We actively engage in advanced training activities, such as conferences and hands-on courses both within and outside EMBL, that enable scientists to improve their skills and expand their horizons.

unique?

Austria
Netherlands
Ireland
Israel
Switzerland
Spain
Finland
Sweden
Luxembourg

We strive to construct and operate infrastructures to serve life scientists in EMBL's member states and beyond and open our doors to the wider scientific community. Every year, around 3000 scientists make use of EMBL's structural biology services at Hamburg and Grenoble, while EMBL-EBI's biomolecular data resources receive 300,000 (virtual) users every month. Around 400 visitors annually come to all EMBL sites to learn about the newest techniques in molecular biology.

We support a number of different outreach initiatives directed not only at the scientific community but also at journalists, students, teachers and the general public.

How do computers help us to understand living

organisms?

How do computers help us to understand living organisms?

The human genome alone contains enough information to fill 200 telephone directories. Add to that all known information about other species' genetic make-up, plus information on protein sequences, molecular structures and scientific literature, and you get an idea of the incredible amounts of data generated by molecular biology. All this data can provide valuable insights in fields from evolution to medicine, but first it must be collected, organised and made available to scientists.

At EMBL we establish, update and curate the databases in which such information is stored, and make them freely available worldwide. Our scientists use and develop computational methods to analyse such data and simulate biological processes, taking full advantage of information technology to increase our understanding of the living world.

- Where do we come from?
- What does it mean to be a gene?
- Can medicines' side-effects be good news?
- How can biologists survive in the data jungle?

Sequence alignment studies help to understand evolution.

Where do we come from?

Peer Bork

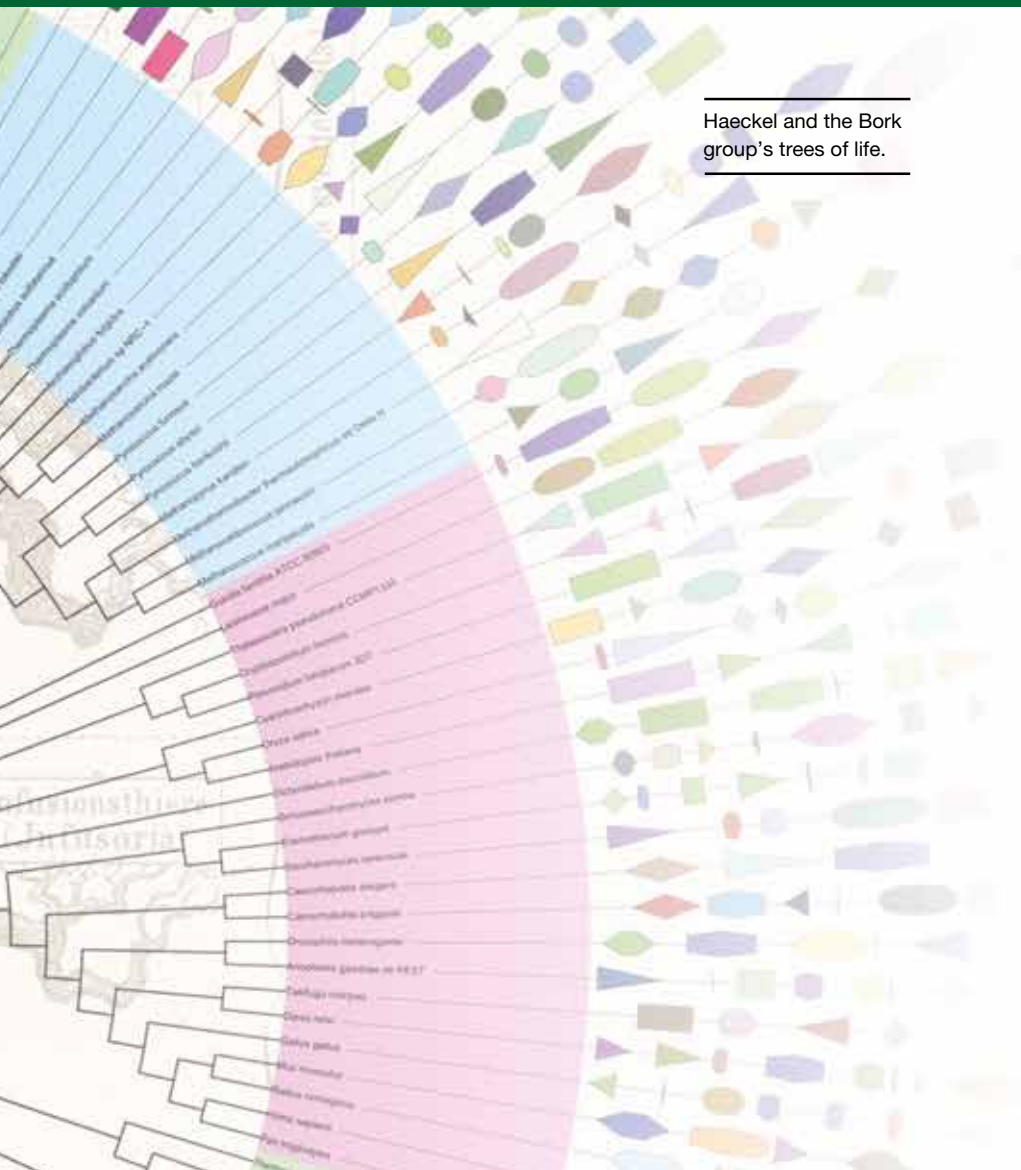
Nick Goldman

The evolution of the tree of life

Ever since Ernst Haeckel mapped evolutionary relationships in the first ‘tree of life’ in 1866 scientists have continuously redrawn and expanded it, adding new organisms and refining relationships, most recently based on genetic similarities.

The four letter code that constitutes DNA changes over time: sometimes letters are added or wrongly copied, sometimes letters get lost. But if a DNA sequence is slightly longer in one species than in another, is this because genetic material was inserted, or deleted?

Nick Goldman and his group at EMBL-EBI developed a computational method which answers this question by looking at other closely-related species, and demonstrated that insertions are more common than previously thought, thus helping to reveal the course of evolution. Peer Bork’s group at EMBL Heidelberg developed computational tools to distinguish between genes organisms inherited from their parents and those obtained by swapping genetic material with other species. They created a more accurate Tree of Life, which they now use to gain evolutionary insights from vast amounts of DNA fragments collected in environments such as the deep sea, soil or human gut.



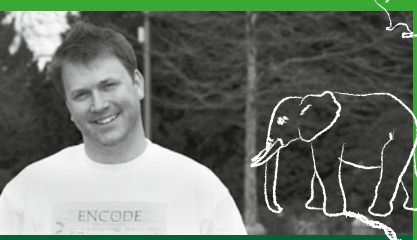
Haeckel and the Bork group’s trees of life.

What does it mean to be a gene?

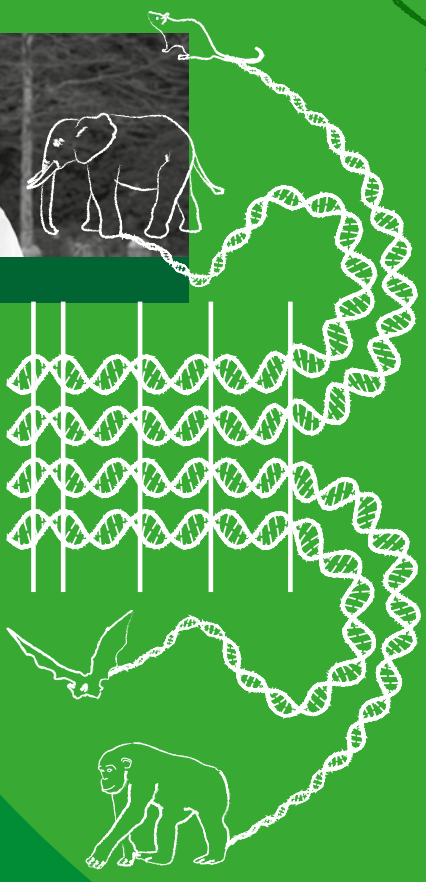
Interpreting the four-letter code of life

Once the three billion chemical letters of our DNA were sequenced a decade ago, scientists were curious to understand how our genetic blueprint really works. Ewan Birney from EMBL-EBI accepted the challenge and led the analysis within a massive international research effort called ENCODE, scrutinising one percent of the human genome to find out which bits of the DNA do what, where, why and how.

Their study indicates that the genome contains few unused sequences. The majority of the genome is transcribed into RNA, a chemical relative of DNA with essential functions in producing and regulating proteins. We now also know that genes, rather than being a tidy collection of independent DNA stretches, interact with regulatory elements and other types of DNA sequences in complex overlapping ways. The new findings help us to better understand how the genome's functional elements have evolved, and could have significant implications for efforts to identify the DNA sequences involved in many human diseases.



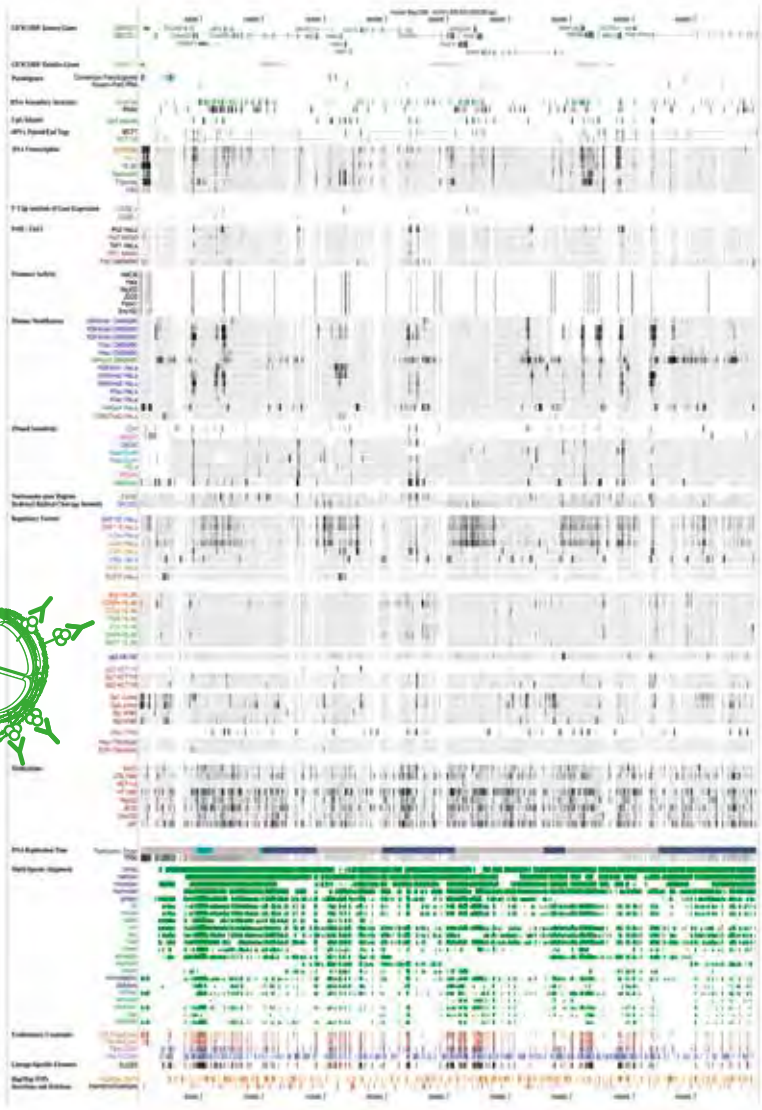
Ewan Birney



The ENCyclopedia Of DNA Elements (ENCODE) aims to identify all functional elements in the human genome.

ENCODE

ENCyclopedia Of DNA Elements



How can biologists survive in the data jungle?

Ernst Haeckel's hummingbirds with code variations.

SRS: A powerful searching tool

The Darwin days when naturalists collected fauna and flora in the field, drawing and describing what they observed, are long gone. Where their findings came exclusively from macroscopic observations of the species they encountered, in all areas of biology today, we instead obtain our data using a huge range of experimental techniques. As a result this data can be very diverse, making it complicated to interpret and integrate. How can DNA sequences, 3-D structures and data about metabolic pathways be compared? Would it be possible to make this range of information accessible via a network and offer it to the scientific community?

As early as 1990, Thure Etzold and colleagues at EMBL Heidelberg started to develop a data retrieval system, SRS, which interconnected various heterogeneous data sources. It was the first web-based service that enabled researchers to query and link several databases at a time and was the catalyst to found bioinformatics company LION bioscience. Today, the enhanced descendants of SRS, developed and hosted at EMBL-EBI, help researchers worldwide to survive in the data jungle.

Thure Etzold

How can side-effects be good?

Peer Bork

Anne-Claude Gavin

Putting old drugs to new uses

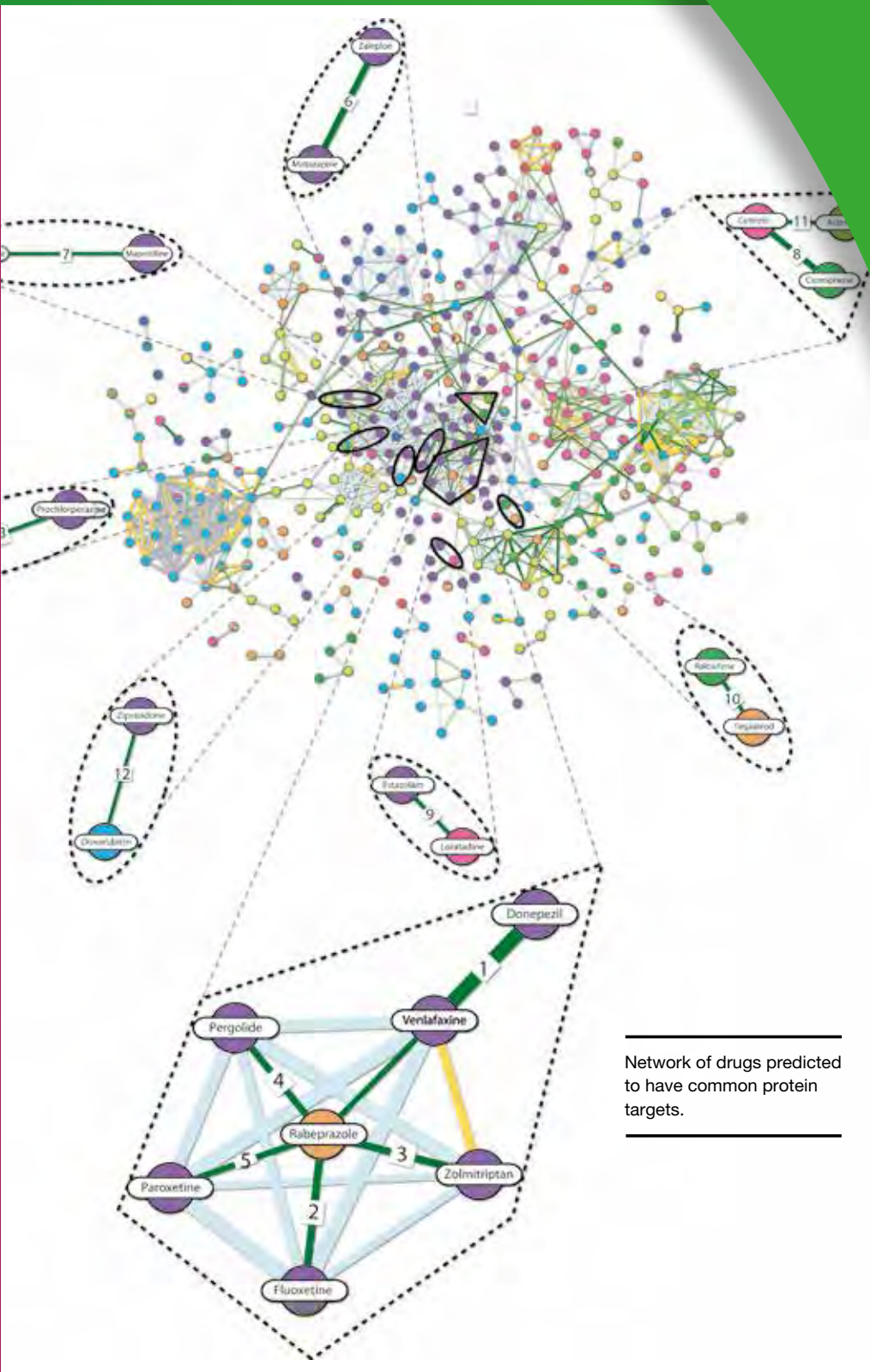
Side-effects are usually seen as negative, the downside of medicines. But scientists at EMBL saw them as a resource: clues to other conditions that a drug might treat.

Drugs are created to target specific proteins, and side-effects usually arise when the same drug interacts not only with its intended target, but also with another protein – an additional target.

Surprisingly, drugs used to treat completely different conditions can have similar side-effects. This implies they may have a shared target scientists were unaware of, and could potentially be used to treat other conditions too.

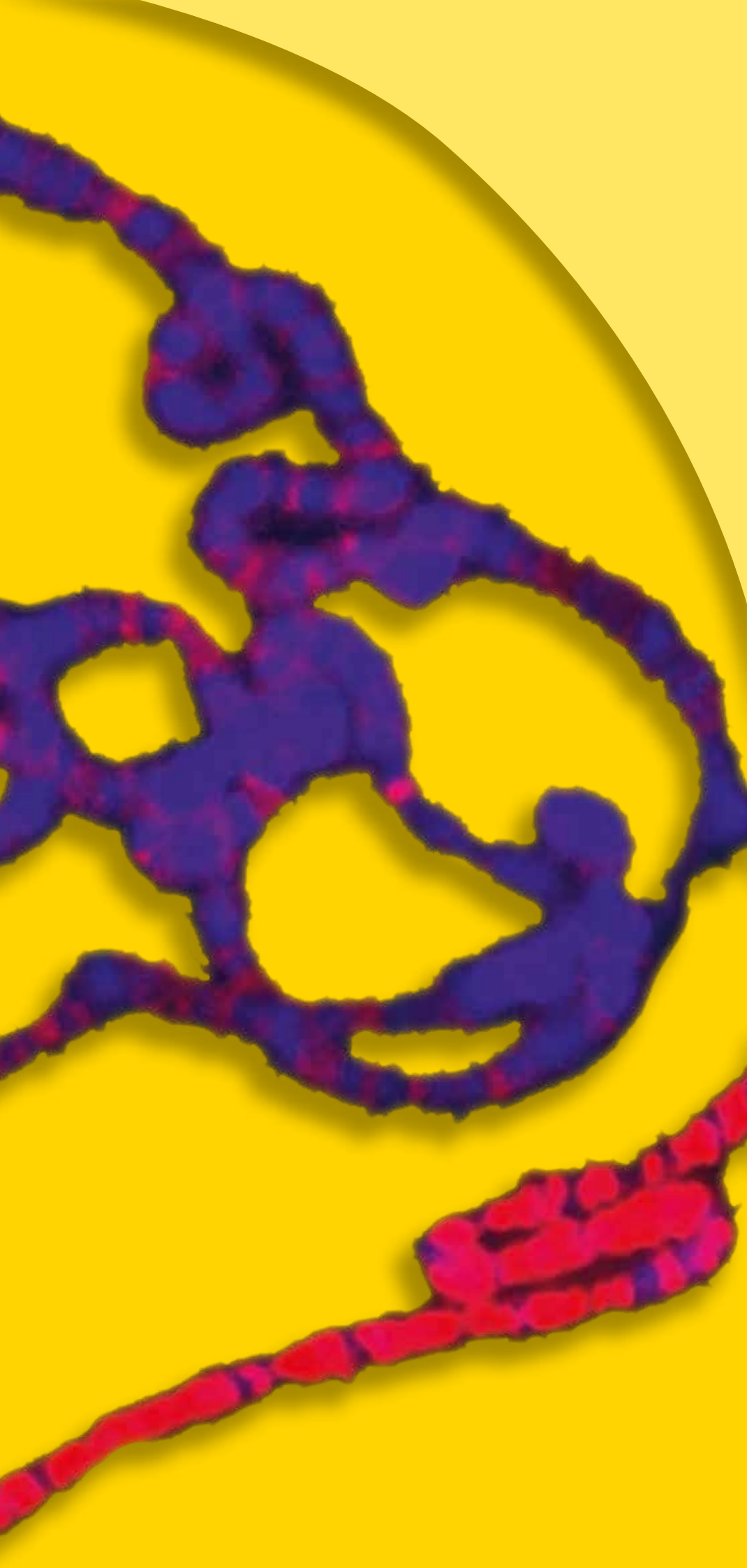
Peer Bork, Anne-Claude Gavin and their groups at EMBL Heidelberg developed a computer program which enables them to predict what additional targets a drug may have. Their predictions have been tested successfully in cells, and they are now trying to use mouse models to test them in a whole organism.

If this method can be applied on a large scale, it could speed up drug development tremendously, allowing us to put old drugs to new uses instead of having to develop new treatments from scratch.



Network of drugs predicted to have common protein targets.

How do we unravel the molecule of life?



How do we unravel the molecule of life?

No molecule in the history of science has reached the iconic status of the double helix of DNA. Since its Nobel Prize-winning discovery in 1953, its spiralling form has been an inspiration to many, including the architects of this building. But the elegance of its structure and its simple sequence of A's, T's, G's, and C's belies the complexity of the information it contains.

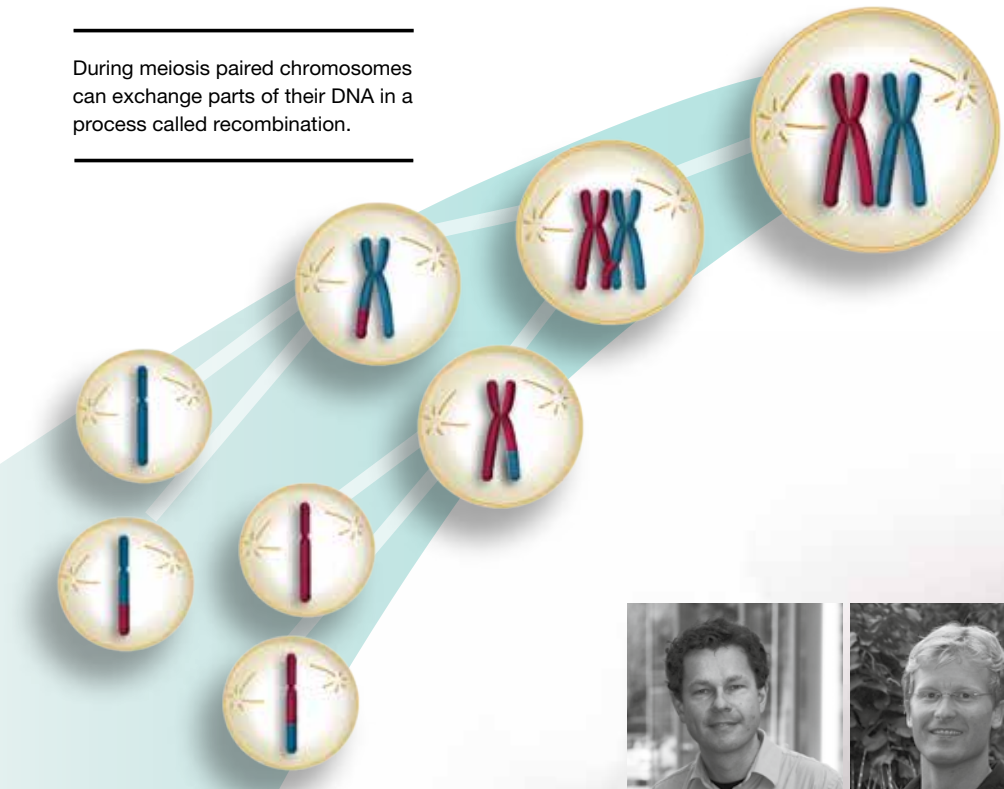
Passed down from our ancestors and encoding the instructions for an entire human being, our whole genome – containing genes and so much more besides – is packaged into a space one hundred times smaller than a grain of salt. As much as we know, we are still far from fully understanding the processes that bring this code to life. At EMBL we are trying to understand what it really takes to get from molecule to organism.

- Can we trace the patterns of genetic inheritance?
- Do genes play hide-and-seek?
- Is there more to RNA than we thought?
- How do you read the genome?

Chromosomes of the fruit fly *Drosophila.*

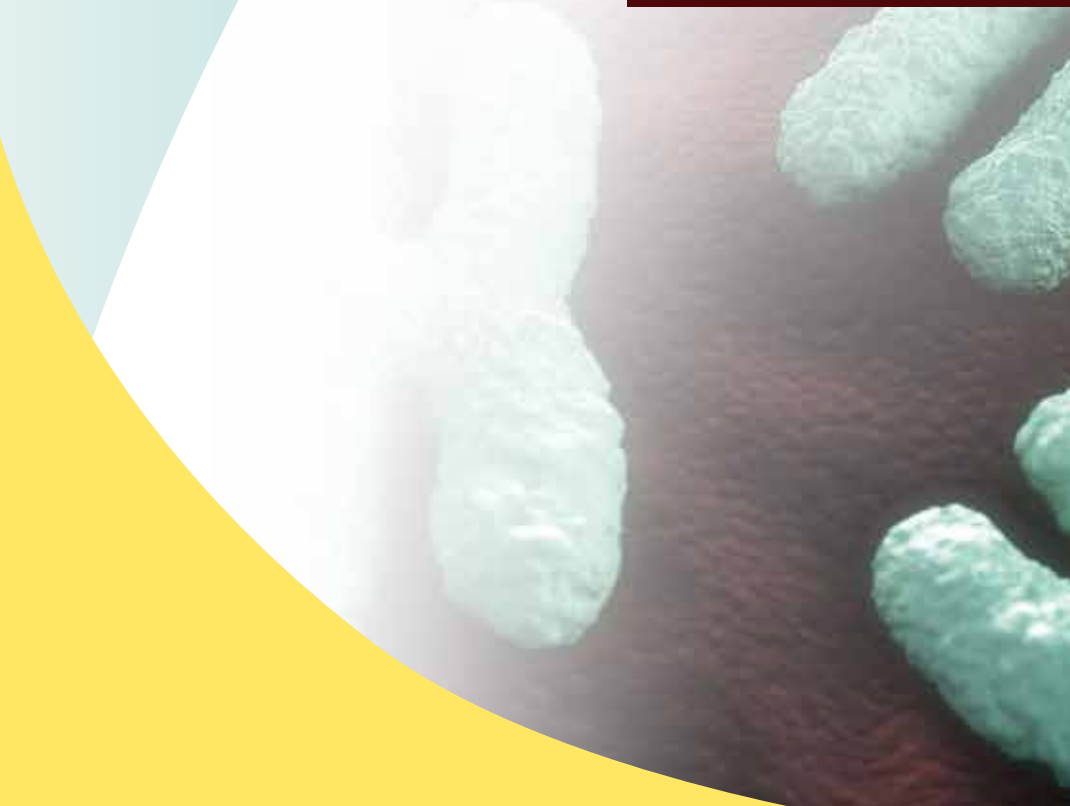
Can we trace the patterns of inheritance?

During meiosis paired chromosomes can exchange parts of their DNA in a process called recombination.



Wolfgang Huber

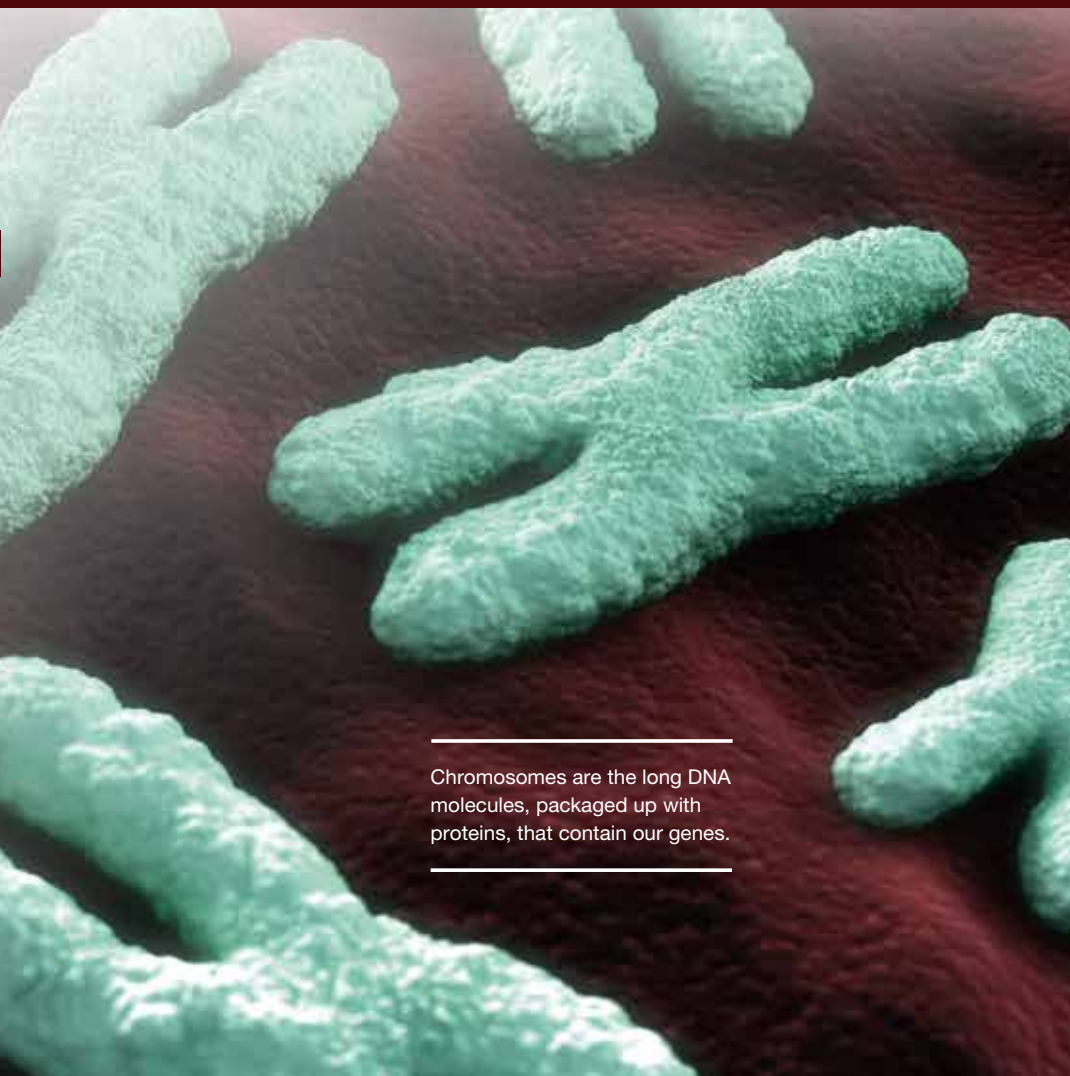
Lars Steinmetz



Zooming in on genetic shuffling

At the start of meiosis – the special cell division that halves the DNA to make egg and sperm cells – chromosomes get together, lining up in pairs along the midline of the cell, ready to be separated from one another. Up close and personal like this, they have the opportunity to swap stretches of DNA – a process called recombination. This shuffling of genes is responsible for much of the diversity of our species.

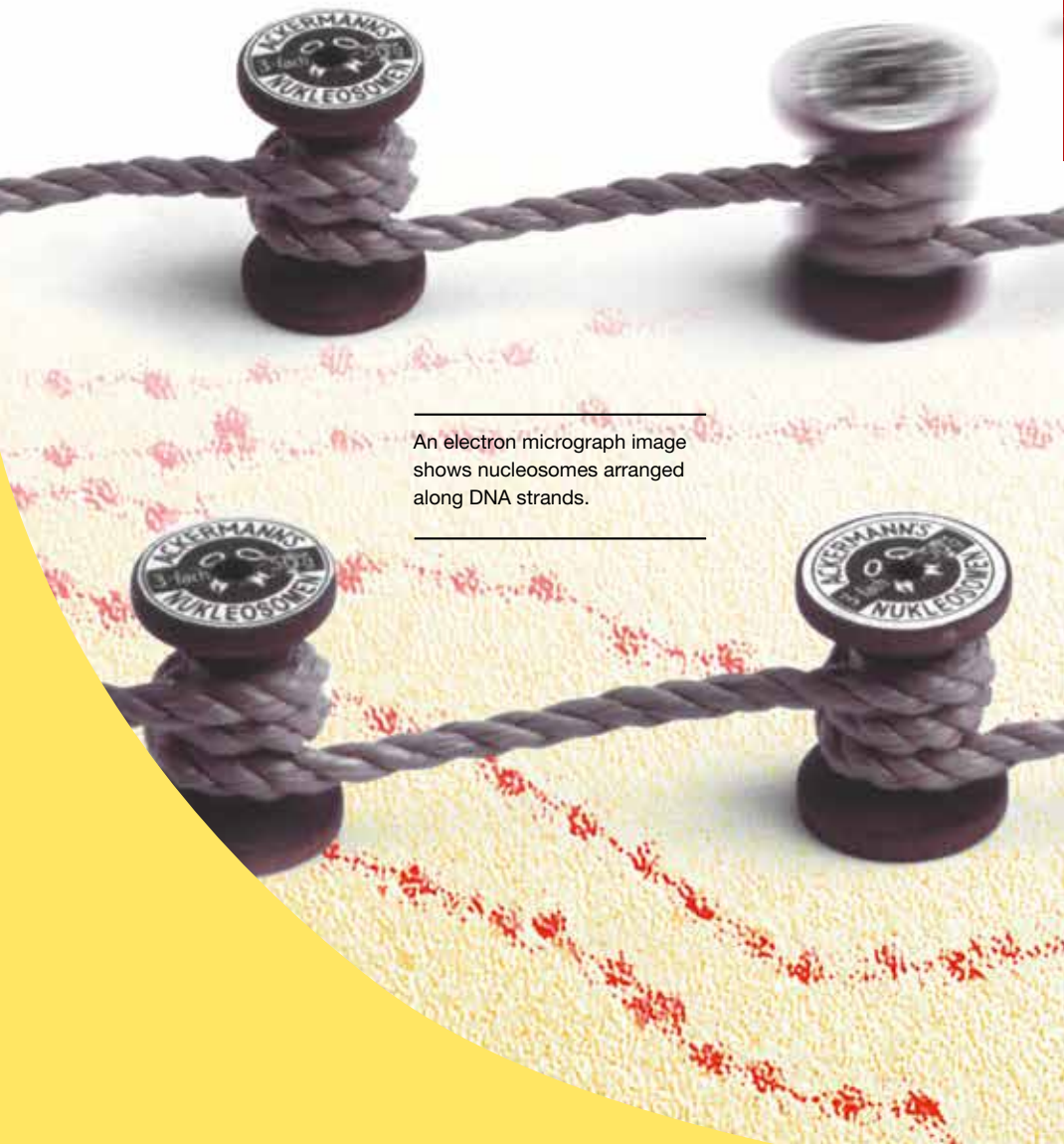
Although fundamental, there is a lot we still don't understand about this process. Lars Steinmetz, Wolfgang Huber and their groups at EMBL Heidelberg and EMBL-EBI sought to find out more: they produced the most detailed map of recombination events in the yeast genome to date, precisely mapping hotspots where it is more common, and even revealing how different types of recombination cluster together. Confident that the lessons learned in yeast will also apply to recombination in the human genome, the scientists hope their work will help to understand how complex diseases are inherited.



Chromosomes are the long DNA molecules, packaged up with proteins, that contain our genes.

Do genes play hide-and-seek?

Peter Becker

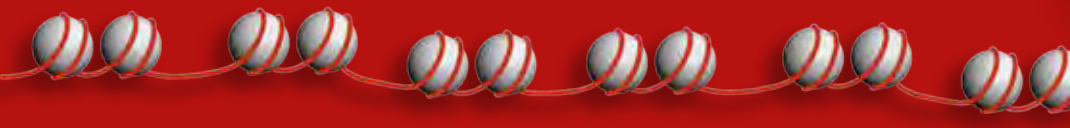


An electron micrograph image shows nucleosomes arranged along DNA strands.

On a roll: the molecular engine that unwinds our genes

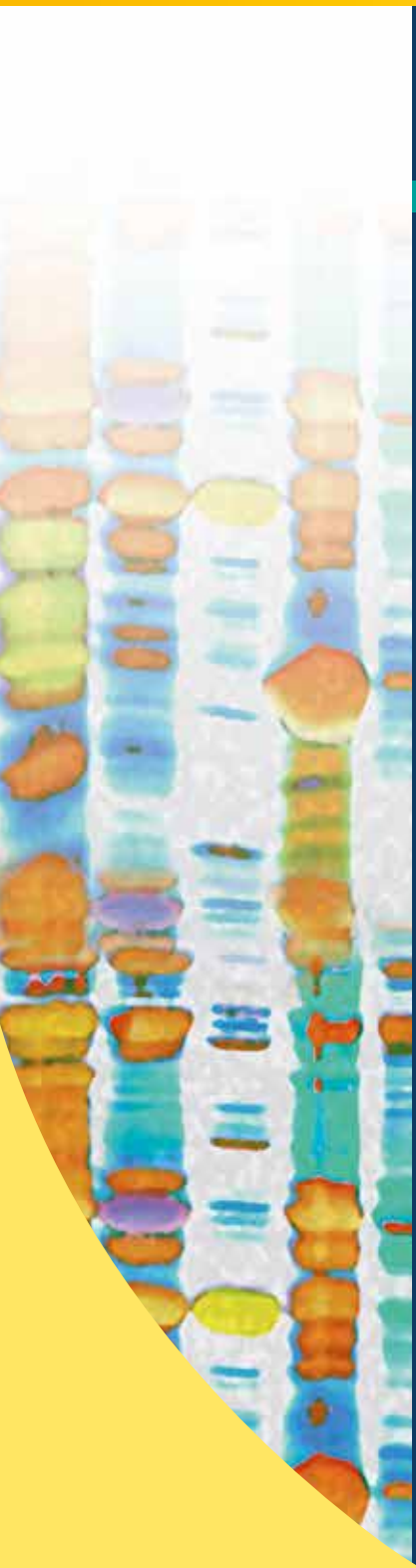
Did you know that each of our microscopic cells contains two meters of DNA? It's a packaging nightmare – equivalent to twisting two kilometres of string into a knot the size of a pea. The cellular solution is chromatin: DNA strands are wound around proteins, making nucleosomes, like spools on a thread, which are wound yet further into a tight but highly organised package. This locks down most genes, keeping them inaccessible and inactive. But in looser-wound regions, where naked DNA can still be found, the genes that the cell really needs can be read out.

Controlling chromatin structure therefore influences which genes can be read. In identifying the Chromatin Accessibility Complex (CHRAC), Peter Becker and his group at EMBL Heidelberg discovered one of the key machines that does just that. An elaborate multi-protein engine, CHRAC rolls nucleosomes along the DNA, hiding or revealing different genes.



DNA is wound around proteins to make nucleosomes.

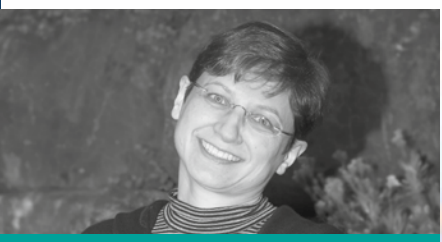
Is there more to RNA than we thought?



Mysteries of the messenger molecule

The central dogma of molecular biology could hardly be simpler: information from the DNA genome is copied into more portable mRNA molecules, like photocopies from an enormous textbook, which are translated into proteins. In this scenario, RNA is little more than a messenger. But to Elisa Izaurralde, and increasingly to the wider scientific community, the reality is far more interesting.

From pioneering studies on mRNA transport from nucleus, where it's made, to cytoplasm, where it's translated, Izaurralde and her group at EMBL Heidelberg shifted focus to look at how the cell regulates RNAs. It seems that around half of the RNAs our cells transcribe are never destined to make proteins, probably acting as regulators themselves or fulfilling more mysterious roles, and many messengers get shot down before they even get the chance to be translated. Their work helped to illuminate the process of Nonsense Mediated Decay – a system of mRNA surveillance that detects faulty mRNAs and destroys them before they can produce harmful proteins.



Elisa Izaurralde

How do you read the genome?

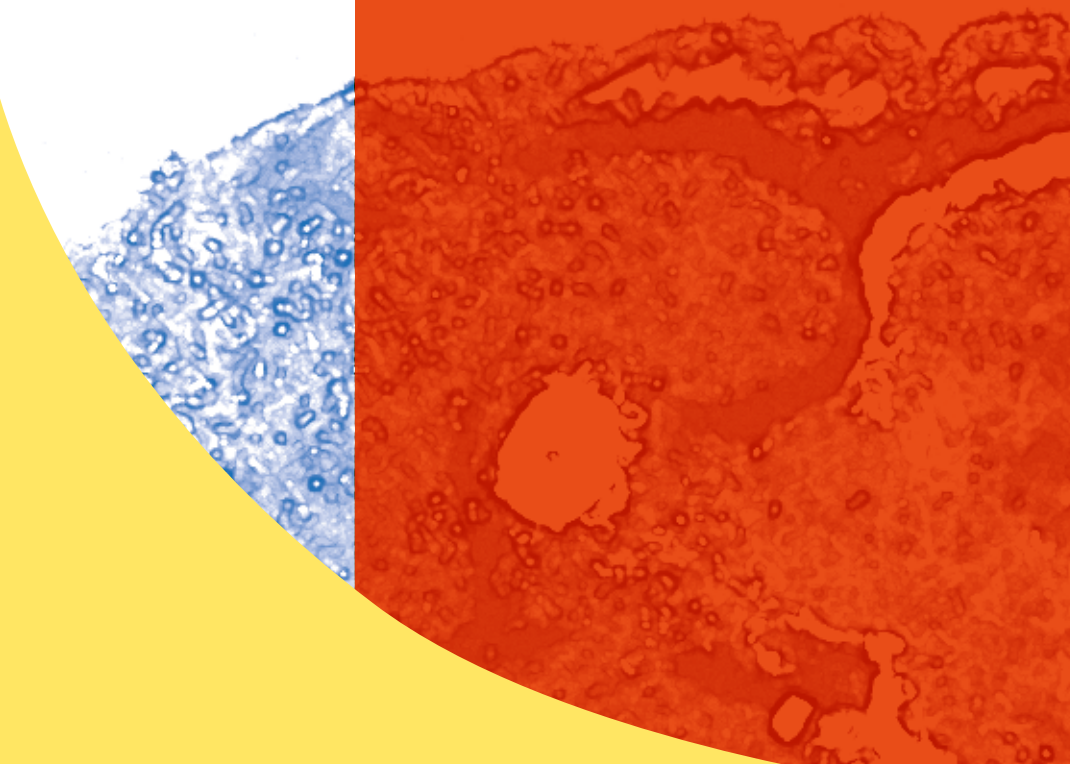
Networking in the nucleus

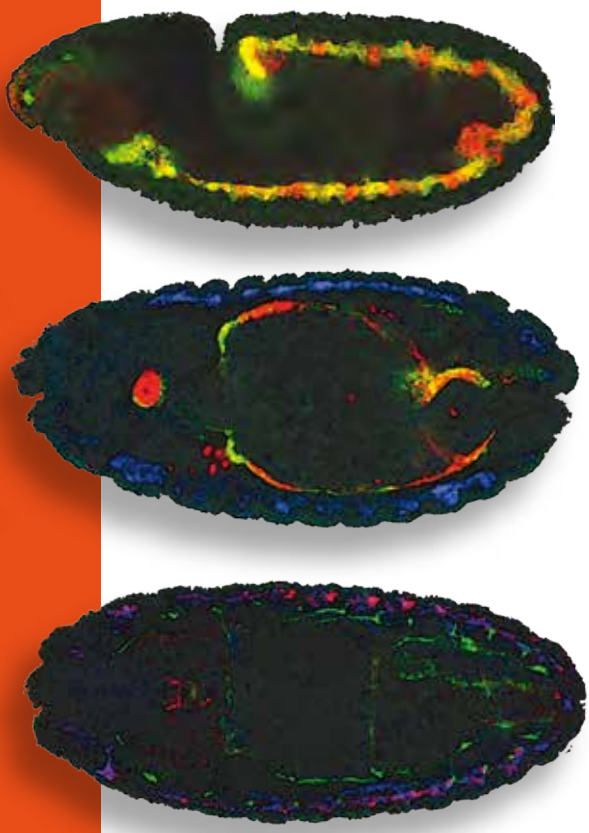
There are around 23 000 genes in the human genome – all the instructions to build a human being – but how do you know where to start reading? This vast library of information is curated by transcription factors – proteins that bind to DNA at or near genes, determining where and when they are switched on.

Rarely independent, they usually work in teams or complexes of differing composition, frequently controlling many different targets, including other transcription factors. Mapped out, these interactions quickly grow into sprawling networks, where key players – those with influence and a knack for mingling – stand out as the darlings of the transcription factor party.

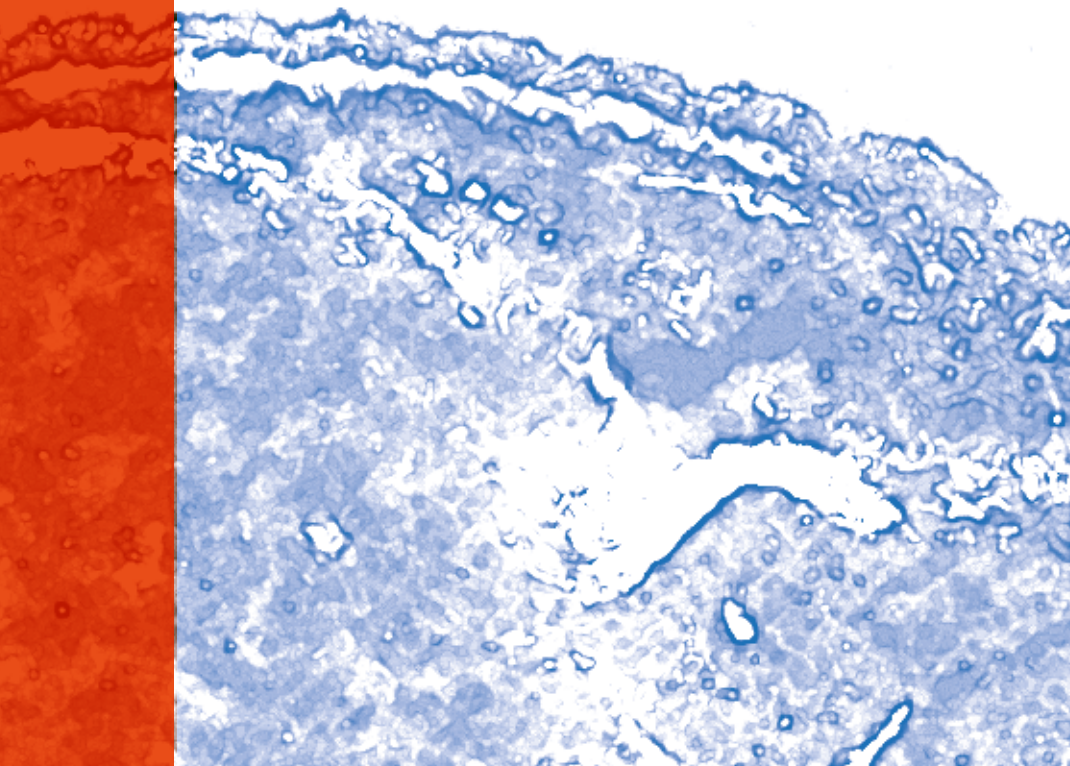
Eileen Furlong and her group at EMBL Heidelberg use powerful genomic techniques to identify the binding sites, genome-wide, of certain star transcription factors, revealing the networks that govern muscle development in embryos of the fruit fly *Drosophila*. Using this information to train a computer program, the group have found they can even forecast when and where genes are active.

Eileen Furlong





Transcription factors switch genes on and off in different tissues during *Drosophila* development.



What are the nuts and bolts

# of life?

What are the nuts and bolts of life?

If we really want to understand the nuts and bolts of life we have to dig deeper and look closer; zooming in on anatomy, past organs, through tissues, deep inside cells to the molecules that build, drive, and control them. But at this level of detail, where biology rubs shoulders with chemistry and physics, observation is difficult. Even with the most powerful microscopes, we can glimpse only a hazy outline of this elusive molecular world. To get a proper look, we have to isolate, purify, and process molecules. Even then, they can only be examined indirectly: their structures inferred from peaks on a chart or patterns of refracted beams.

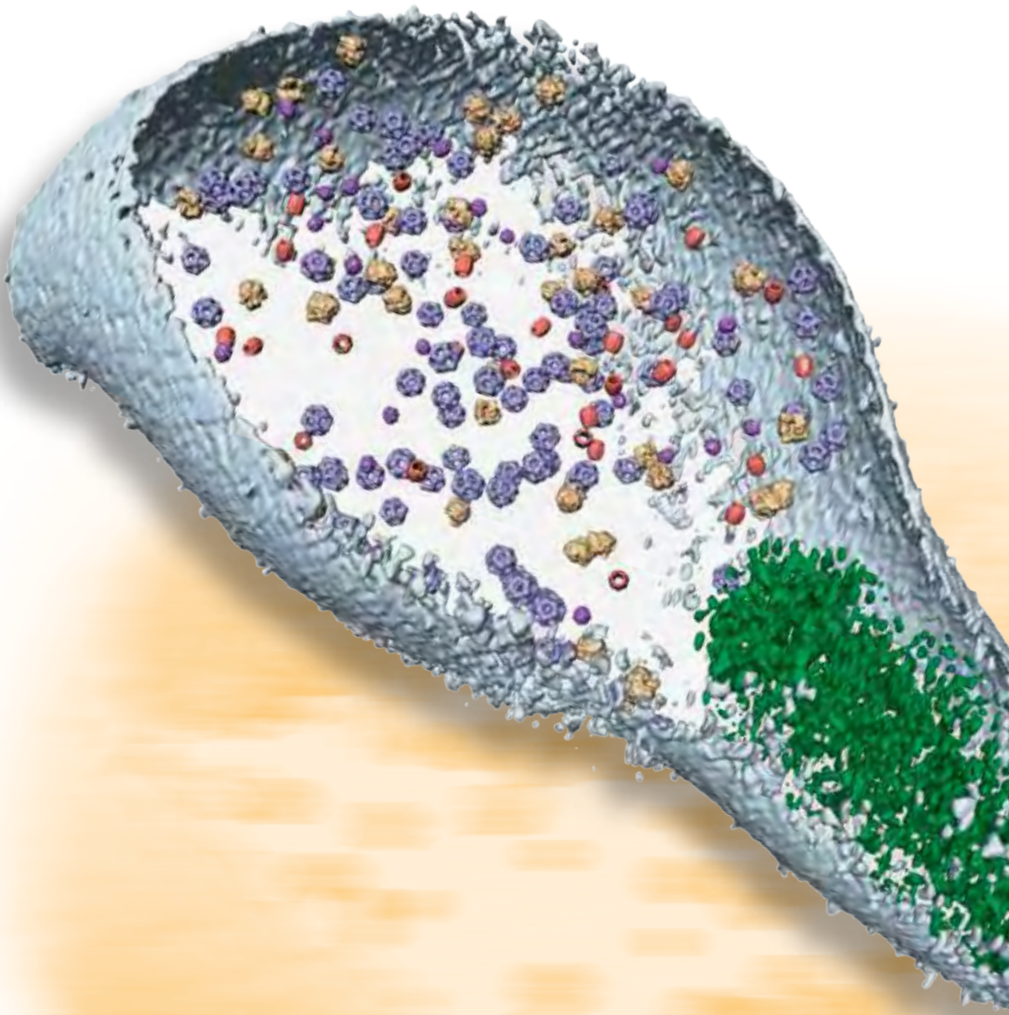
Knowing the shapes and properties of molecules means that we can understand how they work – which parts do which jobs and how different molecules work together. At EMBL, we use and develop state-of-the-art technologies, and have access to some of the most powerful beamlines in Europe to answer these questions – revealing the molecular details that make life tick.

- How do we find the chinks in influenza's armour?
- What are the bare essentials for life?
- Can we find new ways to fight an old enemy?
- What are the keys to communication inside a cell?

We turn proteins into crystals like these to study their structure.

What are the bare essentials for life?

The 3D structures of protein complexes are mapped onto an electron tomogram of a *Mycoplasma* bacterium, reconstructing the whole cell at molecular resolution.

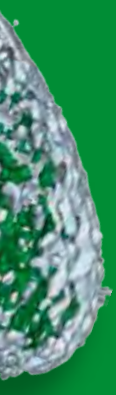


The molecular anatomy of a cell

To understand life at the cellular level the traditional reductionist approach is to break it down into small parts. Ultimately, however, it is the bigger picture – how these parts work together as a system – that matters. This means determining all of the structures and machines that make up a cell, the molecules and atoms they are comprised of, and how they interact with one another.

With a suite of new techniques developed at EMBL Heidelberg – including 'tandem affinity purification' from Bertrand Séraphin and improved methods of mass spectrometry from Matthias Wilm – a team at biotech company Cellzome, led by Giulio Superti-Furga and Anne-Claude Gavin, rose to meet this challenge. They identified the components of hundreds of molecular machines in yeast cells – the most complete parts-list to date.

Heading a consortium of international research groups, Peer Bork, Luis Serrano and the now-returned Anne-Claude Gavin then set about a similar project at EMBL Heidelberg: to fully describe the blueprint of an entire, albeit very simple, organism – the bacterium *Mycoplasma pneumoniae*. They catalogued every single RNA and protein molecule it produces, plus all of its metabolic reactions, finding that life, even at its most minimal, is rather more sophisticated than expected.



Peer Bork

Luis Serrano

Giulio Superti-Furga

Anne-Claude Gavin

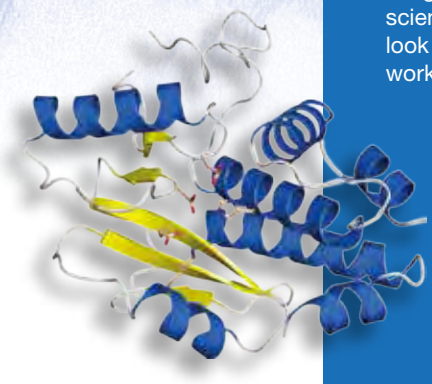
How do we find the chinks in influenza's armour?

Stephen Cusack and Darren Hart

A glimpse of flu's molecular machinations

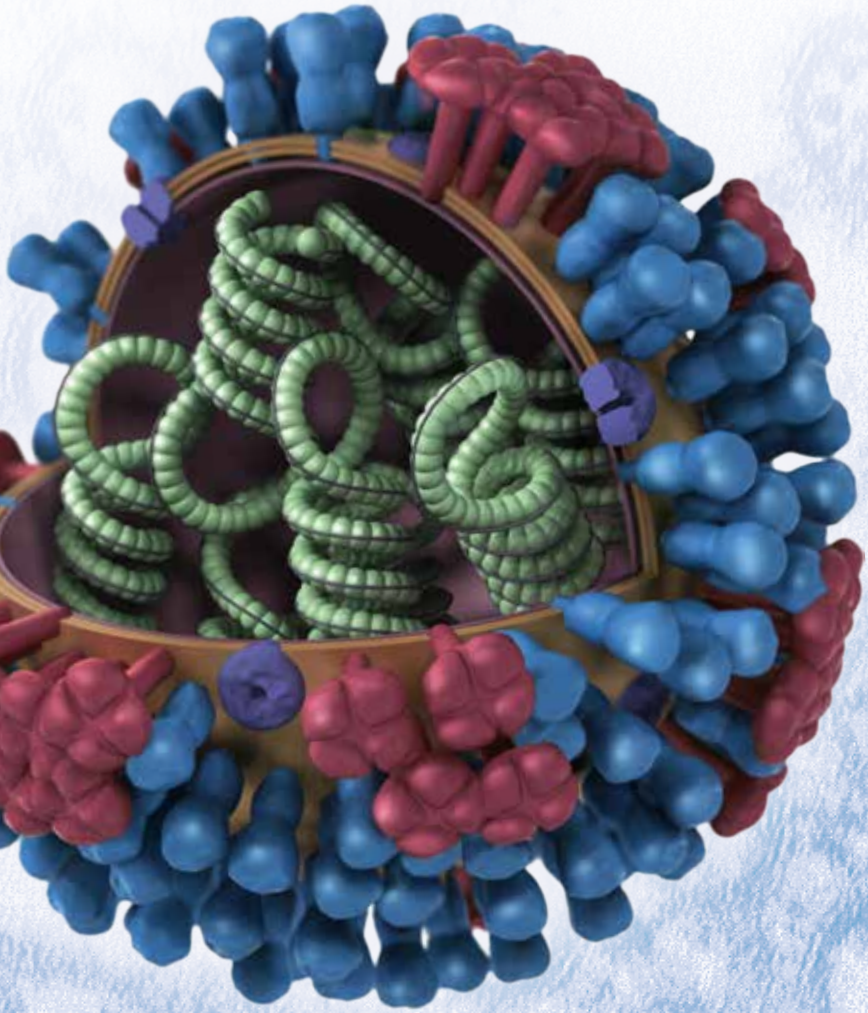
In 1918, 50 million people died during a worldwide influenza pandemic. A perennial headline-grabber and health minister's nightmare, it's only a matter of time before a new killer flu strain emerges. When it does, our best hope to tackle it is through vaccination and anti-viral drugs, reducing both the severity and spread of the virus. As it keeps mutating around our current best solutions we face a constant arms-race to find new vaccines and treatments.

Stephen Cusack, Darren Hart and their groups at EMBL Grenoble, together with colleagues from the Grenoble Unit of Virus Host Cell Interactions and other European laboratories joined forces, focusing their sights on one possible drug target: the flu polymerase. Key to the virus' lifecycle, this protein enables the virus to synthesise its proteins and copy its genome in an infected host cell. The researchers produced a series of high-resolution images of the protein, a feat that had evaded scientists for years. Finally able to take a good look at it, they are steadily figuring out how it works, and how to target its weaknesses.



Structure of a key domain of the influenza virus polymerase.

The inner workings of a flu virus.



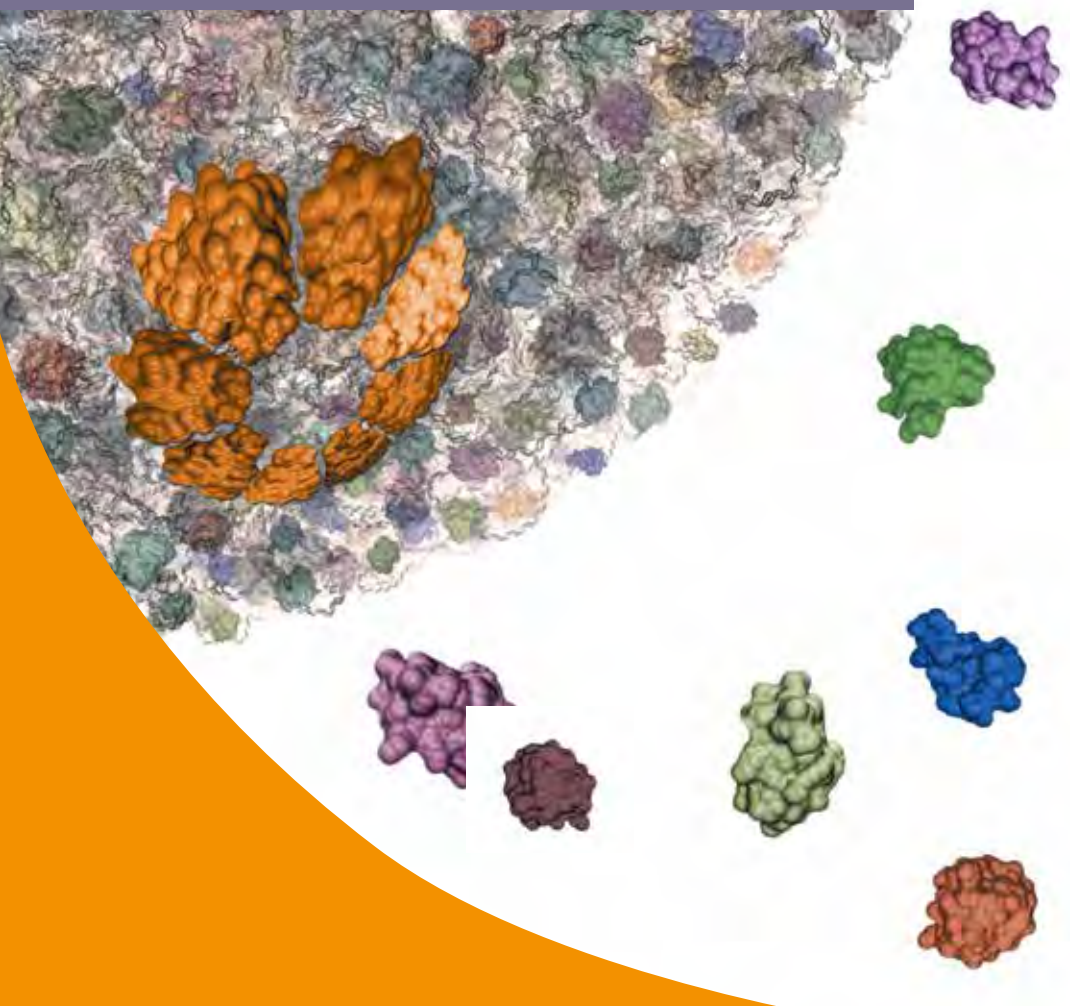
Close-up of flu virus particles, as seen with an electron microscope.

What are the keys to communication inside a cell?

Trading imports and exports across the nuclear membrane

The nucleus is an intensely bookish place, housing a vast library of genetic information that is maintained and managed by curatorial proteins – the keepers of the genes. Outside in the cytoplasm, the industrious factory floor of the cell, coded instructions from the nucleus are brought to life as proteins. These contrasting environments are kept separate by the nuclear membrane, studded with nuclear pores through which only carefully selected molecules are allowed to pass, keeping the lines of communication open. But until the early 1990s almost nothing was known about how transport through these molecular gateways is regulated.

Iain Mattaj, now Director General of EMBL, and his group, with an interdisciplinary band of EMBL collaborators, notably Christoph Müller, Elena Conti, Elisa Izaurralde and their groups, were key contributors to this emerging field. They discovered import and export factors that negotiate passage through the nuclear pores for themselves and their cargo, solved structures and identified interaction partners – revealing many important molecules and mechanisms that control traffic in and out of the nucleus.



An artistic impression of nuclear pores.

Elena Conti

Christoph Müller

Iain Mattaj

Elisa Izaurralde

Nuclear pores control traffic in and out of the nucleus.

How can we fight an old enemy?

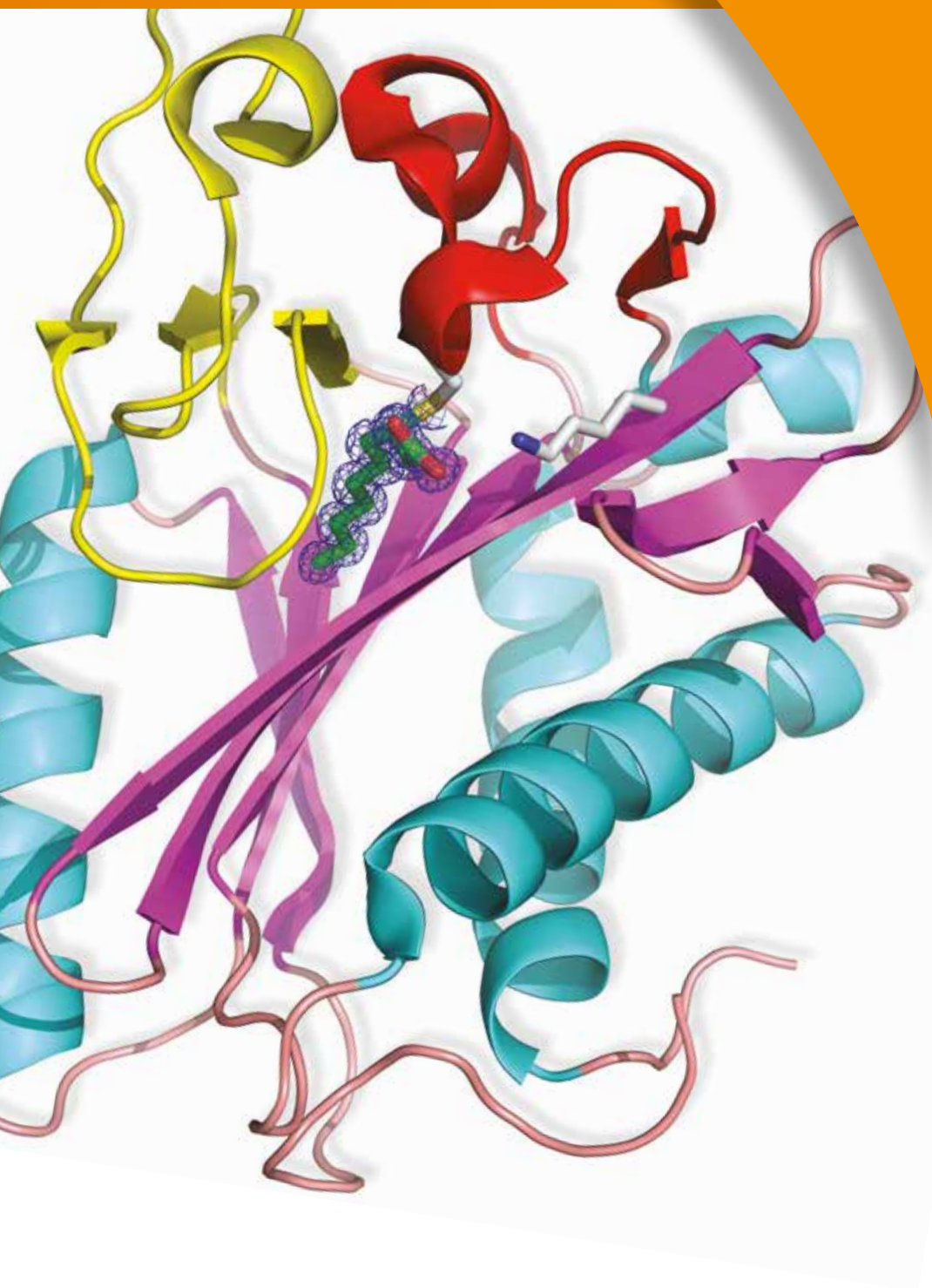
Matthias Wilmanns

Tackling tuberculosis

Tuberculosis, caused by the bacterium *Mycobacterium tuberculosis*, kills an estimated 1.6 million people every year, making it one of the most deadly diseases known to mankind. Treatment has not changed much since the 1940's when the first antibiotics were released onto the market. The recent emergence of multiple resistant strains, and an increase of secondary tuberculosis infections in HIV patients, means a new generation of drugs is urgently needed.

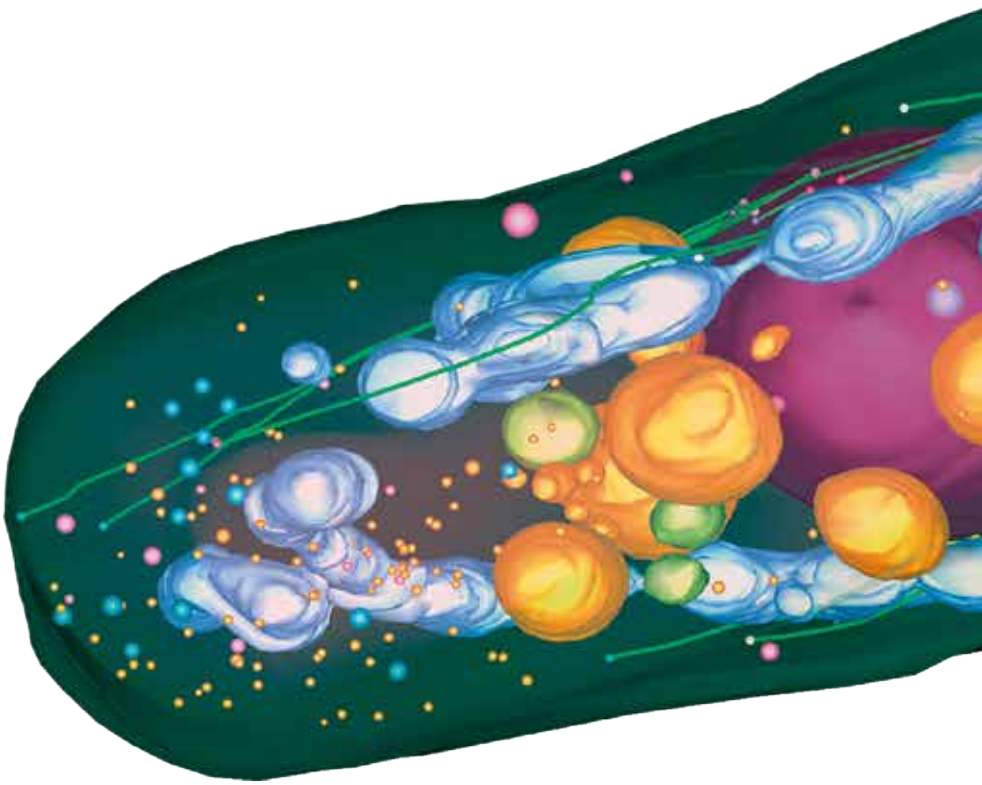
Together with several international research groups, Matthias Wilmanns and his group at EMBL Hamburg use x-ray crystallography to study tuberculosis. To date, they have determined the three-dimensional structures of 40 different proteins from *Mycobacterium tuberculosis*, leading to a better understanding of the life cycle and infection pathway of this bacterium. Being able to see the structure of these proteins may pave the way to developing new treatments to fight this old enemy.

Mycobacterium tuberculosis

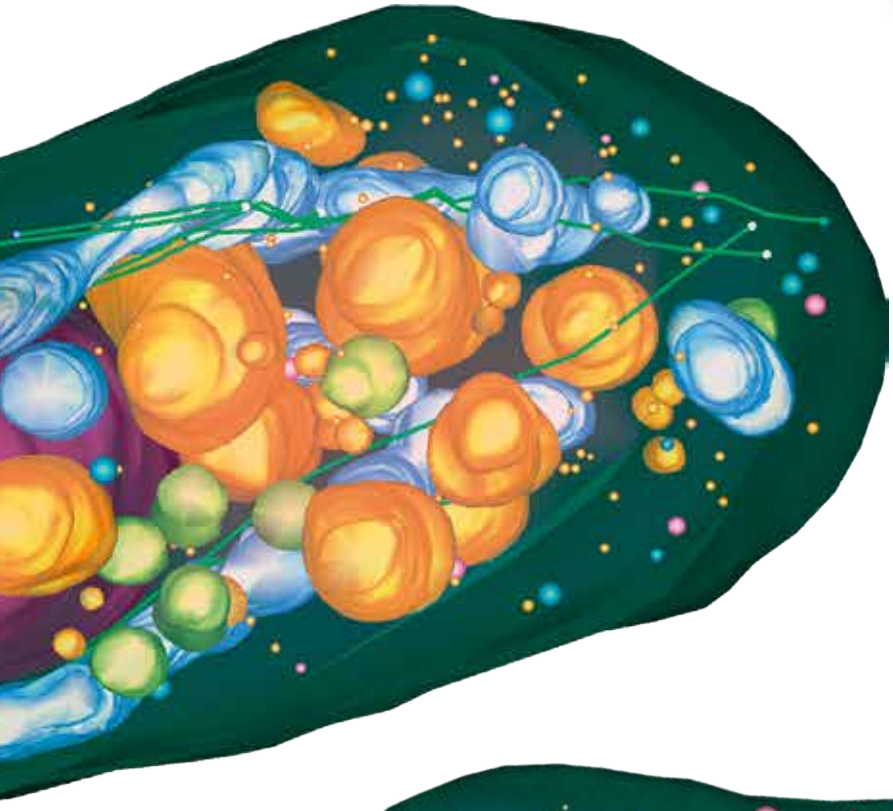


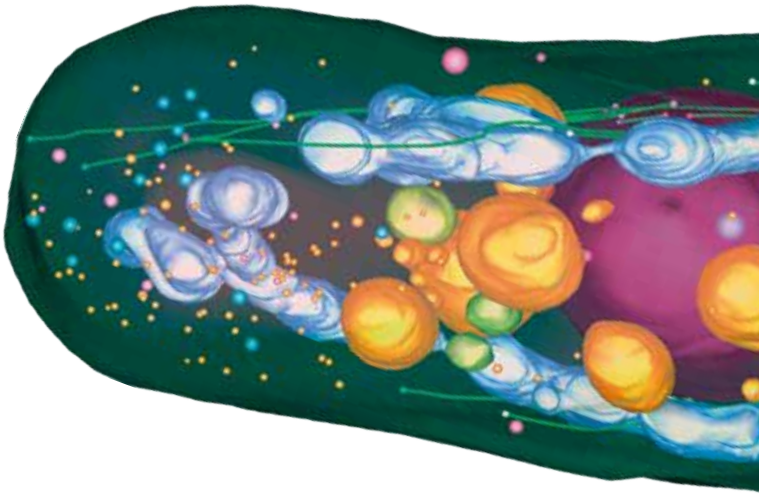
Structure of a *Mycobacterium tuberculosis* protein

How can we learn about and what's



cells inside them?



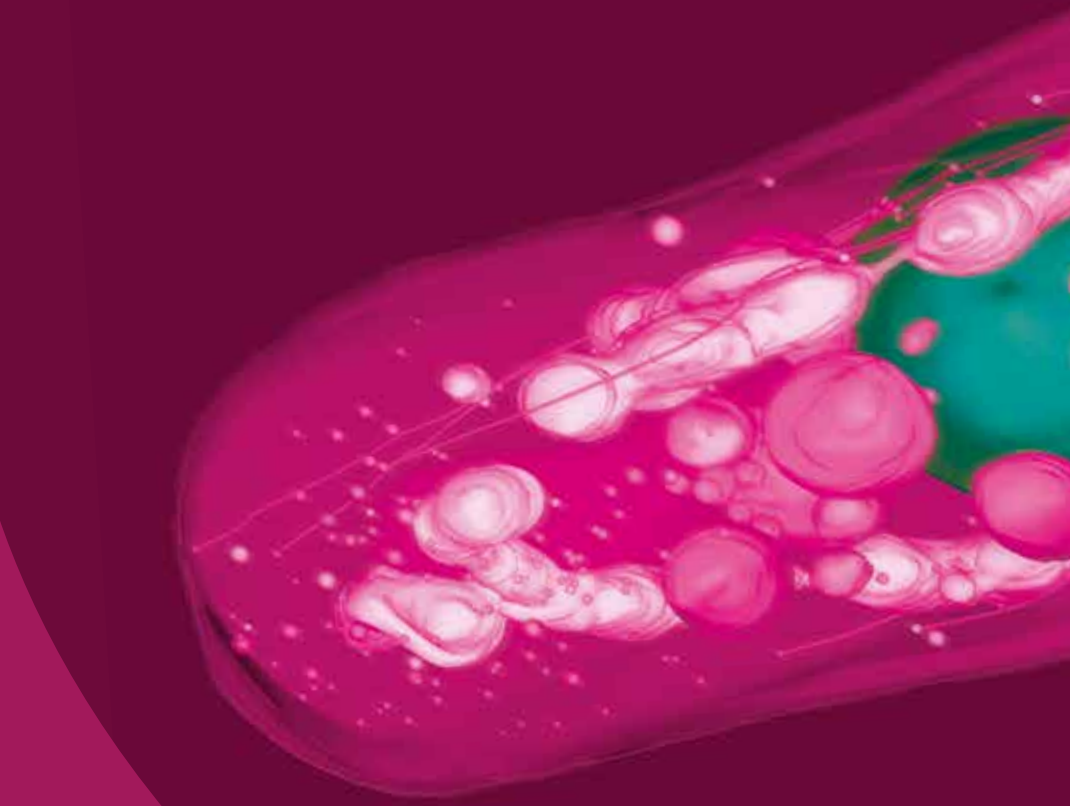


How can we learn about cells and what's inside them?

As one of the first to observe life under the microscope, Robert Hooke first used the term 'cell' in his 1665 book *Micrographia*. Describing the tiny walled units that made up a slice of cork, he could scarcely have realised what this discovery would mean for our understanding of biology.

Thanks to him and the many pioneering biologists and naturalists that followed, we came to see that cells are the fundamental structural and functional units of all living things. But they are by no means irreducible – the sub-cellular world is a strange and fascinating place.

As Hooke himself would attest, technology is the key. At EMBL we push forward our cellular discoveries by developing increasingly powerful microscopes and imaging techniques, peering ever closer into the secret lives of cells.

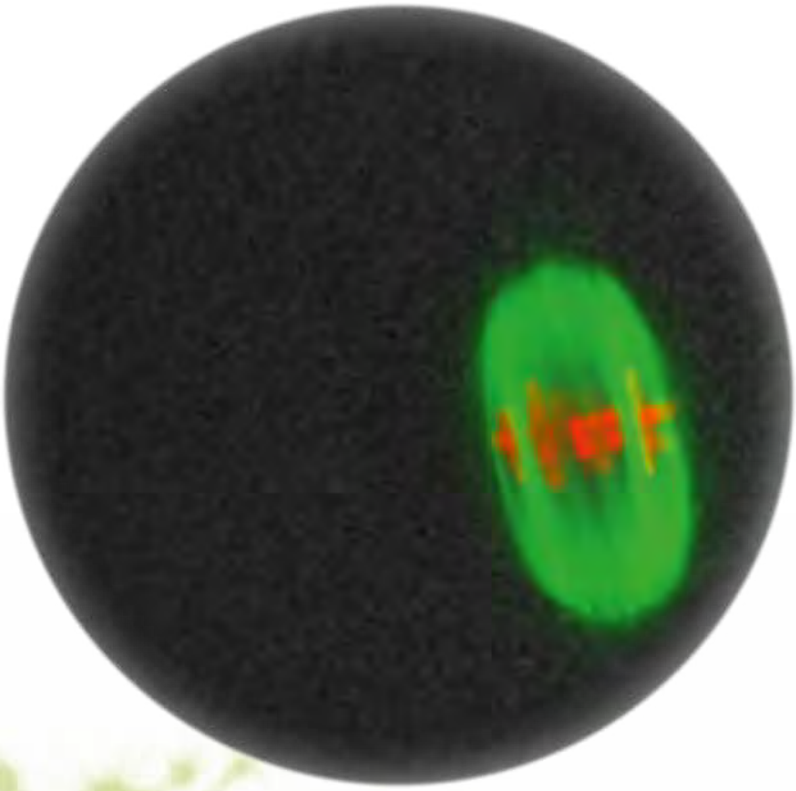


- How do cells work together?
- A cellular multi-tasker: how are actin fibers built?
- How does a cell keep in shape?
- How do mammals make eggs?

Electron tomogram of a yeast cell.

How do mammals make eggs?

Jan Ellenberg with group members.

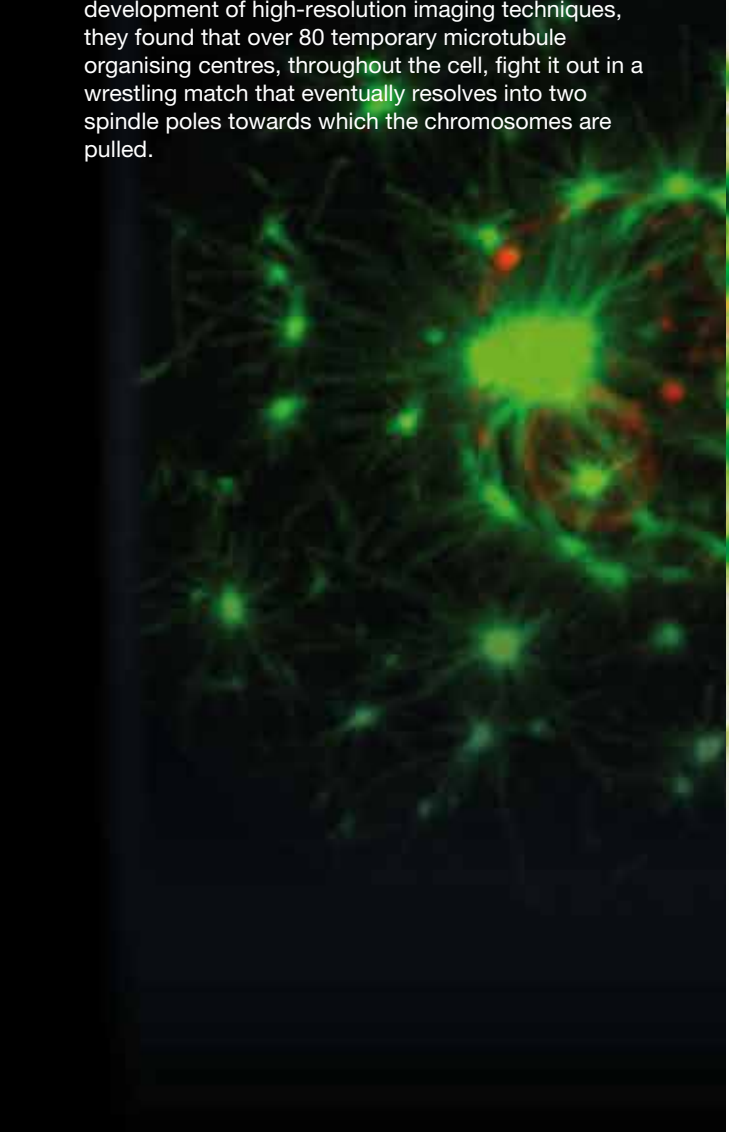


The meiotic spindle (green) with the chromosomes (red) lined up.

Separating chromosomes in a molecular tug-of-war

All our cells contain a double set of the DNA-containing chromosomes, one from the mother and one from the father. To become a mature egg however, an oocyte has to lose one set. In a process called meiosis, the chromosomes line up in pairs along the middle of the cell before being dragged apart: half remain in the egg, the other half are eliminated. It's important to get this right – the wrong number of chromosomes can cause miscarriage, infertility, or genetic disorders like Down's Syndrome.

Jan Ellenberg and his group at EMBL Heidelberg study this chromosome segregation by the spindle, a system of microtubule fibers that separate chromosomes during cell division. In most cells, spindle fibers are anchored by centrosomes, specialised structures at opposite ends of the cell. But not so in mammalian oocytes. So what organises the spindle? Thanks to the development of high-resolution imaging techniques, they found that over 80 temporary microtubule organising centres, throughout the cell, fight it out in a wrestling match that eventually resolves into two spindle poles towards which the chromosomes are pulled.



Star-like microtubule organising centres (green) kick off spindle assembly.

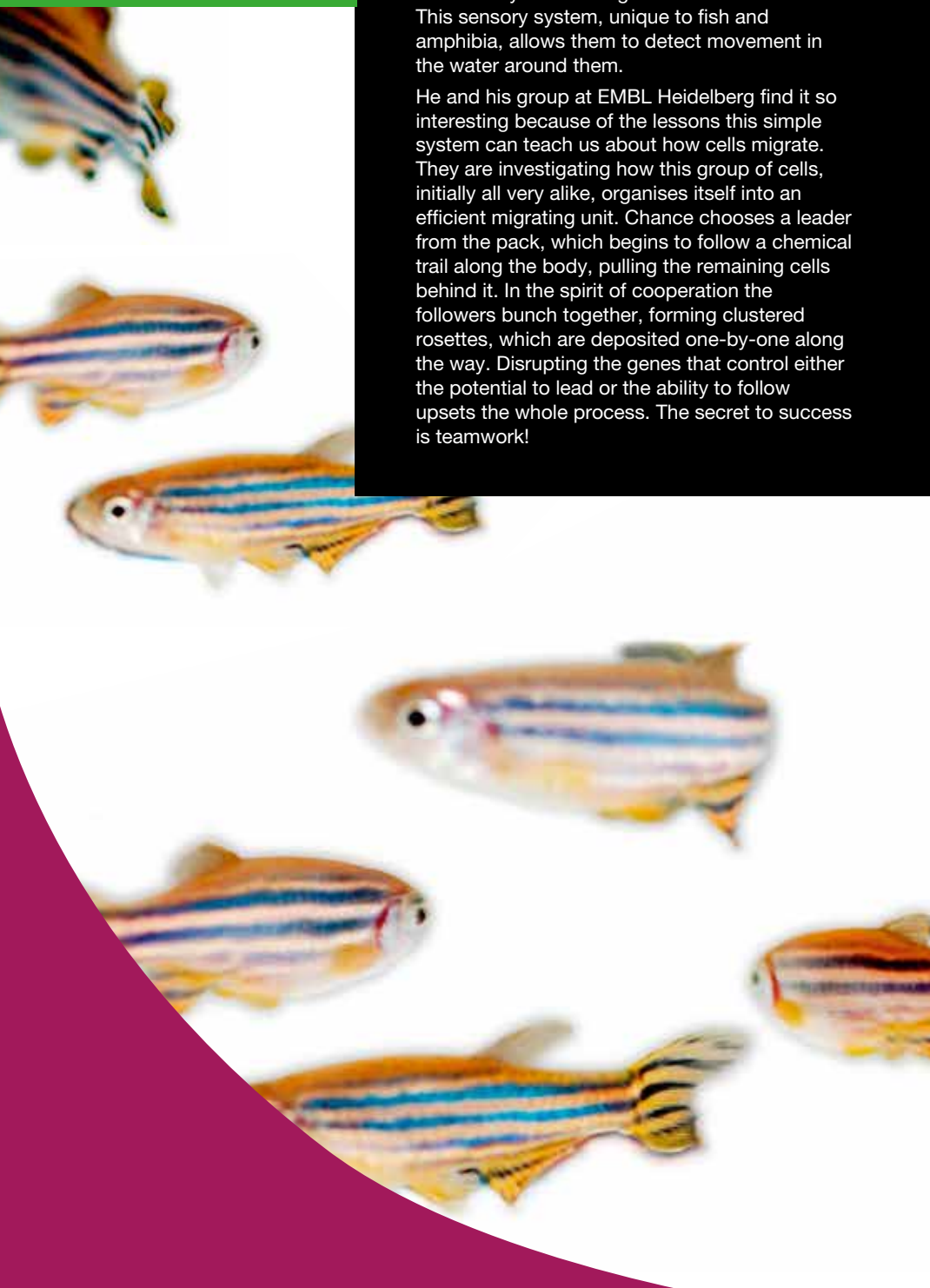
How do cells work together?

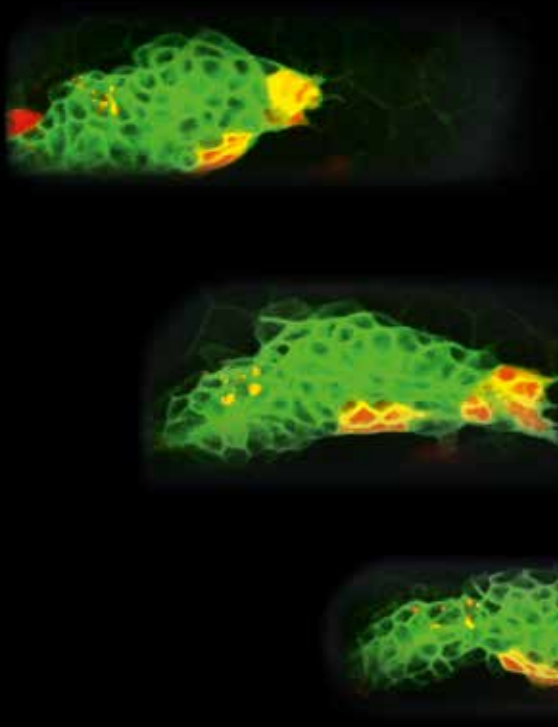
Darren Gilmour

Even for cells, there's no 'I' in 'team'

Darren Gilmour's favourite developmental structure is the lateral line primordium – a transient creeping mass of cells that migrates along either side of a fish embryo laying down the sensory hair cell organs of the lateral line. This sensory system, unique to fish and amphibia, allows them to detect movement in the water around them.

He and his group at EMBL Heidelberg find it so interesting because of the lessons this simple system can teach us about how cells migrate. They are investigating how this group of cells, initially all very alike, organises itself into an efficient migrating unit. Chance chooses a leader from the pack, which begins to follow a chemical trail along the body, pulling the remaining cells behind it. In the spirit of cooperation the followers bunch together, forming clustered rosettes, which are deposited one-by-one along the way. Disrupting the genes that control either the potential to lead or the ability to follow upsets the whole process. The secret to success is teamwork!





Leading cells (red) pull the followers (green) in an organised migration.

Zebrafish

How does a cell keep in shape?

Microtubules form a living scaffolding for cells

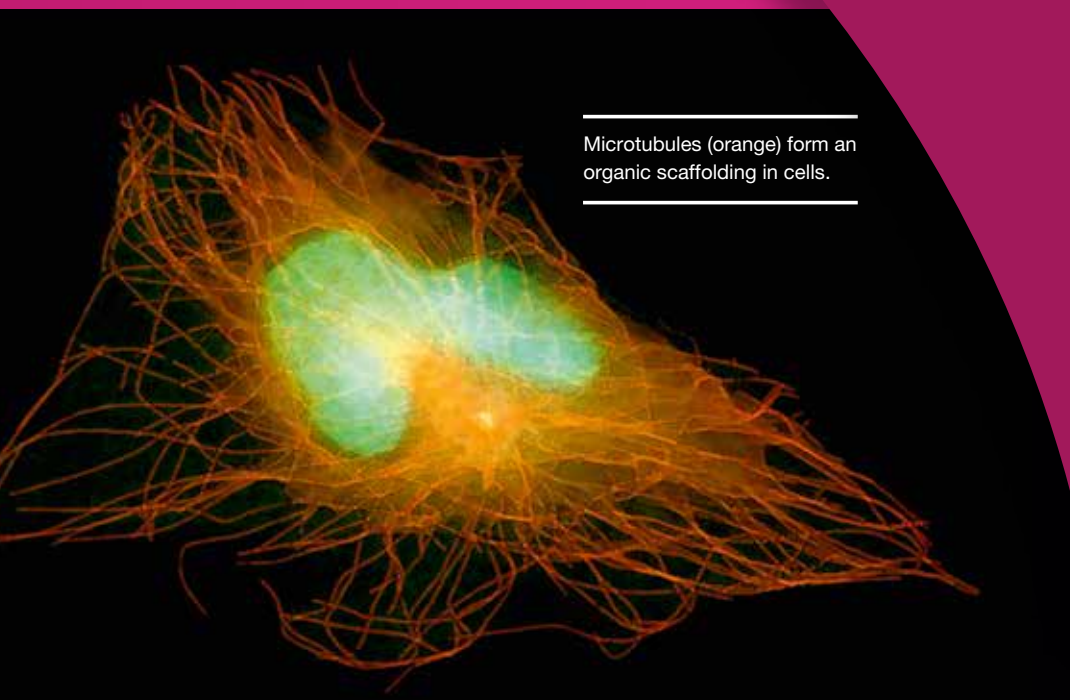
As highly dynamic protein fibres, microtubules constantly grow, retract and rearrange themselves, maintaining or changing a cell's shape whilst keeping everything inside in order. The networks they form also act as highways along which cellular cargo is shuttled around by molecular machines. For more than a decade, scientists at EMBL Heidelberg have been studying these structures – how they are built, what they are for, how they interact with other parts of the cell. For example…

- Thomas Surrey and his group work to understand kinesins – molecular machines that walk along microtubules dragging their cargo with them.
- François Nédélec and his group, using computer simulations and experimental approaches, have figured out how new microtubules are born and line up with existing microtubules.
- Andreas Hönger & Damian Brunner's groups showed how microtubule filaments are stabilised by proteins like Mal3p.
- The Surrey and Brunner groups have developed a special technique to grow microtubules in a lab dish, revealing how specialised proteins keep track of their growing ends.
- Eric Karsenti and his group study how microtubules assemble into the mitotic spindle responsible for dividing up chromosomes during cell division.

François Nédélec and Eric Karsenti

Thomas Surrey

Microscopy image of microtubules.



Microtubules (orange) form an organic scaffolding in cells.

Andreas Hönger, Linda Sandblad and Damian Brunner

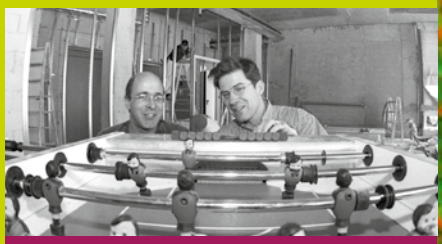
A microscopy image (below) and computer simulation (above) of microtubules forming the mitotic spindle in a cell.

A cellular multi-tasker: how are actin fibers built?

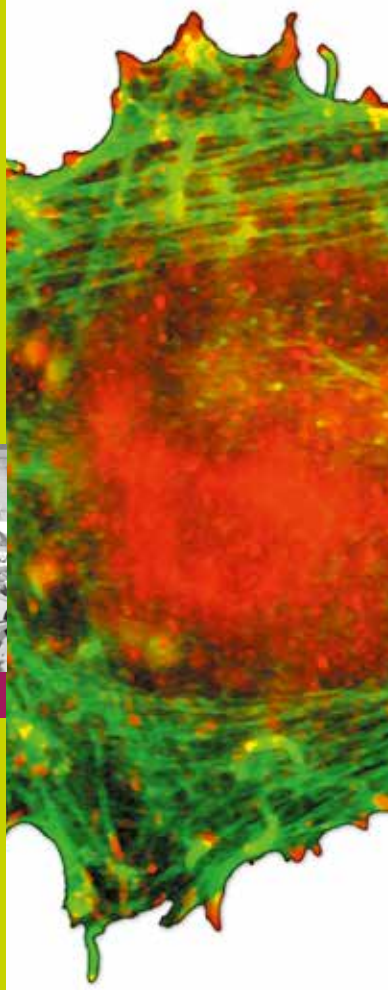
Learning from *vaccinia* virus transport

Vaccinia is a big and complex, but essentially rather harmless virus, most famous for its use as the vaccine that eradicated smallpox. For Michael Way, Giulio Superti-Furga and their teams at EMBL Heidelberg, this mild-mannered beastie was the key to better understanding an essential structural and mechanical component of cells – actin.

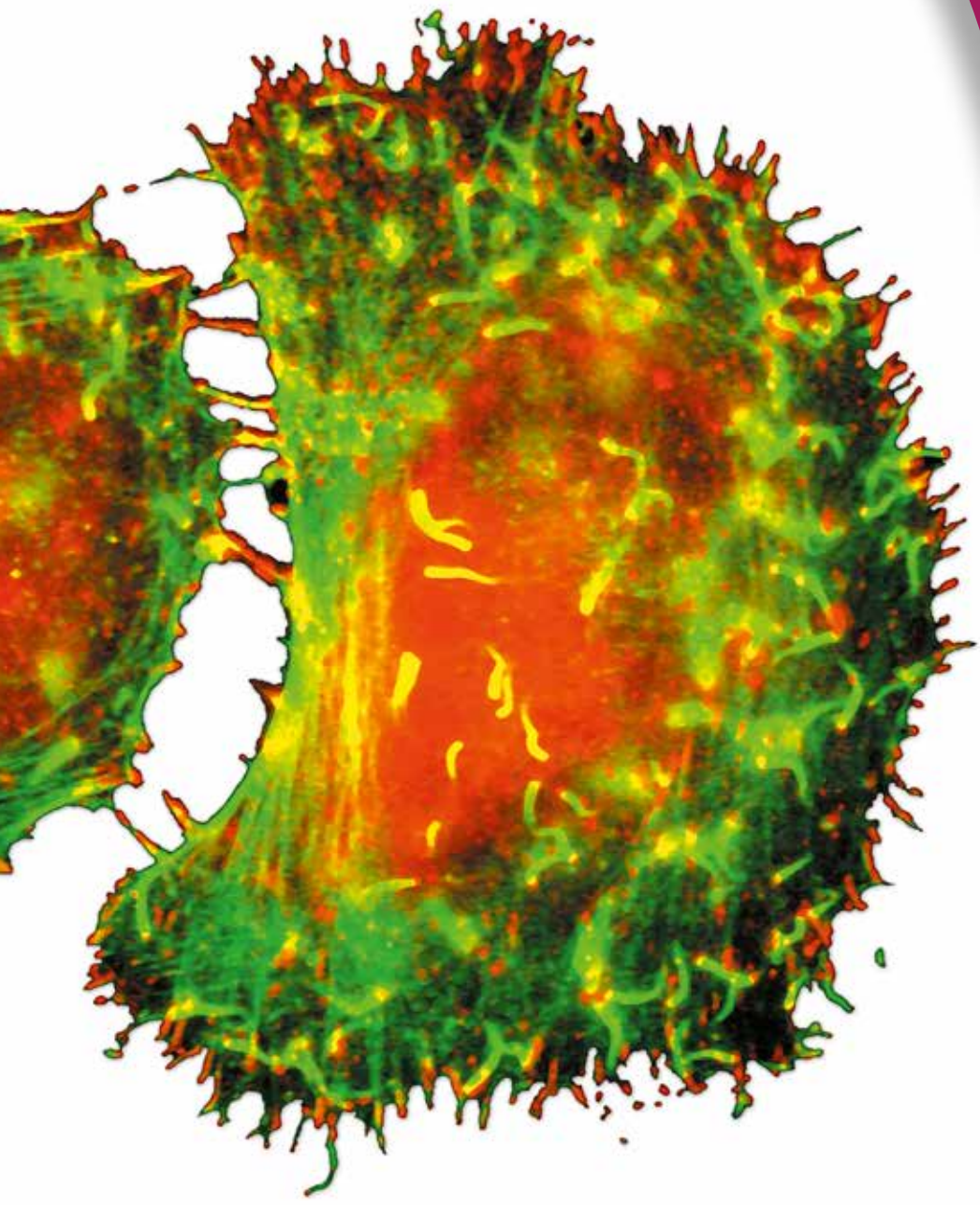
Like microtubules, actin forms long filaments that give support and shape to cells, enable them to move or divide, and help link neighbouring cells together. *Vaccinia*, like all viruses, takes over various bits of its host cell's machinery for its own purposes, and it has found an extra use for actin. At the surface of infected cells, newly-made virus particles push themselves out at the ends of long spindly projections on their journey to infect neighbouring cells, each one propelled on the tip of a growing actin filament. In understanding this process, the scientists deciphered molecular triggers that initiate the building of actin filaments.

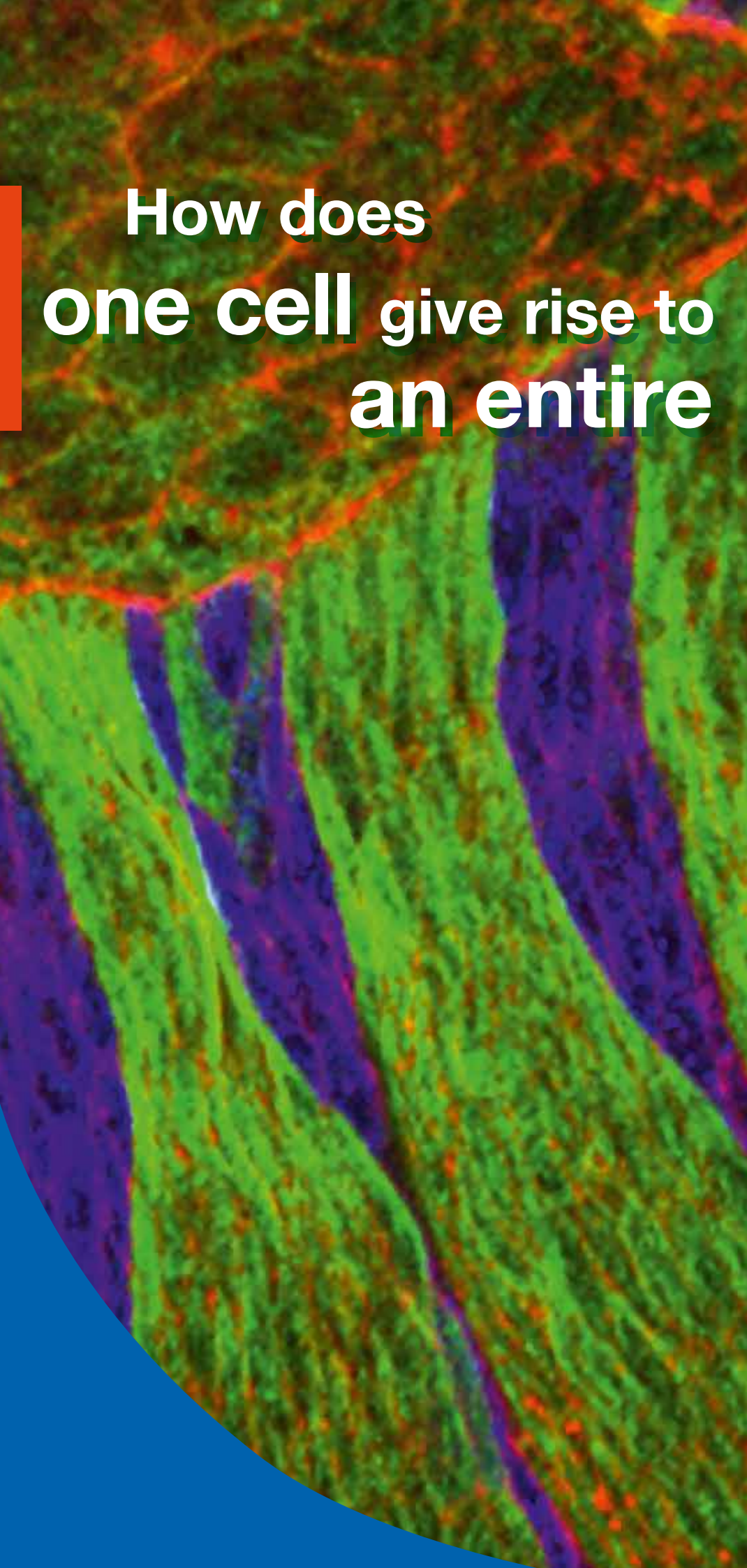


Michael Way and Giulio Superti-Furga



A cell infected with the *vaccinia* virus: actin filaments (green), which help give the cell its shape, are also used by *vaccinia* as transport. Red marks the site on the virus at which the actin filament starts.



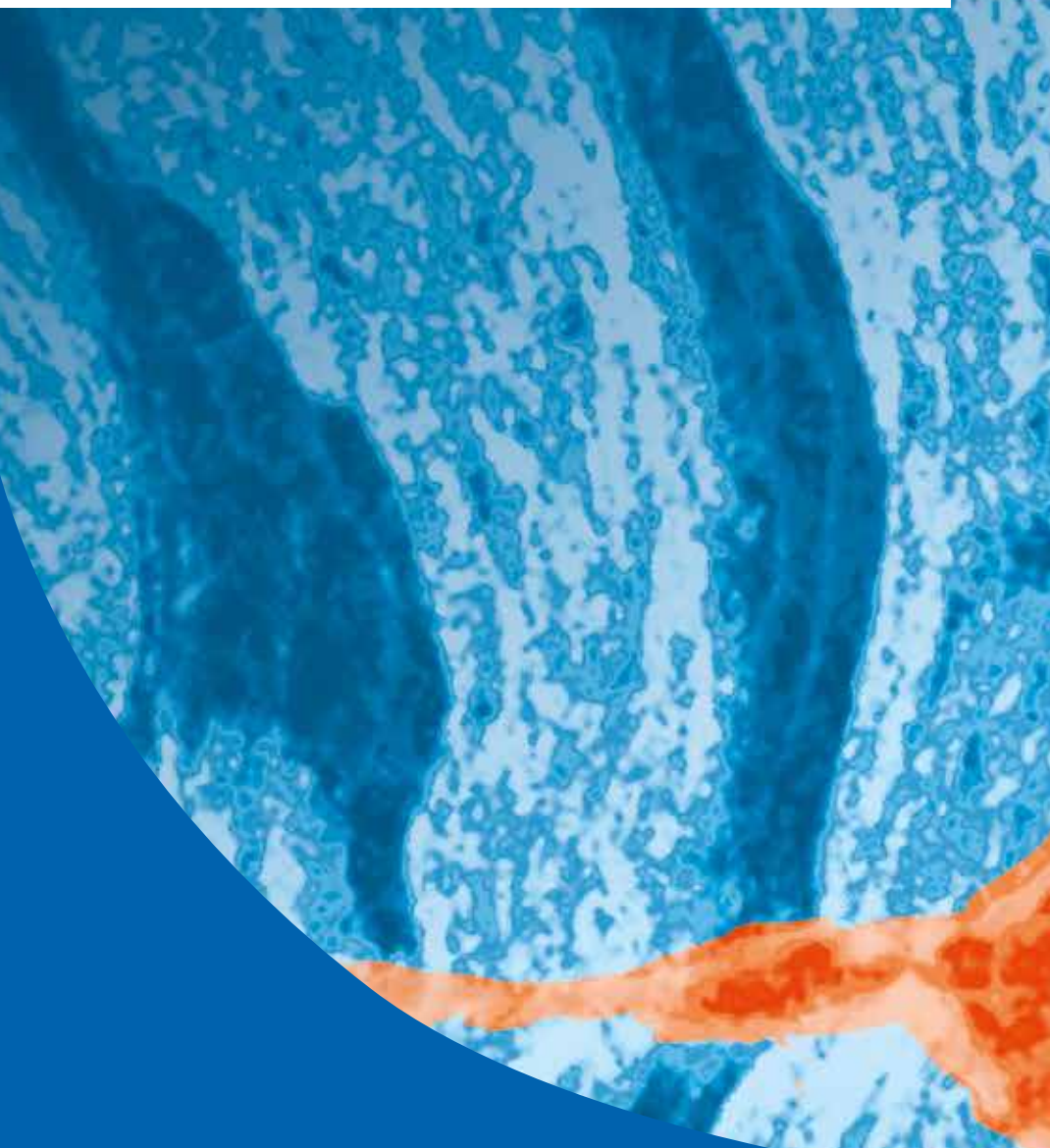

How does
one cell give rise to
an entire


organism?

How does one cell give rise to an entire organism?

Our bodies are composed of trillions of cells, of hundreds of different types, perfectly organised into sophisticated walking, talking, breathing and thinking systems. How they get that way is an incredible feat of coordination, specialisation, growth and refinement, and the instructions are all stored within a single fertilised egg.

At EMBL, we use different model organisms and cutting-edge technology to try to understand the developmental processes that bring this about – from the earliest decisions about what a cell should become to the formation of organs and bodies. Discovering how development has evolved gives us a fascinating insight into our origins and a deeper understanding of why these processes work the way they do.



- How can you capture a digital embryo?
- Evolving intelligence: what are the origins of the human brain?
- Can you pre-programme an egg?
- How do cells know where they are and what to become?

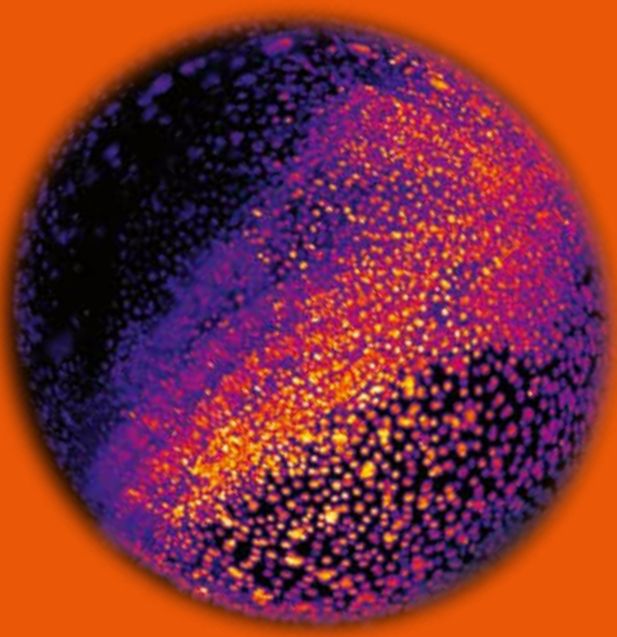
Dorsal closure in a *Drosophila* embryo.

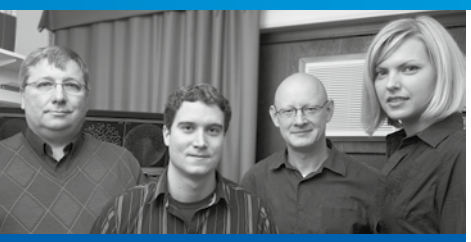
How can you capture a digital embryo?

Google Earth™-like model zooms in on development

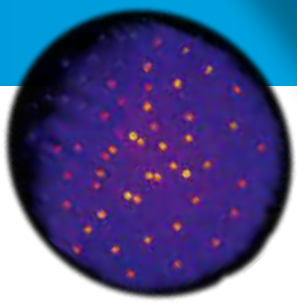
Embryonic development is a complicated choreography of cell division, differentiation and cell movement. A fertilised egg divides and divides, making a simple ball of cells which then begins to fold in on itself; sheets of cells push, pull, curl and envelop, individual cells crawl and squeeze. These cells are exposed to new embryonic environments where they receive new instructions they must integrate with their own genetic programmes.

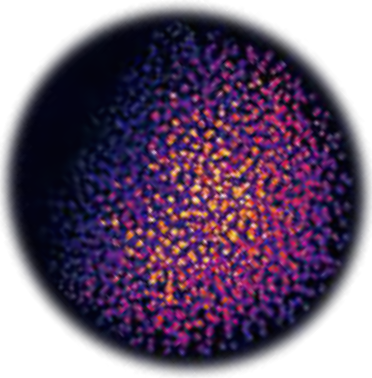
What if you could record every division, every cell movement in 3D, speed it up and play it back? What if you could play it in reverse, tracing the history of each cell: where it came from, the route it travelled, who it met along the way? In 2008 Jochen Wittbrodt and Ernst Stelzer's groups at EMBL Heidelberg managed just that. Pushing the limits of microscopy, they beautifully captured a developing zebrafish embryo in the first hours of life at unprecedented single-cell resolution – the digital embryo.

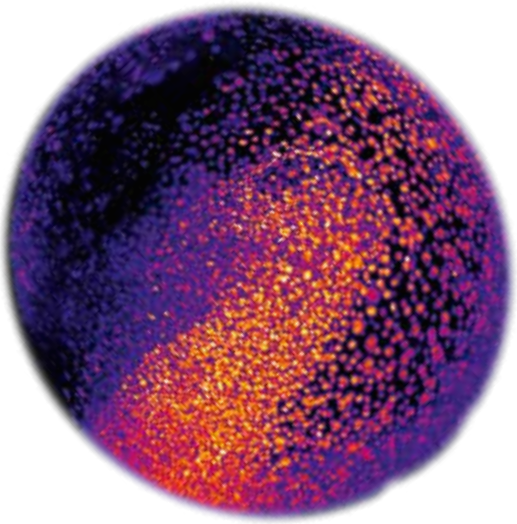




Ernst Stelzer, Philipp Keller, Jochen Wittbrodt and Annette Schmidt with the Digital Scanned Light Sheet Fluorescence Microscope they developed for the 3D imaging of biological samples.







The digital embryo, heralded by *Science* as one of the top ten scientific breakthroughs of 2008

Evolving intelligence: what are the origins of the human brain?

Detlev Arendt with Gáspár Jekely and Alexandru Denes

The marine ragworm *Platynereis dumerilii*

Humble beginnings of a very complex organ

At EMBL, Detlev Arendt and his group have been working to understand the earliest origins of our brains: how did our central nervous system come into existence? What did it look like hundreds of millions of years ago? And how did it function?

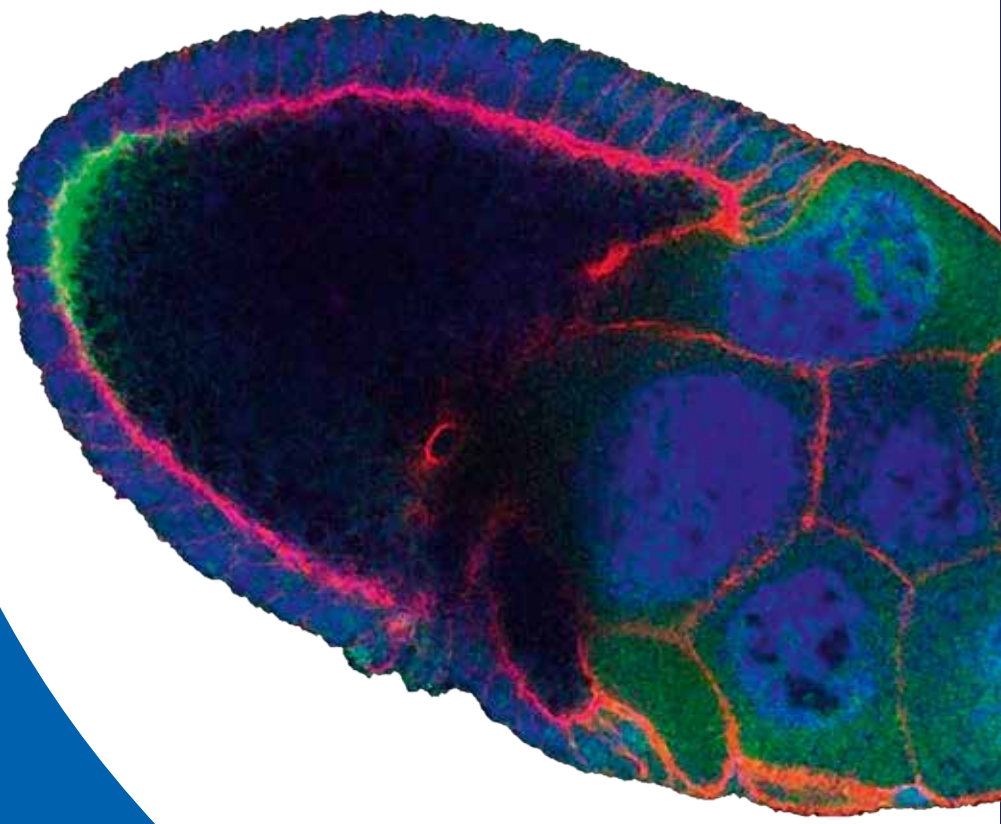
They are trying to reconstruct the brain of the Urbilateria – the roughly 600 million-year-old last common ancestor of all bilaterally symmetric animals, including worms, insects and vertebrates. By studying the marine ragworm *Platynereis dumerilii* – a living fossil still remarkably similar to its earliest ancestors – and comparing its development to that of other species, they learn what the brain of the Urbilateria would have looked like.

Their work is revealing fundamental similarities, suggesting that our central nervous system does indeed share a common origin with those of invertebrates, and shows how the twists and turns of evolution have shaped our complex brain.

Can you pre-programme an egg?

Anne Ephrussi

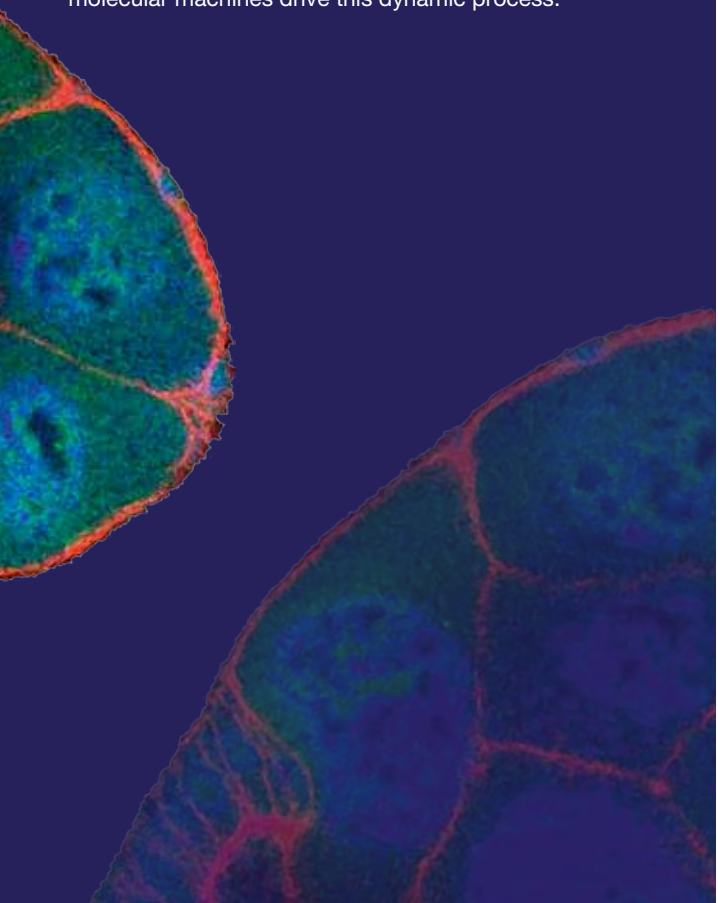
oskar mRNA (light green) is located at the posterior end of the fly's egg.

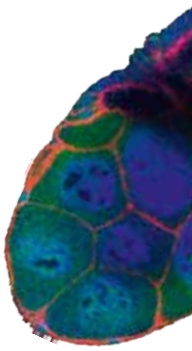


Laying down the molecular instructions for development

In many organisms, including the fruit fly Drosophila melanogaster, the first plans for future development are mapped out in the egg even before fertilisation. The instructions come in the form of messenger RNAs, long molecules that encode information copied from the mother's genes in neighbouring nurse cells. These are passed to the egg where they are transported to different locations, establishing the polarity that defines the future axes of the body.

Anne Ephrussi had identified one such mRNA, oskar, and brought it to EMBL. Remarkably, oskar mRNA travels the entire length of the egg to the posterior end before being translated into protein. At the time, no-one really knew how it was transported. Using state-of-the-art techniques to label and visualise oskar mRNA in transport, the Ephrussi group have revealed how different cellular components and molecular machines drive this dynamic process.





How do cells know where they are and what to become?

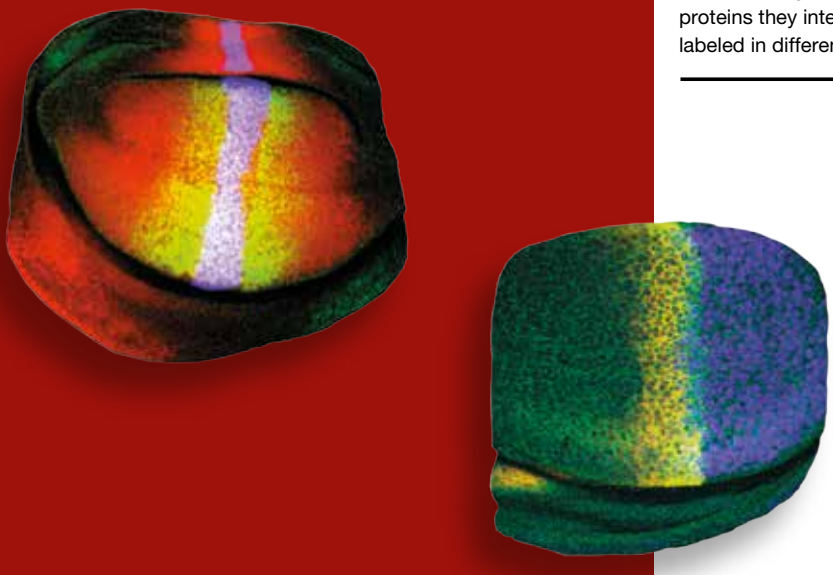
Ya-Wen Chen and Steve Cohen

The fruit fly *Drosophila*.

Molecular signals provide the coordinates for development

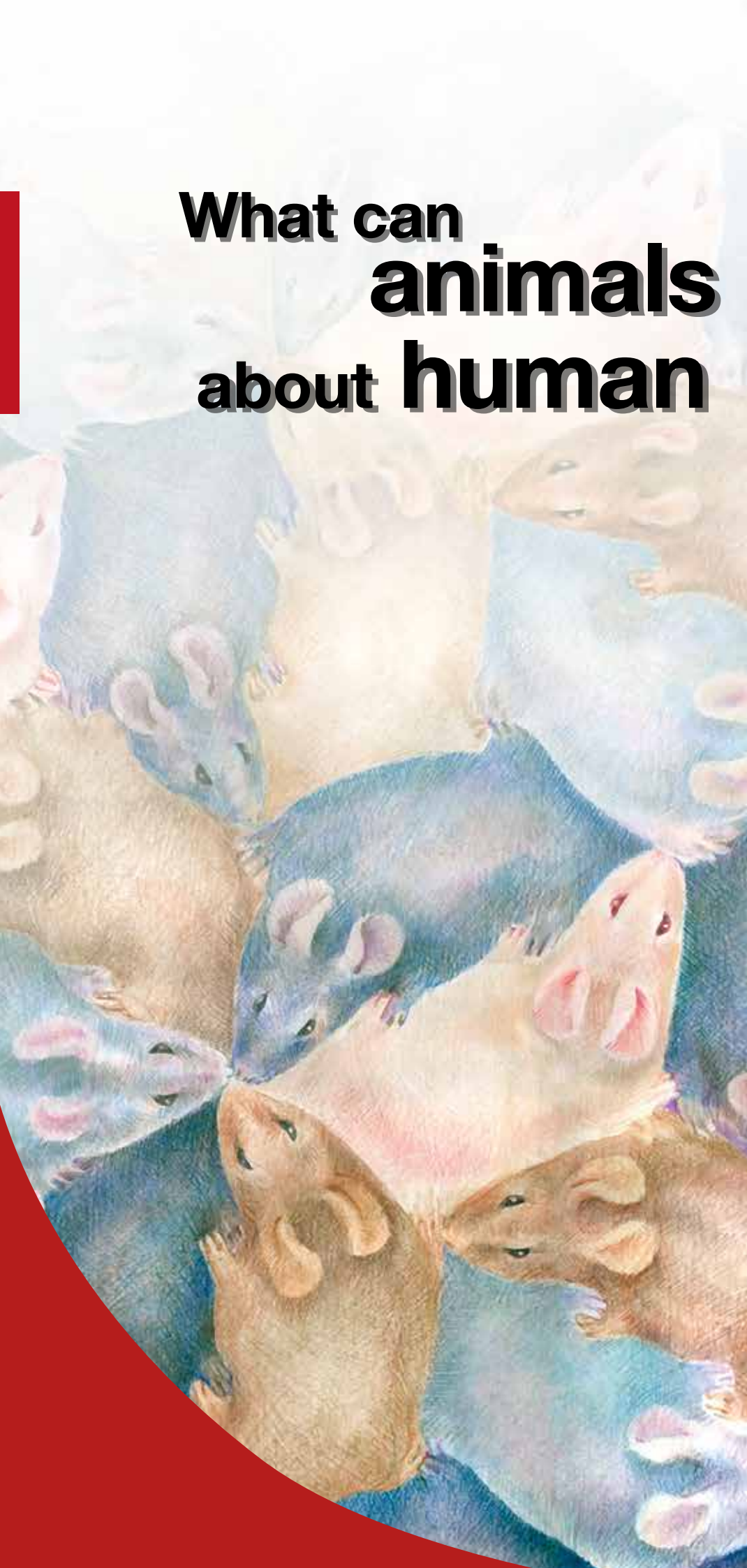
In the embryo, to know where you're going, you first need to know where you are. Cells take on different roles depending on where they find themselves. But how does a cell know where it is? We now know that such positional information is provided by morphogens – molecular signals transmitted from one point, their concentration gradually declining with distance. Cells read and interpret this information, often from combinations of different morphogens at different concentrations, and develop different fates accordingly.

Whilst the idea of morphogen gradients had long been popular, evidence that it could work in multicellular development was difficult to find. Steve Cohen and his team at the EMBL Heidelberg were among the first to clearly demonstrate this phenomenon with studies of how morphogens organise the development of wings and legs in the fruit fly, *Drosophila*.

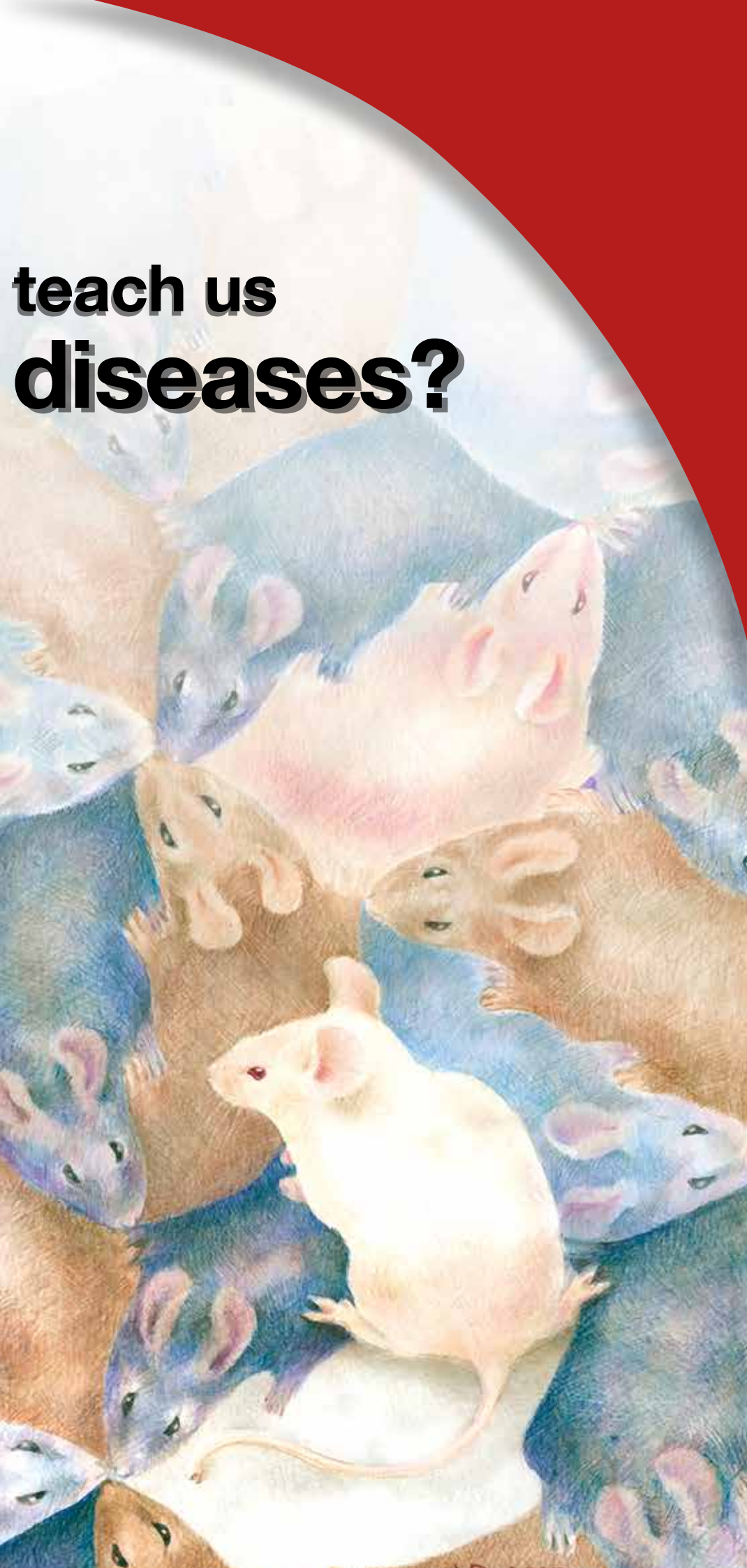


Wing discs of a fruit fly larva with morphogens and the proteins they interact with labeled in different colours.

What can animals about human



teach us
diseases?



What can animals teach us about human diseases?

Humans have been battling disease since time immemorial. In spite of the tremendous advances of modern medicine, there are still plenty of illnesses we cannot cure, and which are far from being fully understood. Technical and ethical issues make studying disease in humans difficult or impossible, but animal models often have the answer.

At EMBL we study diseases and their causes to understand what happens in our bodies, tissues, cells, and even genes when disease strikes.

We use sophisticated genetic techniques to model diseases in mice and look at how viruses and other pathogens attack the body, helping to find new approaches for prevention and treatment.

- Why does anxiety increase fear?
- How does a broken heart heal?
- Can mosquitoes help us to fight malaria?
- How do nerve cells grow?
- When is an intestine disease not an intestine disease?
- What is the secret of staying slim?

Mice are often our key to understanding human diseases.

More than is good for you?

Tackling iron overload disease

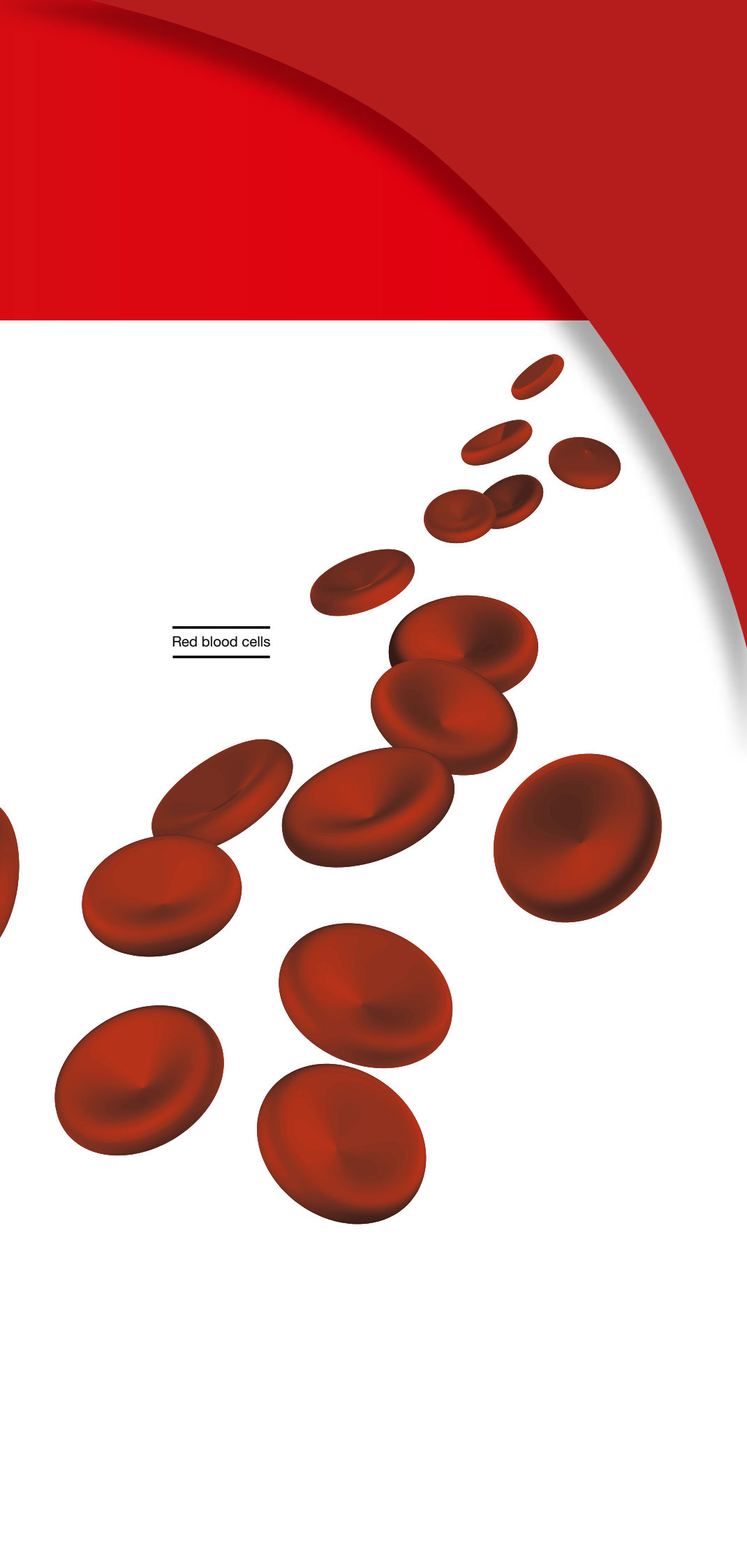
Iron is crucial for red blood cells to carry oxygen throughout our bodies, but too much of a good thing can be bad for you. Iron overload is the defining attribute of a common genetic disease – hereditary hemochromatosis, which affects roughly one in 300 people in Europe.

In people with hereditary hemochromatosis, the intestine absorbs too much iron. However, this is not an intestinal disorder, but a liver disorder, as the group of Matthias Hentze, Associate Director of EMBL, and EMBL Alumna Martina Muckenthaler from the University Clinic Heidelberg discovered.

Hentze, Muckenthaler and colleagues found that a specific gene makes the liver produce a hormone (called 'hepcidin') which decreases iron uptake in the intestine. In hemochromatosis patients, this gene is not sufficiently active, so iron uptake isn't controlled, and the metal accumulates, leading, if untreated, to fatal organ failure.

The scientists have also identified proteins that control how much iron is absorbed in the intestine, and found that a well-known drug used to treat high blood pressure helps remove excess iron from the body.

Matthias Hentze with Martina Muckenthaler from the University Clinic Heidelberg.


Red blood cells

How does a broken heart heal?

Piecing together muscle regeneration

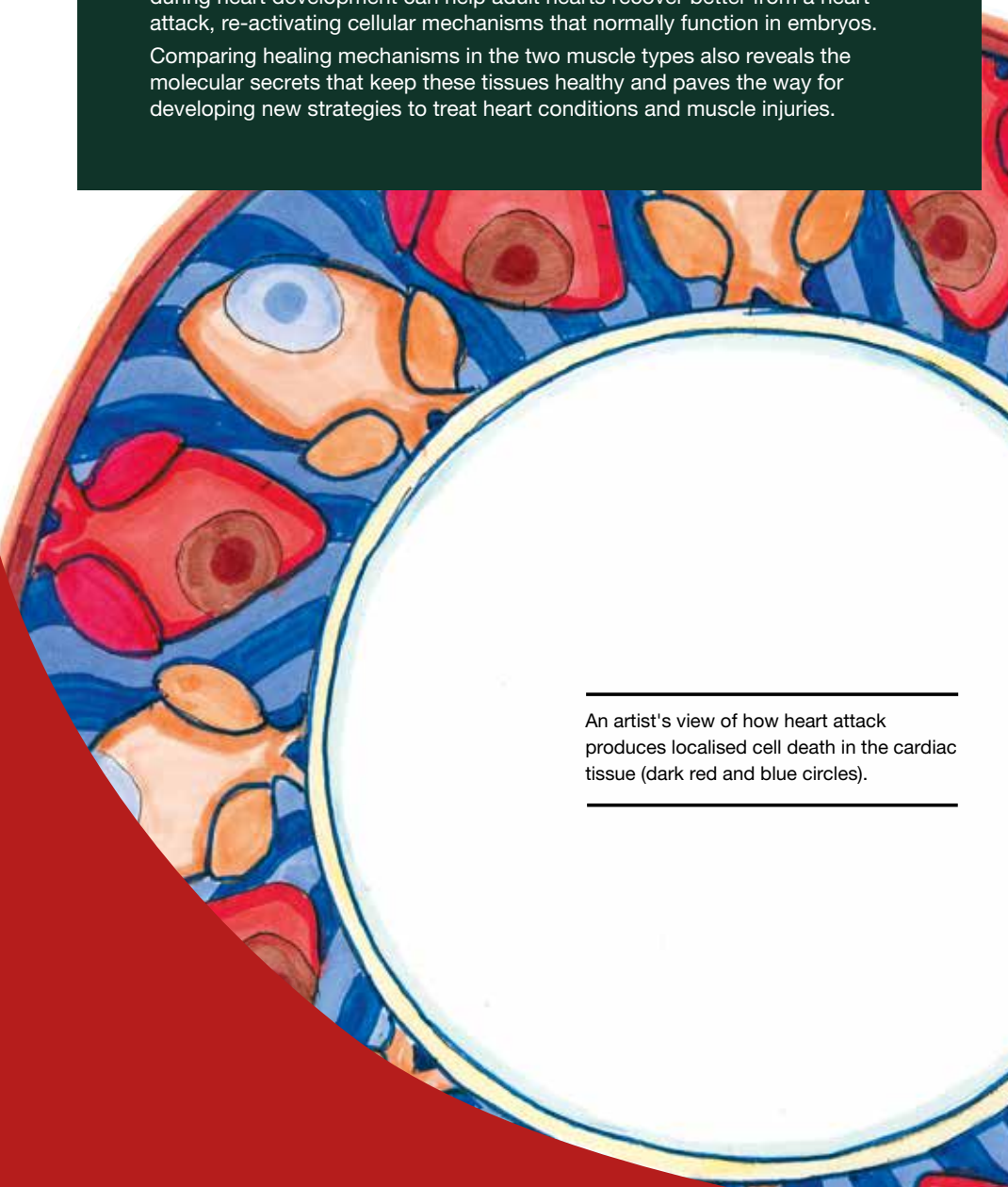
Only when we injure a muscle or know someone suffering from heart disease do we begin to appreciate just how complex muscles really are. Unfortunately, at that stage we are also confronted with the fact that muscles are not as efficient at repairing themselves as other tissues.

Nadia Rosenthal and her group at EMBL Monterotondo study how skeletal and heart muscle regenerate, aiming to find ways to improve muscles' healing ability.

How do muscles heal? The group discovered that white blood cells play a crucial role in promoting muscle regeneration after they remove debris, delivering molecular signals to ensure that lost muscle cells are replaced.

Heart muscle recovers even less well from injury. Rosenthal's group has highlighted how the effects of a single signaling molecule that plays a key role during heart development can help adult hearts recover better from a heart attack, re-activating cellular mechanisms that normally function in embryos.

Comparing healing mechanisms in the two muscle types also reveals the molecular secrets that keep these tissues healthy and paves the way for developing new strategies to treat heart conditions and muscle injuries.



An artist's view of how heart attack produces localised cell death in the cardiac tissue (dark red and blue circles).

Nadia Rosenthal

An artist's view of how, in response to damage (black lightning) the heart must rapidly rebuild the vascular system (dark red), to resume blood flow (orange spirals) to the injured tissues (red cells).

Are you afraid?

Learning, memory, and deciding when to run

Some situations are harmless, some are dangerous. But others are ambiguous: they may become dangerous, or they may not. Most people can cope with such a situation. However, people suffering from pathological anxiety over-react and run away.

Cornelius Gross and his group at EMBL Monterotondo discovered that the hippocampus, a region of the brain involved in learning and memory, may play an important role in this risk assessment process. The other key player, they found, is a receptor for serotonin, a messenger molecule which is known to be involved in depression and anxiety. Mice without this receptor over-react to ambiguous situations but if neural activity in a specific region of their hippocampus is blocked, the balance is restored and they react normally again.

While further investigating the receptor's role in anxiety, the Gross group discovered that serotonin imbalance may also be related to sudden infant death syndrome (SIDS), or crib death, and created a mouse model for this condition.

Cornelius Gross

False-coloured images of the region of the hippocampus involved in anxiety in mice.

What’s the secret to staying slim?

The neuronal connection

Our weight is essentially a balance between how much we eat and how much we move. However, this isn’t as simple as it seems, because a substantial part of our physical activity is actually involuntary movements such as fidgeting while working at the computer. When we are hungry, this spontaneous activity increases and provides us with the drive to go and find food.

Mathias Treier and his group at EMBL Heidelberg identified the protein that makes this connection in mice. When hunger signals from the body reach the brain, this protein regulates the production of hormones that promote feeding. Mice without this protein feel no hunger, so their spontaneous activity decreases. However, such mice in Treier’s lab actually gained weight, because they moved much less, but could eat anyway as food was provided for them without the need to forage. With obesity becoming a rising concern in societies with constant food availability, this protein, which is likely to play a similar role in humans, may help us find the secret to staying slim.

Mathias Treier and Henriette Uhlenhaut

Obesity could be connected to fidgeting – an artistic interpretation inspired by Keith Haring's artwork.

How do mosquitoes do it?

Fotis Kafatos and Thanassis Lourekis

Biting back at the malaria parasite

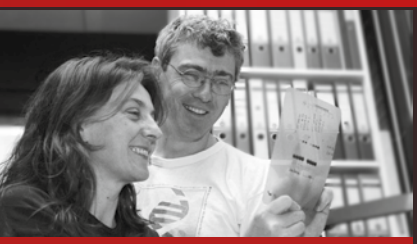
With around 250 million new cases and almost a million deaths per year, malaria is a heavy burden, both on lives and on the economies of affected countries. It is caused by a single-celled organism called *Plasmodium*, which is transmitted to humans by infected mosquitoes. But not all mosquitoes become infected – within the same species, some individuals are resistant to *Plasmodium*, while others are susceptible.

Fotis Kafatos, former Director General of EMBL, who led the effort to sequence the mosquito genome in 2002, looked at why and how some mosquitoes resist malaria, in the hope of making them our allies in the fight against the disease. His group identified a genetic difference that determines whether a mosquito is resistant or susceptible to the parasite.

Mosquito eradication programmes are an important part of the fight against malaria. If we can distinguish between resistant and susceptible mosquitoes in the wild, such programmes could be restricted to areas where they are most necessary: areas where most mosquitoes are susceptible, and therefore likely to carry the disease.

This mosquito had a hearty meal.

How do growing neurons find their way?



Liliana Minichiello and Rüdiger Klein

A tale of role-switching proteins

For brain cells, connections are crucial. A single neuron may rely on tens of thousands of connections to send and receive the impulses that ultimately create thoughts. As the brain forms, each neuron extends a single arm, or axon, which will transmit these impulses to other cells. To find its path, the growing axon tip probes its molecular environment through proteins like ephrins and their receptors, Ephs.

Scientists believed that a growing axon used Eph receptors to detect which kind of ephrins the cells around it were producing, and navigated its route accordingly. Rüdiger Klein and his group at EMBL Heidelberg, however, found that in some areas of the developing brain, a rare role-reversal occurs. Instead of being molecular signposts, the ephrins themselves act as receptors, transmitting information back to the cells they're produced by. The Klein group made their discovery using mouse models, but we now know the same is true for humans, so these proteins' ability to switch roles played an important part in your own development too.

Growing neurons in the developing brain.