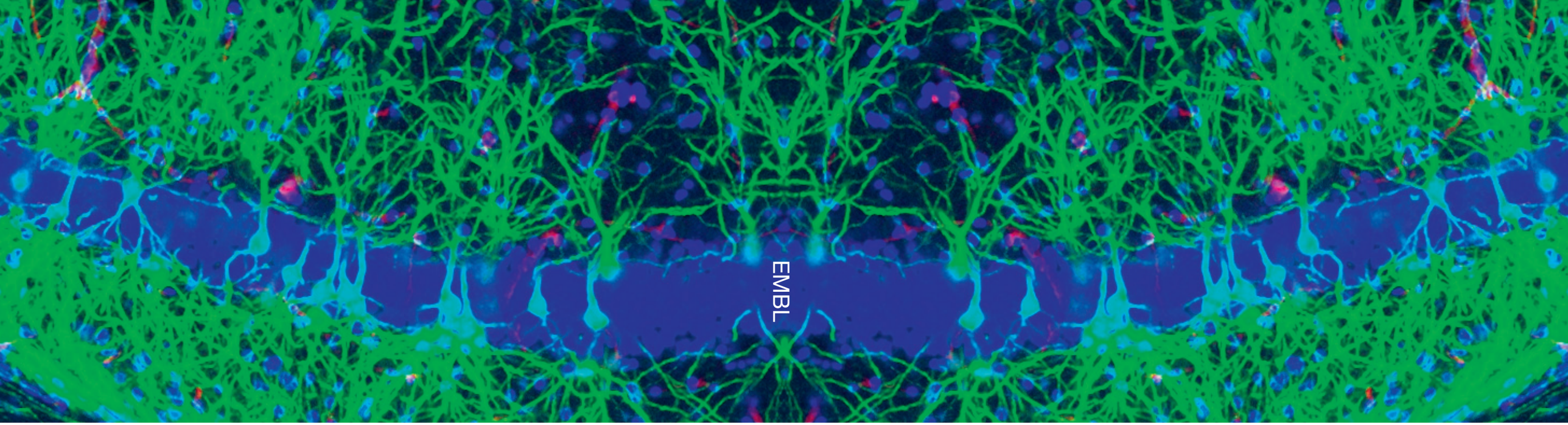

EMBL

EMBL Annual Report 2010-2011

Annual Report

2010-2011

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Iain Mattaj

Contributors
Claire Ainsworth, Chloe Balharry, Adam Gristwood, Dan Jones, Corinne Kox, Angela Michel, Sarah Stanley, Mary Todd, Anna-Lynn Wegener

Photography
EMBL Photolab (Hugo Neves, Udo Ringeisen, Marietta Schupp); p.16: K. Hodivala-Dilke & M. Stone, Wellcome Images; p.17: Annie Cavanagh, Wellcome Images; p.18: Anne Weston, LRI, CRUK, Wellcome Images; p.32/35: ESO/Mario Nonino, Piero Rosati and the ESO GOODS Team; p.98: Norman Seef

Artwork
Petra Riedinger

Layout
Nicola Graf

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EMBL Heidelberg
Meyerhofstraße 1
69117 Heidelberg
Germany

Tel. +49 (0)6221 387 0
Fax +49 (0)6221 387 8306

EMBL Grenoble
6, rue Jules Horowitz, BP 181
38042 Grenoble, Cedex 9
France

Tel. +33 (0)4 76 20 72 69
Fax +33 (0)4 76 20 71 99

EMBL Hamburg
c/o DESY
Notkestraße 85
22603 Hamburg
Germany
Tel. +49 (0)40 89 902 0
Fax +49 (0)40 89 902 104

EMBL-EBI
Wellcome Trust Genome
Campus, Hinxton
Cambridge CB10 1SD
United Kingdom
Tel. +44 (0)1223 494 444
Fax +44 (0)1223 494 468

EMBL Monterotondo
Adriano Buzzati-Traverso Campus
Via Ramarini, 32
00016 Monterotondo (Rome)
Italy
Tel. +39 06 900 912 85
Fax +39 06 900 912 72

www.embl.org

Annual Report 2010-2011

European Molecular Biology Laboratory

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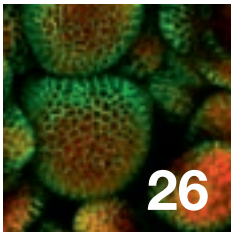
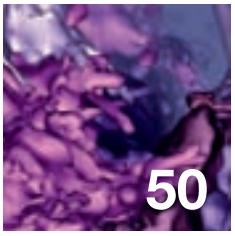


Going with the flow



50 Elementary connections

74 Growing strong

‘It takes all the running you can do...

...to keep in the same place’. Lewis Carroll’s famous quote has been cited countless times in the context of evolutionary biology. I feel it also captures very well how life at EMBL often feels. But, just like the biological systems studied in its laboratories, EMBL is in fact continuously evolving: evolving to pursue new scientific trends, evolving to improve its services and the training it provides to its staff and the scientific community, and evolving to keep trying to offer the greatest possible value to its member states. This constant change profoundly refines the activities of the Laboratory.

The rapid pace of EMBL’s evolution never ceases to amaze me. Looking back to the beginnings of the current EMBL Programme in 2007, I realise that well over a quarter of EMBL’s faculty has turned over. While attracting new talent every year is a challenge, it comes with the unique and exciting opportunity to continually reshape the lab in terms of expertise, skills and focus. In the past few years we have added expertise in the areas of chemical biology, quantitative imaging, biophysics, modelling and simulation, and microfluidics to our research units; we have geared our training programmes towards promoting interdisciplinarity and we have advanced our services to promote the optimal integration of different types of data and technologies.

EMBL is continuously reinventing itself, evolving to meet the changing needs of its member states and their scientific communities. With this Annual Report, and the highlights it features of the past year, I hope to give you a flavour of EMBL evolution at work.

Iain W. Mattaj
Director General

State of the Laboratory

The time when EMBL's dynamic evolution becomes most apparent is every five years, when it produces its strategic outline for the next quinquennium, the EMBL Programme. In the Summer Council meeting last year the EMBL Programme 2012-2016 was presented to Council for the first time, following a very positive evaluation of EMBL's plans by the Scientific Advisory Committee that had taken place in May 2010. The EMBL Programme is an integrated strategy that details the plans for the entire institute, including not only its efforts in basic molecular biology research, but also in activities such as service provision, training, technology development and transfer and the integration of European research. Consequently, the EMBL Programme was developed in a bottom-up process that involved input from faculty and administrative staff from all parts of the organisation. In the course of 2011 the EMBL Programme will be discussed further with EMBL Council, who must both approve the plans and decide on an accompanying Indicative Scheme detailing EMBL's budget for the period of 2012-2016.

The theme of the EMBL Programme 2012-2016 is 'Information Biology', a name chosen to reflect that over the past years the bottleneck in systems biology, the topic of the 2007-2011 EMBL Programme, is shifting from data production to turning data into knowledge and an understanding of biological processes. This is the challenge that EMBL will begin to face in the next five years. The Laboratory is well prepared to do so, on the basis of the interdisciplinary expertise collectively represented by EMBL faculty. Within the framework of Information Biology the thematic research areas will be: bridging the scales of biological organisation; biology in four dimensions; predictive networks and models; generating quantitative data; analysing, integrating and exploiting quantitative data; inter-species variation; intra-species variation; and disease models and mechanisms. There are naturally also ambitious future plans for EMBL activities in the areas of service, training, technology transfer and international relations and integration.

All of EMBL's future plans build on the many current activities ongoing in the Laboratory. Some representative highlights of these from the past year are featured in this report.

Research

Structural and Computational Biology

2010 has been a very successful year for the Structural and Computational Biology (SCB) Unit in Heidelberg. The four-yearly scientific review of the Unit took place on 6 and 7 May. The review panel of external experts highly appreciated the quality and international standing of the Unit and was impressed by the achievements, the perspectives and the collaborative attitude of all members of the SCB Unit (see page xxv for a more detailed report on the SCB evaluation). Much of the Unit's success can be attributed to the joint Heads of Unit, Christoph Müller and Peer Bork. In November 2010, Peer was awarded a prestigious European Research Council Advanced Investigator Grant for pioneering research into microbial communities associated with cancer. The project, entitled 'CancerBiome', was selected from more than 600 proposals. For this project, Peer will use the metagenomics approach that he has developed in the past year while studying the bacteria of the human digestive system in the context of the international consortium MetaHIT. Sequencing DNA fragments found in the gut environment of people from three different continents, Peer and his team discovered that people can be categorised into three 'Enterotypes' on the basis of the composition of the bacteria that live in their gut. This information is likely to have implications for how people react to diet and drugs (page 60).

Another research highlight produced by the SCB Unit in the past year came from a collaboration of structural biologists in Heidelberg and Grenoble. Teresa Carlomagno and Ramesh Pillai combined their expertise to understand the structural details of the mechanism by which cells shut down genetic parasites, called transposons, that can have detrimental effect on health (page 64). In order to follow up on their investigation of the process of

transposon silencing, the two group leaders now share an EMBL Interdisciplinary Postdoctoral (EIPOD) position.

Like their colleagues in Heidelberg and Grenoble the structural biologists at EMBL Hamburg have had a busy year. The group of Unit Head Matthias Wilmanns determined the high-resolution structure of a key enzyme of the tuberculosis-causing agent *Mycobacterium tuberculosis*. The enzyme is required for the synthesis of two vital amino acids in the bacterium and the Hamburg scientists revealed how it binds to its substrates. The insights gained provide an interesting new angle from which to pursue the development of anti-tuberculosis drugs (see page 25).

Professor Johanna Wanka, Professor Annette Schavan, and Dr Herlind Gundelach with the signed agreement contract for the building of the CSSB.

The ground for more such cutting-edge research in Hamburg was laid in January 2011 when the official agreement to build a new Centre for Structural Systems Biology (CSSB) on the campus of the German Electron Synchrotron (DESY) was signed by Germany's Federal Minister for Education and Research, Professor Annette Schavan; the Hamburg senator for science, Dr Herlind Gundelach; and the minister for science and culture from Lower Saxony, Professor Johanna Wanka. The CSSB will be an interdisciplinary research centre that bridges the gap between structural and systems biology and the cooperation between universities from across northern Germany, as well as EMBL and the Helmholtz and Leibniz institutes, will enable leading research groups to exploit the current and future ultra-modern radiation sources at DESY for biological research. In total, €50 million will be invested in the project and construction of the new facilities is scheduled to begin in 2012.

On 3 November 2010, EMBL Hamburg group leader Dmitri Svergun was honoured with a prestigious international prize for developments in nanodiagnostics for his work in the field of Small Angle X-ray Scattering (SAXS) at a plenary ceremony of the Rusnano Forum in Moscow, opened by the Russian president Dmitry Medvedev. The award recognises the rapidly growing scientific and commercial applications of SAXS in areas such as materials science, biology and medicine.

Cell Biology and Biophysics

Researchers in the Cell Biology and Biophysics (CBB) Unit have made significant advances in instrumentation development over the course of the past year. Head of Unit, Jan Ellenberg, and Head of the Advanced Light Microscopy Facility, Rainer Pepperkok, have developed a piece of software, called Micropilot, that searches through a microscopy sample and locates the right cells on which to automatically perform complex experiments. The new software will be used by two international consortia funded by the European Commission (EC) in which Jan and Rainer participate: MitoSys, to produce high-resolution movies of aspects of the cell division process; and Systems Microscopy, to measure the interactions between proteins inside cells, and to study how these interactions fluctuate over time. The new software has already generated interest from the wider scientific community, to whom it is freely available as open source code (page 39).

EMBL scientific publications and collaborations

Total number of peer-reviewed publications: 345

Internal collaborations: Publications co-authored by more than one EMBL group leader: 28

External collaborations: 878 in total of which 87 resulted in publications

In an inter-Unit collaboration, Marko Kaksonen from the CBB and John Briggs from the SCB Unit have developed a new technique to combine fluorescence microscopy and electron tomography, two imaging technologies that allow biological processes to be studied at very different resolutions. They have applied their new methodology to the mechanism of vesicle formation at cell membranes to help elucidate the details of how viruses infect host cells (page 4).

Bioinformatics & Genome Biology

Last year saw the completion of the pilot phase of the 1000 Genomes Project, a major international collaboration that involves several scientists from both EMBL-EBI and the Genome Biology Unit in EMBL Heidelberg and which aims to build a detailed map of human genetic variation. A team of researchers at EMBL-EBI, led by Paul Flicek, helped to determine the best strategy for characterising more than 95% of the genetic variants that can be found in 1% or more of three different geographic population groups (page 28). Meanwhile, Jan Korbel and his team at the Genome Biology Unit in Heidelberg undertook a detailed analysis of data from 185 human genomes sequenced in the course of the 1000 Genomes Project and identified the genetic sequence of an unprecedented 28 000 structural variants, which are large portions of the human genome that differ from one person to another. The data and insights generated could shed light on how a person's genetic makeup may contribute to specific illnesses and also begin to explain why certain parts of the human genome change more rapidly than others (page 89). All the data from the 1000 Genomes Project, which by the end of 2012 aims to encompass 2500 human genomes, are continuously made publicly available through the databases of EMBL-EBI and the US National Center for Biotechnology Information (NCBI) to enable them to be accessed and analysed by the global scientific community.

Mouse Biology & Developmental Biology

At EMBL Monterotondo the search for a new Head of Unit to replace Nadia Rosenthal has been initiated. Nadia will take up the position of Scientific Head of the EMBL Australia partnership laboratory as well as the post of Director of the Australian Regenerative Medicine Institute at Monash University in Melbourne. In the meantime, Monterotondo's research effort is going strong. Deputy Head of Outstation, Cornelius Gross, has discovered a neural switch that controls fear (see page 76), whereas group leader Donal O'Carroll and his team have identified molecules that ensure continued red blood cell production. In collaboration with Anton Enright's group at EMBL-EBI, they combined experimental and bioinformatics approaches and discovered how two small RNA molecules fine-tune a multitude of genes involved in red blood cell formation (see page 38).

At EMBL Heidelberg, fellow mouse biologist François Spitz of the Developmental Biology Unit developed a new method to study gene regulation. The approach is based on a jumping gene and enables researchers to systematically explore the large parts of the genome that do not encode proteins but control when, where and to what extent genes are turned on, or expressed (see page 57). Another research highlight of the Developmental Biology Unit was Detlev Arendt's discovery of an invertebrate counterpart of the cerebral cortex – the part of the human brain that houses most higher cognitive functions such as consciousness or attention – in a marine worm. Detlev's findings indicate that these brain structures are evolutionarily much older than previously thought, probably as old as the first higher animals (see page 13).

Services

Structural Biology

Both of EMBL's structural biology outstations in Hamburg and Grenoble provide access to state-of-the-art synchrotron infrastructures for application in the life sciences. Over the past years both EMBL sites have started to complement their beamlines with advanced facilities for preparing and characterising samples, as well as for automatic processing and evaluation of data from the X-ray experiments (see pages 46 ff). EMBL Grenoble and Hamburg jointly registered 2911 users in 2010.

The PETRA III experimental hall.

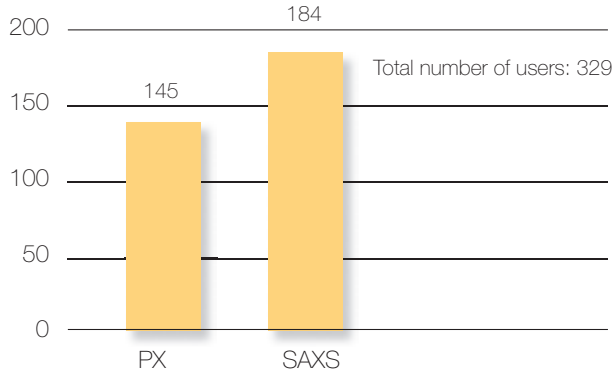
Following three-and-a-half-years of development, EMBL Hamburg has seen the first beams in its BioSAXS and macromolecular X-ray crystallography (MX) beamlines that take X-rays from PETRA III, the new high-brilliance synchrotron radiation source on the DESY site in Hamburg. Just eight months after PETRA III was officially inaugurated with the help of Germany's Federal Minister for Education and Research, the first beam was successfully guided into the SAXS beamline on 15 July 2010. Less than five months later, the first monochromatic beams were achieved on EMBL's two MX beamlines: MX1 and MX2. Both are microfocus beamlines with the ability to work with crystals much smaller than those used in regular X-ray crystallography.

The first users to benefit from the facility are expected at the BioSAXS beamline before the end of the year. They will be able to take advantage of the integrated EMBL facilities available for structural biology in the new PETRA III annex building. Alongside the three synchrotron radiation beamlines, the EMBL@PETRA3 facility houses laboratories for sample characterisation using biophysical methods, an automated pipeline for high-throughput crystallisation, and software services for automated processing of X-ray data. The high-throughput crystallisation facility has been serving the general user community since 2005. Last summer, the facility was moved from the other side of the DESY campus to its new building 48e, adjacent to the PETRA III experimental hall.

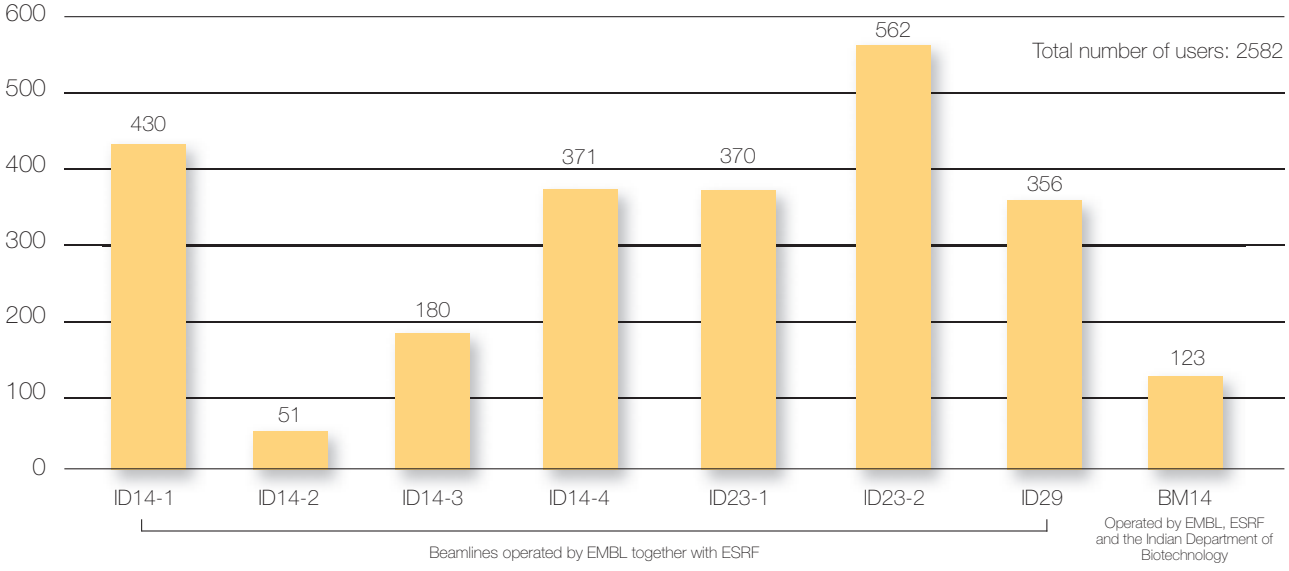
The integrated services offered by EMBL@PETRA3 as well as the ESPRIT and MultiBac platforms at EMBL Grenoble and the Advanced Light Microscopy Facility in Heidelberg, are available to the general user community through the European FP7 initiative, P-Cube. P-Cube reached its halfway mark in March 2011 and during its first two years has enabled almost 100 European scientists to carry out high-profile research projects at the EMBL technology platforms. In addition to providing access to structural biology infrastructure, the project supports activities to further improve and automate methods at each of the participating infrastructures and aims to disseminate know-how through specialised training courses.

In Grenoble two prestigious grants under the French 'Invest in the Future' initiative have been awarded to the Unit of Virus Host Cell Interactions (UVHCI), the joint research unit involving EMBL, the University Joseph Fourier and the French National Centre for Scientific Research (CNRS) and several other partners. The €14.7 million Grenoble Alliance for Integrated Structural Biology (GRAL) project brings together UVHCI, the Institute for Structural Biology (IBS) and the Institute of Life Sciences Research and Technologies (IRTSV) to combine structural and integrative cell biology to study

Beamline Users EMBL Hamburg 2010



Beamline Users EMBL Grenoble 2010



cellular metabolism and virus–host interactions. The second grant, for the French Infrastructure for Integrated Structural Biology (FRISBI) project, awarded around €12 million to UVHCI and IBS to finance large structural biology equipment for, for example, nuclear magnetic resonance (NMR) and electron microscopy (EM) studies to further our understanding of how viruses and bacteria interact with their cellular environment.

Bioinformatics Services

The service mission of EMBL-EBI is to provide biomolecular data resources and the tools to explore them for biological and medical research. These services are used by scientists working in academia and industry within Europe and beyond. Several hundred thousand independent users access the EMBL-EBI's resources every month through its website, which in 2010 received an average of 4.6 million hits every day.

At the beginning of 2011 the EMBL-EBI services were reviewed by an external panel of experts, who acknowledged EMBL-EBI as a leading force and a key partner in global life science projects and judged its services as world class (see page xxvii). The EMBL-EBI's current leadership, Director Janet Thornton and Associate Director Graham Cameron, were highly praised for their roles in developing the EMBL-EBI. For Graham, who directly oversees the EMBL-EBI services, this will be his last review. He announced that he will be retiring at the end of March 2012 and EMBL's leadership will soon initiate the search for an adequate successor.

EMBL-EBI is continuously updating and improving its databases and tools to provide the best possible service to researchers around the world. For example, ChEMBL, EMBL-EBI's database of bioactive compounds (drugs and drug-like molecules), was launched in January 2010 to address a crucial gap in the landscape of publicly available biomedical data. Since its launch it has grown substantially in size (an increase of over 50% in bioactivity content) and already contains more than 3 million experimental bioactivities and 750 000 compounds. A further addition to the EMBL-EBI's data repertoire is the European Nucleotide Archive (ENA), which was launched in May 2010 (page 95). It contains carefully annotated and cross-linked sequence records from the EMBL Nucleotide Sequence Database (EMBL-Bank) and provides direct access to raw sequence data. Furthermore, over the past year, a pilot version of the BioSample Database, which will contain information about biological samples used in experiments, has been developed.

An ongoing effort at EMBL-EBI is the integration and standardisation of different types of data. The EMBL-EBI service teams are developing new portals and mechanisms to allow data that have been traditionally held in different resources to be seamlessly integrated using both the web and programmatic interfaces. One such development is the new EMBL-EBI search and browse engine, which was launched in January 2011. Its unique, intuitive search service is a huge simplification for non-expert users exploring the data (page 68). With more than 300 million entries indexed and updated daily, the search provides an efficient gateway to all of the major EMBL-EBI data collections. Integration is also a key issue with regard to the organisational and managerial structure of the EMBL-EBI service teams. In the past year some internal restructuring took place that has created a more layered management structure that is better suited to handling integration demands. Three new team leaders have joined EMBL-EBI services to support the Functional Genomics group and the protein structure database (PDBe).

Apart from data integration, unprecedented data growth is a second major challenge for EMBL-EBI. Owing to the wide uptake of next-generation sequencing and other ultra-high-throughput technologies, current submission rates of DNA sequencing data already exceed half a million bases per second. Large-scale projects such as the sequencing of 25 000 cancer genomes, planned by the International Cancer Genome Consortium, will greatly increase the current demand on manpower and storage capacity. It is hoped that the emerging European Life Science Infrastructure for Biological Information (ELIXIR) (see page xv for more detail) will provide a sustainable solution to this problem.

Core Facilities and IT Services

EMBL operates eight Core Facilities in the areas of genomics, proteomics, protein expression and purification, monoclonal antibody production, chemical biology, advanced light microscopy, electron microscopy and flow cytometry. The Core Facilities offer cutting-edge technology and support to researchers at EMBL and, when sufficient capacity is available, to external users.

In August 2010 the Advanced Light Microscopy Facility (ALMF) moved into a newly refurbished facility, which now houses all 29 microscope systems including those for high-throughput microscopy. Offices for visitors and ALMF staff, tissue culture and wet-lab facilities for visitors are now in close proximity to the microscopes and thus significantly enhance the efficiency and quality of the service provided.

In January 2011 the central information technology (IT) Services, which operate the IT infrastructure and provide

services to users in Heidelberg and Monterotondo, moved to a newly established IT centre in the remodelled building 13 of the main Laboratory. With the growing demands for central IT infrastructure it became clear that the old Heidelberg data centre would soon reach its maximum capacity. The new data centre implements the latest technologies to improve efficiency and resource use and to reduce overall operational costs. The shift to a largely virtualised server infrastructure during the past year further rationalised the needs for energy and space. The capacity of the new facility can grow incrementally in terms of energy and cooling and it should be sufficient to cover the Laboratory's increasing demands for IT infrastructure for the next eight to ten years.

Training

The EMBL International Centre for Advanced Training (EICAT) offers a variety of intramural and extramural training activities for EMBL staff and the scientific community at all of EMBL's sites and in the EMBL member states. In 2010 EICAT underwent some management restructuring. In addition to her leading role in the EMBL International PhD Programme, Helke Hillebrand, Dean of Graduate Studies, took on the responsibility for the Postdoctoral Programme and now has overall responsibility for EMBL's intramural training activities. Instead of refilling the position of overall EICAT coordinator, a second position, analogous to Helke's but dedicated to extramural training, was created and filled by Andy Robertson, who used to be the scientific organiser of the Keystone conference series.

The EMBL International PhD Programme, founded in 1983, is approaching the completion of three decades dedicated to training and inspiring the next generation of scientists. Interest in the Programme remains strong, making it one of Europe's most competitive PhD Programmes in the life sciences. Applicant numbers in 2010 again exceeded 1000 and the 55 students attending the predoc core course held in Heidelberg from October to December 2010 formed the largest PhD starting class to date. The core course is intended to provide students with an overview of all of EMBL's activities and introduce them to the breadth of topics covered by EMBL's research. In the second year of their studies all students benefit from a hands-on course in bioinformatics organised at the EMBL-EBI, which, starting from 2010, also includes an entire day dedicated to scientific writing. Moreover, EMBL offers a set of complementary skills courses that students can choose to follow during the course of their PhD to enrich their communication, IT or language skills.

The cafeteria in Hinxton.

In the Postdoctoral Programme, the 'second mentor scheme' was initiated in 2009 to provide EMBL postdocs with an additional source of advice and guidance during their time at EMBL, and is actively used by the majority of the postdoc community. Training initiatives, such as the biannual Workshop "Preparing for the Academic Job Market" and the general Career Development Courses organised by Human Resources have also found a very positive response among EMBL's postdocs. In its fourth year, the EMBL Interdisciplinary Postdoctoral (EIPOD) Programme, co-funded by the EU FP7 Marie-Curie actions, has expanded to reach its steady state level of 60 fellows. The current EIPOD population represents 26 different countries. Building on the strong collaboration between the EMBL-EBI and the Wellcome Trust Sanger Institute and modelled after the successful EIPOD Programme, fellowships are now available for postdocs to work on projects that involve two laboratories based at the two Hinxton institutes.

The European Learning Lab for the Life Sciences (ELLS), which aims to bridge the gap between cutting-edge life science research and the classroom, organised four courses for 94 secondary school teachers in Germany and Italy in the course of the past year. In December, ELLS realised the first of a new series of lectures – the EMBL Insight Lectures – that are aimed at students aged 16 years and above. Genome Biology group leader Jan Korbel presented recent advances in DNA sequencing technology and human genome analysis, and the

possible implications that these might have for disease research in the future. The ELLS team in Monterotondo participated in a pilot project within the framework of the University of Milan's uniStem initiative. This long-term project involved almost 500 students and 20 teachers for half a school year, and has established a network of schools, scientists and educators in Italy through a discovery journey on stem cells.

On 9 March 2011 the EMBL Advanced Training Centre building at EMBL Heidelberg celebrated its first birthday and looked back on a year that has surpassed all expectations. All in all the 35 conferences and meetings and 26 courses that took place there brought together nearly 7000 delegates, organisers, speakers and exhibitors at EMBL. Particularly successful were the events of the Vision 2020 lecture series that was designed for the EMBL Advanced Training Centre's inaugural year. In these lectures, which regularly reached the capacity of the 466-seat Klaus Tschira auditorium, five Nobel Prize laureates shared their vision of the future of life science research with EMBL staff and the interested public. Capitalising on the EMBL Advanced Training Centre as a new platform for life science learning and conversation, events such as the new joint EMBO|EMBL symposia have helped put Europe, and both EMBO and EMBL, more strongly into focus in the world scientific community as a place where high-quality research and groundbreaking scientific conferences take place. A more detailed report on the first year of the EMBL Advanced Training Centre can be found on page 86.

In its first year the EMBL Advanced Training Centre has been generously supported by over 70 organisations, 48 of which exhibited at the numerous meetings organised. Particular thanks should be extended to the 16 members of the Corporate Partnership Programme, whose contributions have helped EMBL to raise €200 000 in 2010. Half of these contributions were used to support courses and conferences on diverse topics such as stem cells, tissue homeostasis and cancer, transcription and chromatin, cryo-electron microscopy and three-dimensional image processing, and experimental approaches to evolution and ecology. The other €100 000 were used for 169 fellowships for delegates from 40 countries who would otherwise have been unable to attend the EMBL Advanced Training Centre events.

Training activities at other EMBL sites are also going strong. The EMBL-EBI training facility, which opened in 2007, is already operating to capacity, and demand for hands-on user courses in bioinformatics remains very high. EU funding through the SLING Integrating Action has allowed the EMBL-EBI to train researchers in countries with comparatively small research budgets, including several new EU member states. In 2010, 25 training roadshows were delivered in 14 countries, providing more than 750 researchers with hands-on experience of using Europe's core biological data resources. Good progress has also been made towards developing an e-learning programme, which will complement face-to-face teaching and reach a larger audience.

Alumni

In the past year EMBL's alumni network has exceeded 5000 members. 67% are former EMBL scientists and 81% of all EMBL alumni return to one of the member states after completing their stay at EMBL. In this way EMBL alumni act as local ambassadors throughout Europe, and in some cases beyond, and help disseminate the successful EMBL model and culture into national systems.

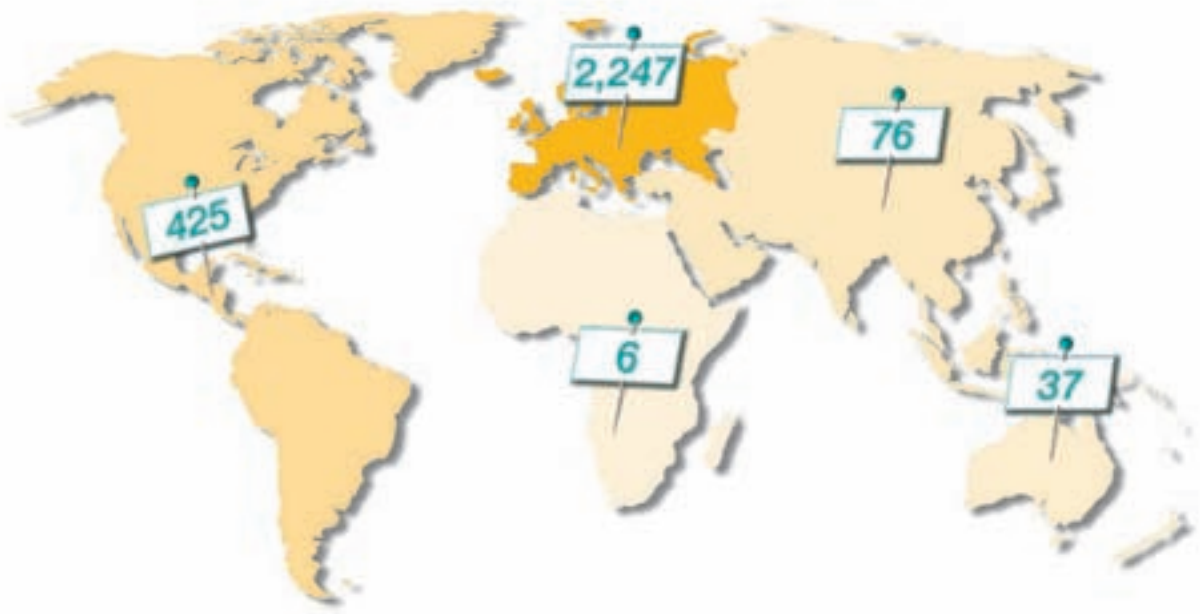
As the EMBL alumni network grows, so does the need for EMBL to track, support and engage in this network. The EMBL Alumni Association is dedicated to this task and organises a variety of activities. For example, local chapter meetings took place in Greece and Spain last year. The Spanish meeting was held in the context of the annual EMBO Meeting and brought together Spanish and Portuguese alumni. Also the next two EMBO Meetings, held in 2011 in Vienna and in 2012 in Nice, will serve as a platform for EMBL alumni to meet in Austria and France.

A generous donation by Roland Specker helped the Alumni Association to secure the future of the John Kendrew Award until 2020. The prize is awarded annually to an EMBL alumnus in recognition of excellence in science communication or academic achievement. The 2011 winner, Amaicha Depino, who worked as a postdoc at EMBL Monterotondo, was selected for her success in communicating science through children's books and workshops to a wide audience of non-scientists. Amaicha now works as a group leader at the University of Buenos Aires where she has set up a mouse facility.

The EMBL Alumni Association has also used the previous year to discuss and define its new initiative for a European Molecular Biology Archive, which is still in its start-up phase.

Outreach

EMBL's diverse outreach activities, organised through its Office of Information and Public Affairs (OIPA), the EMBL-EBI Outreach and Training team, the Science and Society Programme and EICAT, continuously support and complement the laboratory's scientific endeavour.



Worldwide distribution of EMBL Alumni.

With the opening of the EMBL Advanced Training Centre in spring 2010 the number of visits to the Laboratory has reached new dimensions. In the past year 35 groups, mostly students from schools and universities, from all over Europe came to EMBL to gain insight into its activities and to visit the spectacular new EMBL Advanced Training Centre building. It is particularly rewarding to learn that their visit to EMBL inspires some of these students to study natural sciences.

In 2010 an average of 6000 people per day visited the EMBL websites and explored new features like the full text search engine, listened to podcasts reporting on a variety of scientific topics or watched one of the live streamed lectures. Also the outreach section of the EMBL-EBI webpage was redesigned to make information more accessible and to better reflect the EMBL-EBI's missions. To reach out to a global community EMBL has successfully started to interact with the public via social media channels such as Facebook, YouTube and Twitter. In 2010 EMBL's science also continued to be popular with the national and international media in its member states.

Following a successful FP7 grant application, EMBL is now a partner in a European-wide consortium of ten research institutions with the goal of increasing public awareness and knowledge about EU-funded health research.

Held in the EMBL Advanced Training Centre for the first time in November 2010, the Science and Society Programme's annual conference drew a record crowd of 350 participants. The two-day event 'Differences Between the Sexes: From Biology to Behaviour' attracted scientists, journalists, students and members of the public from more than 35 different countries (page 70). The Heidelberg Forum 'Bioscience and Society' – a joint initiative of EMBL, the German Cancer Research Centre (DKFZ), and the Medical Faculty of Heidelberg University – celebrated its 10th birthday in 2011. The Forum lectures bring personalities from within the world of biosciences to Heidelberg to debunk myths, answer questions and discuss their science in relatable language. Just in time for the anniversary, Manfred Lautenschläger – the founder of insurance broker MLP – pledged to continue his financial support of the highly successful lecture series for another three years.

Administration

In the course of the past year, EMBL's modest Administration (fewer than 200 full-time staff) has continued to upgrade and improve its services in all support areas. Highlights of this activity include:

- The successful launch of e-recruitment by Human Resources, which allows more efficient management of recruitment and sharing of information;
- The preparation of the Indicative Scheme, which is currently under negotiation with EMBL Council;
- Consolidation of advances made in the previous year, such as the introduction of online reports of grants in the currency in which the grant was awarded, and team visits to other sites for problem-solving, advice and training;
- Adapting the General Services, especially security, cleaning and catering to the needs of the new EMBL Advanced Training Centre building;
- Refurbishment of the new centre for IT Services and a new building for the Titan Krios of the Electron Microscopy Core Facility in Heidelberg;

- In Hamburg, building 48e, which is directly connected to PETRA III, was completed and administrative offices have been moved to the new facility;
- In Grenoble, EMBL Administration participated in the launch of the Grenoble Innovation for Advanced New Technologies (GIANT) project for an integrated programme of urban development;
- In Monterotondo, the sale of the campus from the European Neuroscience Institute (ENI) to the Consiglio Nazionale delle Ricerche (CNR) came with a wealth of implications for administrative work and organisational issues;
- In Hinxton, EMBL Administration was engaged with the establishment of the new London data centre.

Most importantly, across the board, the administrative management started a strategic reassessment in 2010. In order to support the ambitious strategic goals outlined in the EMBL Programme and Indicative Scheme for the period 2012-2016, and after extensive consultation, a new strategic plan for EMBL's Administration was drafted. The plan comprises five strategic objectives aimed at developing EMBL into a model for scientific research administration. Priorities have been identified and relevant projects are currently being developed in areas such as risk management, grants, re-engineering and staff rules and regulations.

Integration of European Research

As Europe's only intergovernmental laboratory for life science research, EMBL has a central and strategic position in the European research landscape. It fulfills a multitude of functions for its member states and the wider European community, and greatly contributes to the development and integration of research in Europe.

Member state relations

EMBL engages in close interactions with all of its member states and welcomes visits from Council delegates or other representatives.

Bärbel Brumme-Bothe and Iain Mattaj

Throughout the year EMBL hosted several high-profile representatives of the German Ministry for Education and Research (BMBF). The new head of Life Sciences-Health Research department, Bärbel Brumme-Bothe, and State Secretary Georg Schütte, who is responsible for research organisations within the BMBF, visited EMBL in July 2010 and November 2010, respectively. They gained first-hand insight into EMBL's diverse activities and discussed future collaborations between EMBL and Germany, the host country of two of the EMBL sites. EMBL Australia Council Observer, Julia Evans, also experienced EMBL research and culture first-hand during her first visit to EMBL Heidelberg in October last year. Julia, who is General Manager of the Research Infrastructure Branch within the Australian Department of Innovation, Industry, Science and Research, visited as a representative of the Australian government, which became EMBL's first associate member state in 2008. In June 2011 EMBL expects the first visit of John Savill, who has been appointed Chief Executive Officer of the UK's Medical Research Council in October last year and as such is responsible for EMBL's relations in the UK, the host country of EMBL-EBI.

EMBL has close ties with Russia with numerous scientific collaborations taking place. Building on this burgeoning relationship, a Memorandum of Understanding was signed when a delegation led by Vladislav Panchenko, President of the Russian Federation for Basic Research, visited EMBL on 3 and 4 December 2010, with a view to Russia becoming an EMBL member state. Russia's particular expertise in mathematics and physics, as well as biochemistry and zoology, will provide a good complement to EMBL's strength in basic molecular biology. On 25 April 2011 the EMBL Director General participated in the Board of Trustees Meeting of the Skolkovo Foundation chaired by President Medvedev to discuss closer collaborations between this large biomedical cluster and EMBL and to sign the Memorandum of Understanding. This can be viewed as another important step towards a potential future Russian membership in EMBL.

EMBL Partnerships

EMBL engages in a few selective, formal partnerships with scientific institutions in its member states. The

scope of these partnerships is to promote excellence in life science research throughout Europe and to disseminate the successful EMBL organisational model, which is based on international recruitment, staff turnover and regular external reviews throughout the member states. Currently EMBL engages in eight partnerships. Four of them – the Molecular Medicine Partnership Unit in Heidelberg, the Partnership for Synchrotron Radiation Applications in Hamburg, the Partnership for Structural Biology and the Unit for Virus and Host Cell Interactions in Grenoble – are local partnerships that developed out of close collaborations at one of EMBL's sites. The other four – the Partnership for Marine Molecular Biology with the Sars Centre in Norway, the EMBL/CRG Systems Biology Research Unit in Spain, the Nordic EMBL Partnership for Molecular Medicine in Scandinavia and the EMBL Australia Partnership Laboratory – fall into the category of remote partnerships that have been initiated based on requests by member state organisations. On 7 May 2011, EMBL's Scientific Advisory Committee discussed the EMBL Partnership Programme in detail for the first time since the build-up of remote partnerships, including the concept behind the Programme, its level of success to date and the possible future development of partnerships.

Nordic EMBL Partnership for Molecular Medicine

The Norwegian 'node' in the Nordic EMBL Partnership for Molecular Medicine officially opened on 11 November 2010 when Norway's Centre for Molecular Medicine (NCMM) was inaugurated. Established in 2007, the partnership includes the universities of Oslo, Umeå and Helsinki, with established nodes at NCMM, the Laboratory for Molecular Infection Medicine Sweden (MIMS) and the Institute for Molecular Medicine Finland (FIMM). The partnership seeks to combine complementary expertise to investigate the molecular basis of disease and explore molecularly- and genetically-based treatments. Key research at NCMM will include neurobiology, medical genetics, infection medicine and cancer. The Norwegian government has allocated NOK 50 million (around €6.3 million) over a five-year period. It will double this amount should the centre prove successful.

The Danish Ministry of Science, Technology and Innovation has approved the establishment of a Danish node of the Nordic EMBL Partnership for Molecular Medicine, which will be funded by a private foundation. The Danish host university will be selected in a national competition to be completed by the end of 2011. With its primary focus on neuroscience, the new node will complement the molecular medicine activities in the three existing nodes.

EMBL Partnership with Sars International Centre for Molecular Marine Biology

The Sars Centre performs basic research on marine organisms using molecular methods. Its scientific profile follows two main directions – the study of animal evolution and the establishment and use of marine animals as model organisms. Close collaborations have been established with the EMBL groups of Detlev Arendt and the newly appointed group leader Péter Lénárt. The Sars Centre and EMBL are both partners in the European Marine Biological Resource Centre (EMBRC), which is a new European Strategy Forum on Research Infrastructures (ESFRI) project. The Norwegian Research Council has given initial approval for a ten-year funding of Sars, which will allow extension of the partnership beyond its initial period.

EMBL-CRG Partnership Unit for Systems Biology

EMBL's Partnership with the Centre for Genomic Regulation (CRG) in Barcelona is dedicated to achieving a better understanding of complex systems combining EMBL's expertise in computational biology with the CRG's know-how in specific areas of genomics and proteomics. In November 2010 the EMBL-CRG Partnership Unit was evaluated as part of a broader scientific review of the CRG. The external expert panel appreciated the outstanding scientific quality of the Unit, highlighted the strong leadership of Luis Serrano and recommended that the Spanish ministry consider funding the Unit for at least ten years after the expiration of the initial five-year period.

European Research Infrastructures

EMBL plays a very active role in the ESFRI process aimed at developing Europe's next generation of international research infrastructures. It coordinates two – ELIXIR and Euro-BioImaging – and participates in another five of the ten ESFRI Biomedical Science projects – Instruct, BBMRI, Infrafrontier, EU-Openscreen and the European Marine Biology Resource Centre (EMBRC).

ELIXIR

The European Life Science Infrastructure for Biological Information (ELIXIR) is a pan-European initiative to construct and operate sustainable infrastructure for biomolecular data in Europe. The EU FP7-funded ELIXIR preparatory phase consortium, coordinated by EMBL-EBI Director Janet Thornton, encompasses 13 European countries and consists of 32 organisations. The project will provide public access to information to support life science research and its translation to medicine and the environment, the bioindustries and society (see page 90 for an interview with Janet Thornton).

ELIXIR will adopt a distributed 'hub-and-nodes' model in which EMBL-EBI as the central hub will coordinate a network of nodes distributed throughout Europe. For the purpose of constructing the ELIXIR hub on the Wellcome Trust Sanger campus in Hinxton, the UK Biotechnology and Biological Research Council (BBSRC) has earmarked resources from the UK's Large Facilities Capital Fund in February 2011 subject to approval of the business plan by the UK government. In 2009 the BBSRC had already contributed GBP 10 million (approximately €11.5 million) to construct a new Data Centre at the EMBL-EBI in the context of ELIXIR.

An open call for suggestions for ELIXIR's nodes was issued in April 2010 and in response has received suggestions for 54 nodes, from 23 countries. Several European countries have put ELIXIR on their national roadmaps for research infrastructure, and some (Denmark, Finland, Spain and Sweden) have already committed funds to prepare for the construction of ELIXIR nodes. The next step will be to secure commitment from further national funders that realise the importance of biological data to the future economic prosperity of their countries and are willing to contribute to this pan-European effort. For this purpose, ELIXIR's business case has been disseminated to European ministries for research at the beginning of 2011 to collect expressions of interest. The next step will be setting up a consortium of countries that are interested in joining: this group will develop a process for deciding which sites are best suited to ensuring a stable data infrastructure, and how they will be funded.

It is our hope that ELIXIR will enable Europe to handle the growing requirement for large biomolecular data resources in a sustainable manner. It has become clear that it will be necessary to set up a distributed infrastructure and to share the work and funding among several organisations and countries. EMBL will continue to play a central role by hosting the ELIXIR hub at EMBL-EBI, which will continue to host the core biomolecular data resources, and ELIXIR will provide the services and ensure good connectivity to the ELIXIR nodes. None of this will be possible without a significant increase in funding.

Euro-BioImaging

The second major research infrastructure project for the biomedical sciences that EMBL coordinates in the framework of ESFRI is Euro-BioImaging, which will provide coordinated and harmonised deployment of biomedical imaging infrastructure in Europe.

Euro-BioImaging started its preparatory phase funded by the EC under FP7 in December 2010. The consortium comprises 39 beneficiaries and more than 130 associated partners coming from 25 different ESFRI member states and has already been endorsed by over 185 universities, research councils, funding bodies, ministries, as well as industry.

The preparatory phase of Euro-BioImaging aims to develop a plan to construct and operate a set of complementary and strongly interlinked imaging infrastructure facilities based on the comprehensive assessment of user needs regarding their requirements for service, access and training. Based on the consultation of all stakeholders in 2011, Euro-BioImaging will develop eligibility criteria and prepare an open call in 2012 for future nodes that will be evaluated by an independent panel. Furthermore, the legal, governmental and financial framework for the research infrastructure will be developed and the commitment of future partners will be assured.

INSTRUCT

The ESFRI project for integrated structural biology (INSTRUCT) is coordinated by Dave Stuart from the University of Oxford and completed its EU FP7-funded preparatory phase project in March 2011. INSTRUCT is now in the process of establishing the membership of European member states to start construction and operation and provide user access to a range of structural biology technology platforms, to engage in research projects, to organise training events and to liaise with industry. A coordinating office will be located at the University of Oxford, and EMBL (with participation from Grenoble, Hamburg and Heidelberg) is one of the six core centres. As discussed earlier (page ix), the French government has provided significant funding under 'Invest in the Future', which will benefit INSTRUCT.

Relations with the European Commission

EMBL maintains tight links with the EC on various levels. To formalise their desire to maintain and further develop their cooperation a Memorandum of Understanding was signed by European Commissioner for Research, Innovation and Science, Máire Geoghegan-Quinn, and EMBL on 4 March 2011 in Heidelberg. By signing this statement, the EC and EMBL have renewed their commitment to cooperate to further the development of European research in the life sciences. The Memorandum of Understanding follows on from an Administrative Agreement between EMBL and the EC that was first signed in 1995 and granted the EC observer status at EMBL Council. A detailed plan has already been generated on how to implement the new Memorandum of Understanding over the coming years. The main areas of cooperation will be research programming, training and mobility of research, research infrastructures, technology transfer, international collaboration and women in science.

Máire Geoghegan-Quinn and Iain Mattaj

EMBL has received significant funding from Framework Programmes 5, 6 and 7 and, with a contribution of €12.4 million in 2010, the EC is EMBL's single largest external funding body. This funding is obtained competitively and allows EMBL to engage in new research projects, to provide user access to its infrastructure and facilities and to extend its training programmes to scientists from non-member states. As a beneficiary of the EC's funding schemes and as an international research organisation with substantial experience in running large infrastructures and collaborations, EMBL takes the responsibility to provide input into the development of the new Common Strategic Framework very seriously. In the past year EMBL has already contributed to the evaluation of FP6 and has published a position paper as a response to the Commission's Green paper announcing the public consultation on the new Common Strategic Framework.

EIROforum

EMBL is a member of EIROforum, a partnership of intergovernmental research infrastructure organisations in Europe. The mission of EIROforum is to support European science to reach its full potential by facilitating interactions with the bodies of the European Union, national governments, industry, science teachers, students and journalists.

In 2010 the seven founding organisations of EIROforum – EMBL, CERN, ILL, ESA, ESO, ESRF, EFDA-JET – were joined by the European X-Ray Free-Electron Laser Facility (European XFEL). Located on the DESY site in Hamburg, the European XFEL is currently under construction. From 2014 it will generate intense X-ray flashes at a brilliance one billion times higher than conventional X-ray radiation sources. Researchers from academia and industry worldwide will use the facility.

After a successful year of chairing EIROforum, EMBL handed over the chairmanship to the European Fusion Development Agreement, EFDA-Jet, in June 2010. Highlights of EIROforum activity in the past year include the publication of a position paper entitled 'Towards the next Framework Programme for Research, Technology and Innovation – EIROforum position paper on FP8'. The paper shares the EIROforum organisations' experience of constructing and exploiting world-class research infrastructures and provides input to the early-stage discussion on the formulation of the EC's new funding programme.

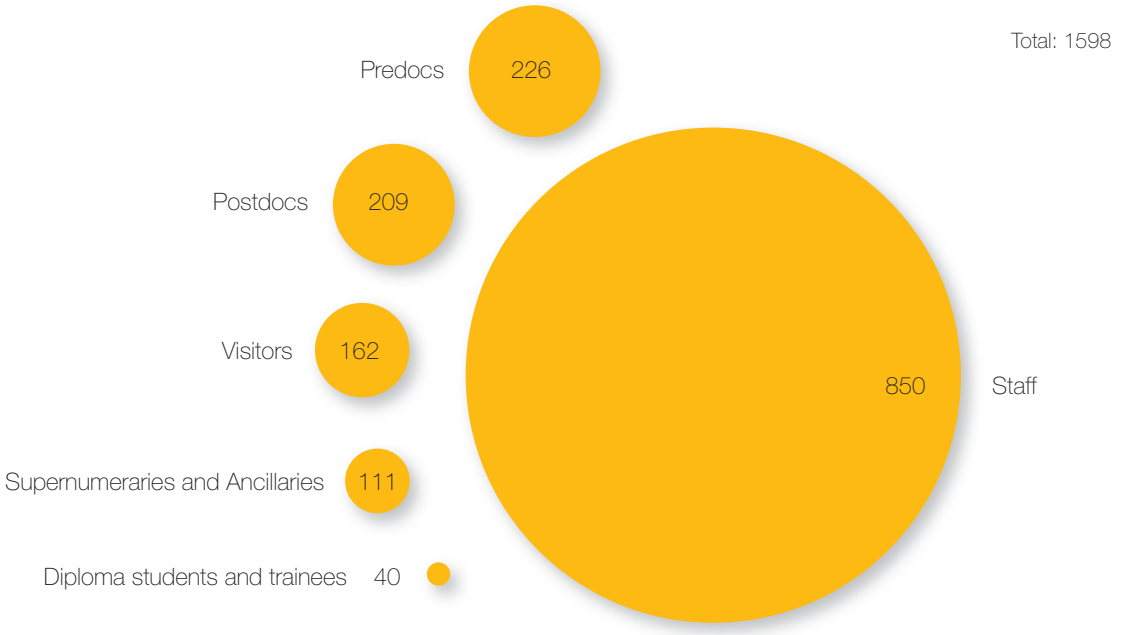
To reach a broader public and inform them about the activities of Europe's international research organisations, EIROforum also participated in the European Science Open Forum (ESOF) that took place between 2 and 7 July 2010 in Torino, Italy.

EMBL continues to host the editorial office of the EIROforum publication 'Science in School', which is produced for European science teachers and showcases research and training activities at the EIROforum partner organisations.

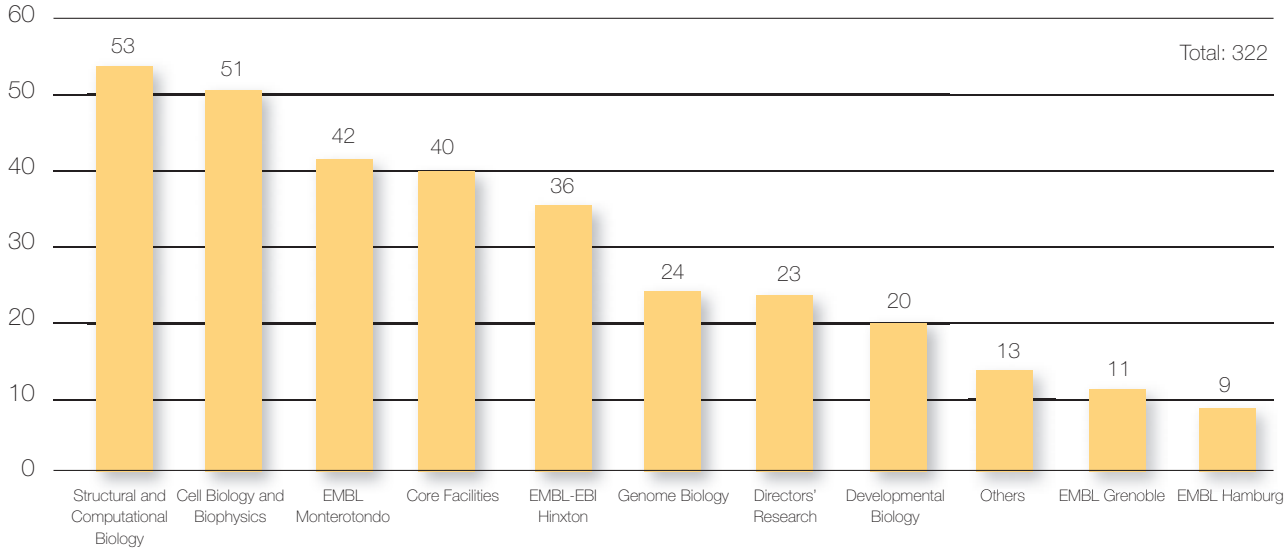
Personnel statistics

On 31 December 2010, 1598 people, including visitors, from more than 60 nations were employed by EMBL.

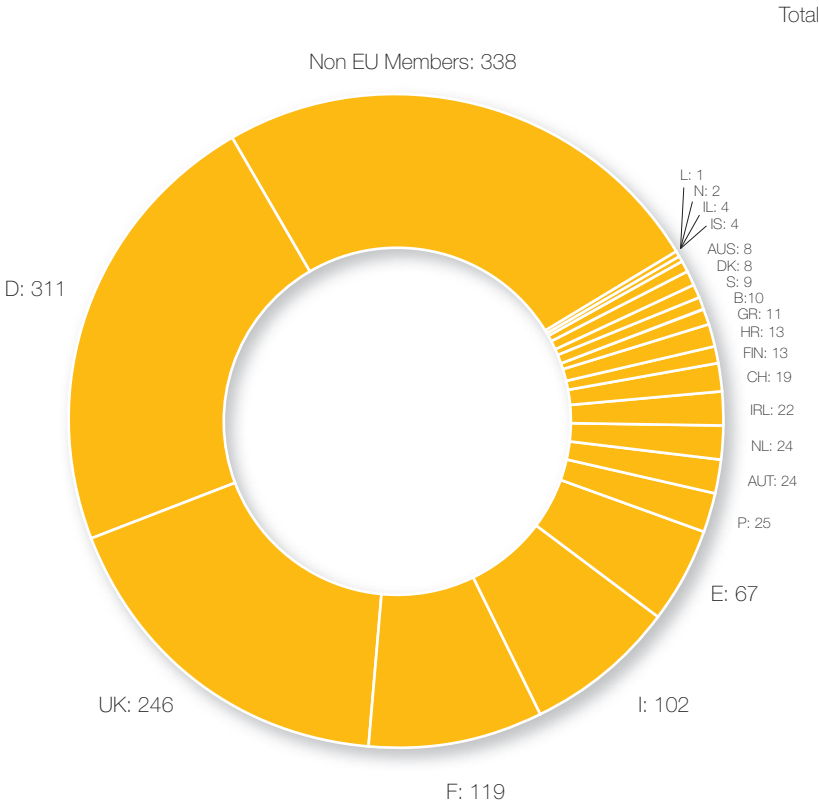
Personnel on 31 December 2010



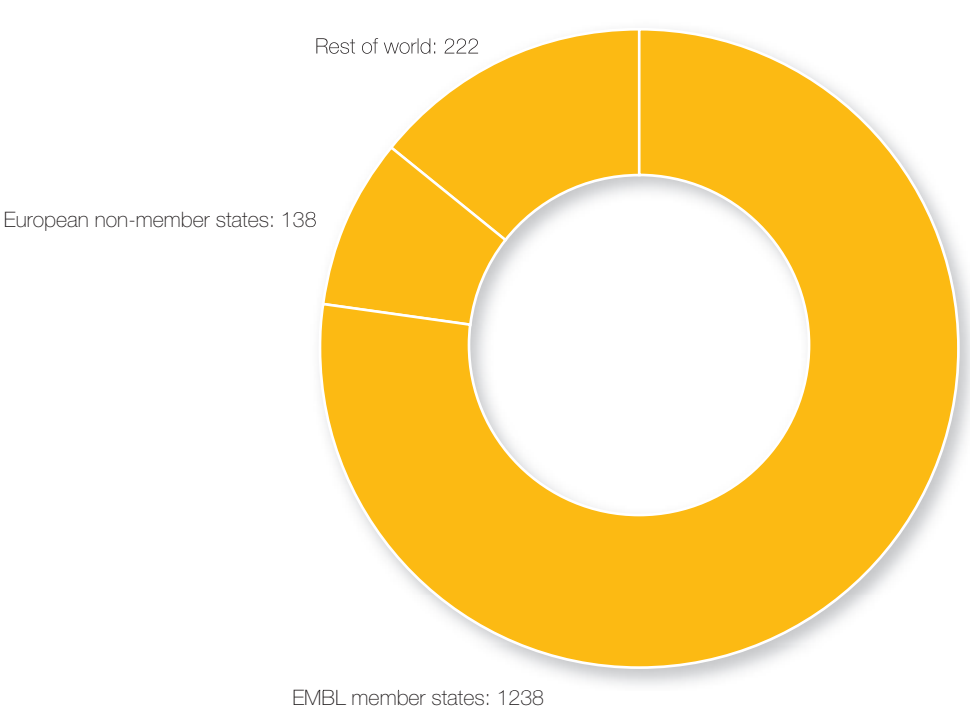
Visitors to EMBL Units during 2010



Staff Nationalities – Research



Staff Nationalities – All



Financial report

Member state contributions

	Contributions				Pension contribution	
	2010		2009		2010	2009
Ordinary contributions	**€000**	**%**	**€000**	**%**	**€000**	**€000**
Austria	1,927	2.2	1,859	2.2	28	27
Belgium	2,352	2.7	2,268	2.7	34	33
Croatia	124	0.1	119	0.1	2	2
Denmark	1,503	1.7	1,449	1.7	22	21
Finland	1,202	1.4	1,159	1.4	17	17
France	14,091	15.9	13,589	15.9	206	200
Germany	18,201	20.6	17,554	20.6	266	258
Greece	1,865	2.1	1,799	2.1	27	26
Iceland	88	0.1	85	0.1	1	1
Ireland	1,052	1.2	1,015	1.2	15	15
Israel	769	0.9	742	0.9	11	11
Italy	11,368	12.9	10,963	12.9	166	161
Netherlands	4,075	4.6	3,930	4.6	59	58
Norway	1,759	2.0	1,697	2.0	26	25
Portugal	1,079	1.2	1,040	1.2	16	15
Spain	6,833	7.7	6,590	7.7	100	97
Sweden	2,316	2.6	2,234	2.6	34	33
Switzerland	2,714	3.1	2,617	3.1	40	38
United Kingdom	15,081	17.1	14,544	17.1	220	214
	88,399	100.0	**85,253**	100.0	**1,290**	**1,252**
Other ordinary contributions						
Luxembourg	177		119		3	2
	88,576		**85,372**		**1,293**	**1,254**
Special contributions						
Special contribution Croatia	23		23			-
Special contribution Luxembourg	-		41			-
	23		**64**		-	-
Associate contributions						
Australia	2,475		1,000			
	2,475		**1,000**			
Additional contributions						
Germany – to ATC	2,663		1,648			
United Kingdom – to ELIXIR	11,203		-			
	13,866		**1,648**			

EMBL budget 2010: € 183 million

External grant funding

	2010		2009	
	€000	%	€000	%
BBSRC	1,759	5.2	1,675	5.0
BMBF	3,644	10.7	4,144	12.4
BW	95	0.3	-	0.0
DFG	1,298	3.8	1,404	4.2
EC	12,372	36.5	11,695	35.0
ERC	117	0.3	-	0.0
HFSPO	416	1.2	457	1.4
HUMBOLDT	5	0.0	-	0.0
MRC	338	1.0	8	0.0
NIH	6,309	18.6	7,750	23.2
VW Foundation	111	0.3	243	0.7
Wellcome Trust	5,100	15.0	4,160	12.4
Others	2,351	6.9	1,890	5.7
	33,915	**100.0**	**33,426**	**100.0**

Other external funding

BIOMS	458	13.4	-	0.0
EMBL-EBI industry support	1,554	45.6	415	48.4
India beamline project	580	17.0	-	0.0
Other external funding	818	24.0	442	51.6
	3,410	**100.0**	**857**	**100.0**

Income/expenditure statement

Income

Member state contributions		
Ordinary contributions	88,576	85,253
Special contributions	23	183
Associate contributions	2,475	1,000
Additional contributions	13,866	1,648
Internal tax	20,255	18,609
External grant funding	33,915	33,426
Other external funding	3,410	857
Other income	20,869	15,479
Total income	**183,389**	**156,455**

Expenditure

Staff costs	90,877	82,933
Operating costs	62,742	54,001
Capital expenditure & depreciation	24,317	23,555
Total expenditure	**177,936**	**160,489**
Surplus (deficit) for the year	5,453	(4,034)

2010/2011 Reviews of EMBL Scientific Units

To ensure that its research and service activities continue to operate at the cutting edge, EMBL regularly submits them to stringent external reviews. Research and Service Units are evaluated every four years by members of the Scientific Advisory Committee and additional international experts. The following section features summaries of the scientific reviews that have taken place in the past year and presents the Director General's responses to the review reports.

EMBL Core Facilities and IT Services Unit Review

Heidelberg, 30 and 31 March 2010

On 30 and 31 March 2010, an external panel of experts conducted the second review of the EMBL Core Facilities and the first review of the central IT Services in Heidelberg. The panel of 12 evaluators, including three members of EMBL's Scientific Advisory Committee (SAC), was chaired by Roberto Di Lauro, currently the Chair of SAC.

Evaluation Summary

The Core Facilities are one of EMBL's highlights and a key component of the successful EMBL model. They are central facilities that host the institute's big and expensive equipment, providing all EMBL scientists and a limited number of external users with access to cutting-edge technology and expert support and services.

We believe that this concept works extremely well and offers several important benefits:

It facilitates the provision of state-of-the-art technical support, equipment and expertise to a broad range of EMBL researchers compared to the alternative model of incorporating technologies into individual research groups. The excellent interdisciplinary support provided by the Core Facilities strongly contributes to EMBL's scientific output.

Organising equipment into Core Facilities that serve all EMBL groups avoids duplication and is financially efficient.

The Core Facilities are particularly attractive to new group leaders setting up their research groups and thus greatly help EMBL recruit the best young scientists.

Through their interactions with visitors and external users, their involvement in advising other institutes on setting up their own Core Facilities, and the organisation of training courses for young scientists, the Core Facilities transfer expert knowledge and provide a very useful service to the EMBL member states.

EMBL currently operates eight Core Facilities: Advanced Light Microscopy, Chemical Biology, Electron Microscopy, Flow Cytometry, Genomics, Protein Expression and Purification, Proteomics, and Monoclonal Antibodies. Their overall performance was perceived as excellent by the review panel. This is also reflected by an internal user survey that was carried out in 2009 to assess the quality of services and the general user satisfaction. The response was overwhelmingly favourable, with all eight facilities scoring good, very good or excellent for accessibility, comparison with other facilities elsewhere, staff competence, staff support, and standard of results obtained.

It was the first time that the central IT services in Heidelberg were included in a review. While our impression was overall very positive, we recommend an evaluation of this specialist fast-moving field by a dedicated expert review panel.

The review panel congratulates Christian Boulin, Head of Core Facilities and Scientific Services together with the heads of each of the facilities and services, for the high quality support they offer to EMBL researchers and to the European scientific community at large.

Director General's Response to the Review Panel's Recommendations

The panel made the recommendations listed below. Because acting on some of them will depend on decisions taken by EMBL Council in relation to the Indicative Scheme for 2012-2016, I only respond to those where short-term actions are possible.

The panel noted that the capability, complexity and cost of state-of-the-art equipment for life science is increasing rapidly and that it is important to provide additional funding to the facilities if they are to remain both useful and competitive. For different reasons, that is because of the huge increase in demand, considerable additional future investment will be required to maintain the IT services in a functional state. I note these comments and will discuss them with Council as part of the preparation of the 2012-2016 EMBL programme.

Aside from ensuring that a sufficient number of additional staff positions are available to meet future challenges, for example in data handling and advanced microscopy technology (light and electron microscopy), the panel also recommended careful succession planning to ensure that important expertise is not lost from the Core Facilities with the departure of individual staff members. The panel recommended ensuring the provision of a sufficient period of staff overlap to enable replacements to be trained before critical staff members leave EMBL. I will work with the Head of Unit and Human Resources to develop mechanisms to tackle this issue.

The panel was very surprised to learn that Christian Boulin carries out his many tasks with the direct support of only one part-time secretarial position. They strongly advised the appointment of a second full-time administrator who would not only provide additional support for Christian but also, for example, review charging policies and develop and implement new policies based on a complete financial picture of the real costs of the Core Facility activities. It was felt by the panel that this was particularly important in order to charge external users adequately. Another important task is to ensure that complete statistics on the 'outputs' of Core Facility activities are collected, for example lists of the publications or intellectual property generated that depended on support provided by the Core Facilities. They noted that this information will also be a valuable aid to future review committees. I have already spoken to the Head of Unit about this recommendation and intend to create such a position.

The panel noted that user satisfaction was generally high and that communication between facility heads and staff and their users was generally very good. However, they noted that the user committees of two facilities were not very active. They recommended that the Head of Unit remedy this and we intend to follow this recommendation.

Finally, although this review report included a positive evaluation of the Heidelberg-based IT services, the opinion of the panel was that, in this specialist fast-moving field, a dedicated review panel might be more appropriate. We will discuss this recommendation internally before deciding on how best to implement future reviews of IT services.

Iain W. Mattaj
Director General
9 June 2010

EMBL Structural and Computational Biology Unit Review

Heidelberg, 5 and 6 May 2010

The review of the EMBL Structural and Computational Biology Unit (SCB) took place at EMBL Heidelberg on 5 and 6 May 2010.

Evaluation Summary

The 2010 evaluation of the Structural and Computational Biology Unit was extremely positive and the Scientific Advisory Committee was very pleased with the status of the Unit. The panel highly appreciated the quality and international standing of the Unit and were very much impressed by the achievements, the perspectives and the collaborative attitude of all the people involved. The SCB Unit is an important asset for EMBL and for Europe at large.

The review took place against a very high level of staff turnover. No fewer than eight of the 12 group and team leaders reviewed in 2006 have since left, including the then Joint Head of Unit, Luis Serrano. Aside from one retirement, all but one of the departing group leaders were at or near the end of their nine-year contract period. Christoph Müller, previously Senior Scientist at EMBL Grenoble, substituted Luis Serrano as new joint Head of Unit. His transition from EMBL Grenoble to Heidelberg has been very smooth and the collaborative leadership with Peer Bork works extremely well. The six group leaders who left EMBL since 2006 all took up prestigious positions in the member states, which illustrates how EMBL fulfils its role of disseminating science and seeding Europe with top scientists. The changes in faculty were taken as an opportunity to partially refocus the strategy of the research activities towards the exciting perspective of bridging the space and time scales of biological processes. The recruitment of new faculty has been very successful and has brought outstanding group leaders in the areas of X-ray crystallography, single particle electron microscopy and tomography, nuclear magnetic resonance, chemical biology and biophysics to EMBL. This development means the SCB Unit has substantially broadened its expertise and complements X-ray crystallography-based research in Hamburg and Grenoble.

The SCB Unit aims to bridge molecular to cellular scale, applying complementary techniques at different resolutions. An excellent means to promote this approach and foster collaboration are so-called 'Unit projects', which involve all groups in the Unit applying their methods and expertise to different aspects of the same biological problem. One highly successful example of such a project is the multidisciplinary approach to a systematic characterisation of the organisation and function of the simple prokaryote *Mycoplasma pneumoniae*. This has resulted in three publications in the journal *Science* and is of great value to the scientific community beyond EMBL. Future 'Unit projects', for example applying classical structural biology studies and biophysical and biochemical characterisations to a thermophilic fungus, show similar potential.

In addition to several other outstanding research highlights, the review panel particularly noted computational resources developed by the Unit, including SMART, STRING and

REFLECT, which are very heavily utilised by external scientists. These software tools are highly valuable for the community and extremely helpful in increasing the recognition of EMBL in the scientific community.

Finally, the review panel would like to congratulate joint Unit Coordinators Peer Bork and Christoph Müller for their achievements and effective leadership. Their own scientific excellence and international standing inspires and guides especially junior group leaders.

Director General's Response to the Review Panel's Recommendations

The panel noted that several new computational biology groups had recently been hired in other Heidelberg Units, and were positive about this development. They affirmed that the core of computational competence in the SCB Unit is a very useful source of mentoring and coordination for these dispersed groups. They recommended that we develop mechanisms to make such a role for SCB possible. I feel that this is a valuable recommendation and indeed have already begun to explore this with the SCB leadership. We intend to mobilise the computational expertise in SCB, at the EMBL-EBI and elsewhere in EMBL to good general effect through the mechanism of EMBL Centres in the 2012-2016 EMBL Programme. SCB groups will have an important role in the realisation of these Centres.

A more general recommendation related to the ongoing, and increasing, need for infrastructural and technological support in the Unit. Topics highlighted include additional needs in mass spectrometry, in the updating, maintenance and operation of both high resolution EM and NMR, and in the heavy and rapidly increasing requirement for computational resources. I note these recommendations and will discuss them both with EMBL senior faculty and EMBL Council in preparing the new EMBL Programme.

Finally, the panel noted that due to renovation there is currently no visitor laboratory in SCB. As pointed out by the review panel, this has two disadvantages. First, fewer member state visitors can be accommodated in the Unit. Second, it means that postdoctoral fellows do not have the opportunity to help supervise and teach visitors, an opportunity which they greatly appreciate. The reason for closing the visitor lab was that three new groups arrived essentially simultaneously shortly before the review (Orsolya Barabas, Martin Beck and Carsten Sachse), and their laboratories required some renovation work. There was therefore a temporary shortfall of laboratory space. This will be dealt with, and the visitor lab reopened, within a short time period.

Iain W. Mattaj
Director General
9 June 2010

EMBL-EBI Services Review

Hinxton, 9 and 10 February 2011

Just like its research Units, EMBL's service activities are subject to regular external review. The third review of the EMBL-EBI services took place at EMBL-EBI in Hinxton on 9 and 10 February 2011. A panel of 16 evaluators, including three members of EMBL's Scientific Advisory Committee (SAC), was chaired by Gunnar von Heijne of Stockholm University. Unlike the research reviews, which concentrate on the performance of individual groups, the EMBL-EBI service review focussed on the seven areas in which data resources are provided.

Evaluation Summary

EMBL-EBI is regarded by the panel to be a leading force and key partner in global life-science projects that rely on its biomolecular databases and associated tools. Its combination of technical and scientific developments creates a unique environment that is one of the strongest assets of European life science. The currently planned future developments of European infrastructures will make the role of EMBL-EBI for the biomedical sciences even more important and obvious.

The panel notes that it is essential that there are robust and sustainable international organisations that serve as repositories for the massive explosion of data generated by modern biology, and provide the stimulus and coordination to supply users with the tools and expertise needed to retrieve, interrogate and analyse that data. It is therefore central to the future of European science that there is an institute with the stature and capabilities of EMBL-EBI to lead developments worldwide and to support European science at the forefront of bioinformatics and computational biology. Such research is of fundamental importance for future advances in health care and agriculture. The review panel appreciates the considerable increase in support provided to EMBL-EBI by the EMBL member countries in the four years covered by the review period but notes that the continuing increase in data production in the life sciences and diversification of data types that need to be stored means that further investment in both the EMBL-EBI and the planned European ELIXIR infrastructure will be essential to meet future needs.

EMBL-EBI has prepared itself very well for future challenges in the areas of genomics, proteomics and systems biology. An efficient management structure is in place, and the service teams are on top of current developments in their respective fields and ready to respond appropriately to demands from the rapidly changing environments of academia, commerce and the public sector. Given the dynamic landscape, these matters need to be kept under regular review.

The quality of EMBL-EBI services is, and has always been, high, particularly in terms of integrity of data and annotation, which must continue to be considered a first priority. This has been a traditional strength of EMBL-EBI and clearly this legacy is in good hands. EMBL-EBI Services team leaders also play a leading role in the necessary international work on standardisation of data collection and presentation methods.

The protein and nucleotide sections of the PANDA group together represent a cornerstone of the EMBL-EBI edifice. They stand for the European contribution to a key instance of global scientific collaboration. EMBL-EBI also provides important resources and services in proteomics, structural biology and functional genomics. The Review Panel especially welcomes the new initiative in the area of chemicals of biological and pharmaceutical interest, and the long-awaited addition of literature services (scientific publications, patents) to the EMBL-EBI portfolio.

In conclusion, the Review Panel wishes to congratulate the Director Janet Thornton, Associate Director Graham Cameron, team leaders and service staff for the very collaborative working

atmosphere at EMBL-EBI, for the highly effective and professional way that they have dealt with one of the most rapidly developing areas in modern science and for the massive effort made to provide world-class services to the large and rapidly growing user community. The Director and Associate Director have shown excellent management skills in steering EMBL-EBI into its current position as an internationally leading service provider.

Director General's Response to the Review Panel's Recommendations

The panel noted that data integration is a key characteristic of the EMBL-EBI services, which to date has been handled well through a collaborative effort by the teams to interlink their data resources. They considered a particularly successful recent example of such integration has been the integration of DNA and protein sequence resources into one large resource, called PANDA. For the future, the panel suggested that in order for this to continue to succeed across all the data resources it might be necessary to install additional management structures to address overall data integration strategy at the top level. We take this recommendation seriously and I will discuss with the EMBL-EBI leadership this suggestion and other possible ways of implementing future integration strategy.

The panel commented that the current management and organisational scheme, with a richer hierarchical leadership structure compared to the previous review, was a considerable step forward. They also pointed out that further organisational changes might become necessary in future to meet new challenges. It will also be necessary to regularly monitor and to subdivide big service teams in order to facilitate management and distribute the managerial burden more evenly. Again, we feel this is wise advice and will endeavour to continue to update our management structure as required.

The panel appreciated that extensive changes have been made to the IT infrastructure at the EMBL-EBI, especially the response to the demand for a large increase in data storage and the provision of safe backup structures to combat failures. They felt that these measures have been appropriate and, at least for the present, sufficient to cope with the growing data volumes. We acknowledge and agree with the recommendation to continue to use multi-year projections to predict future demands on the IT infrastructure and to guide appropriate responses. Such projections are, and will remain, an integral part of internal evaluation strategies.

Both of the above paragraphs reflect concerns that arise from the 'data deluge', that is the huge increase in data production and storage in the life sciences. We acknowledge and agree with the panel's conclusion that the ongoing exponential growth of data production and the huge demand from the scientific community will be the major challenges the EMBL-EBI services will face over the next review period. To meet the first challenge we are exploring various ways to achieve data compression without compromising the usefulness of the databases produced and we have developed and are continuing to develop criteria by which EMBL-EBI data resources are prioritised. As the panel pointed out, these criteria have to, and will be, continuously modified taking into account such criteria as size of user community, ease of integration within existing EMBL-EBI resources and promise of future benefit to society. Nonetheless, as the panel foresees, expenditure on computational hardware will continue to require a substantial and increasing portion of the EMBL-EBI's budget. We agree with the review panel's conclusion that there will be a need for additional investments in EMBL-EBI and ELIXIR over the coming years and that these investments are key to the future competitiveness of the large community of European life scientists.

Iain W. Mattaj
Director General
11 May 2011

Scientific Report

Team spirit

When recruiting a new employee, most employers look for a 'team player' – someone who can work as part of a group, while bringing their own unique expertise, talents and views to the table. This is also the case in science, especially as projects become ever more multidisciplinary. The Proteomics Core Facility in Heidelberg, for instance, is a hub for scientific collaborations across EMBL and beyond, bringing specialised expertise to a vast array of projects (page 10).

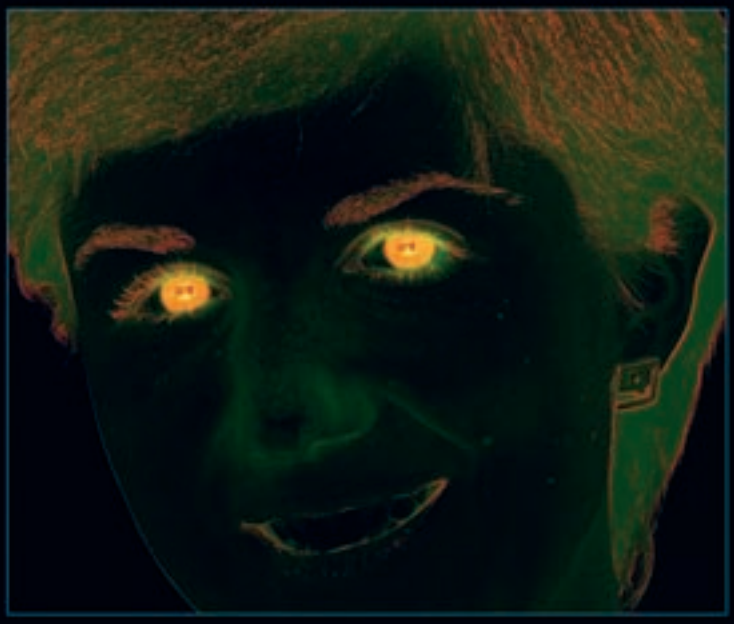
In an example of collaborative working, structural biologists at EMBL Grenoble teamed up with EMBL Alumni working in genetics to understand how male fruit flies compensate for the fact that they have one less X chromosome than females (page 20). While at EMBL Heidelberg, two groups developed a new method that teams up two different microscopy techniques for the first time (page 4).

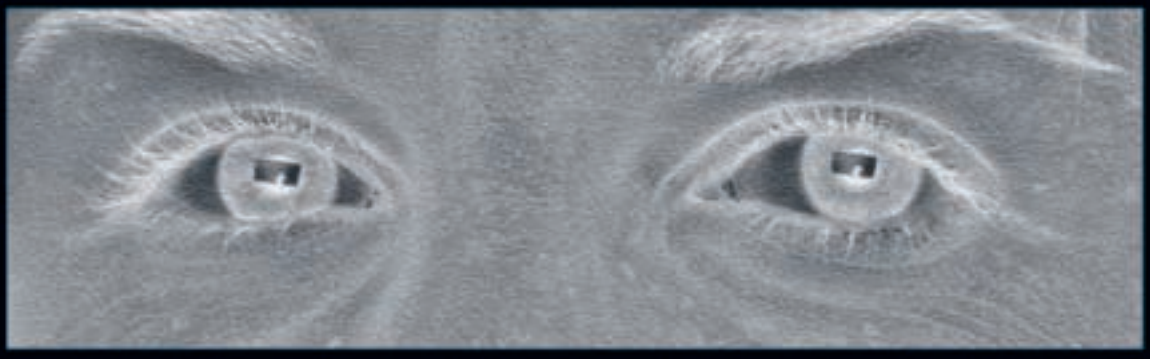
Part of the challenge of recruitment is finding someone who is right for the team: one person's ideal crew can be another person's nightmare. A Heidelberg group has found that the bacteria that live in the human gut also seem to have this issue: they gather in three different types of community, meaning that, based on our bacterial inhabitants, humans have three different gut types (page 12).

Like people whose personality seems to change depending on the company they keep, a protein in the bacterium that causes tuberculosis changes shape to bind to two different interaction partners – an EMBL Hamburg discovery that opens up new avenues for fighting this deadly disease (page 25).

John Briggs, Wanda Kukulski and
Marko Kaksonen

One vision





Anyone who has suffered from double vision – perhaps from a bang to the head or serious over-indulgence at the bar – will tell you just how disorientating it can be. You can see two images of the same object at once, but you can't align them to see clearly, which makes navigating your way around extremely difficult. It might sound rather odd, but cell biologists encounter a similar problem on a regular basis. Not because they have been partying too hard, but because they often have to look at cells with two different kinds of microscope to really understand the process they are studying. Trouble is, it's often very tricky to get both microscopes to focus on exactly the same point in the cell.

The problem arises when the microscopes are using vastly different powers of magnification: a cell is a small place when you magnify it a mere 100 times, and objects in it are easy to find. But zoom in 100 000 times with a different kind of microscope and the cell becomes a massive space in which to find the thing you are looking for. John Briggs and Marko Kaksonen at EMBL Heidelberg have now found a way of using two very different microscopy methods to pinpoint rare events in the cell, and then zoom in thousands of times magnification to see them with absolute precision and in unprecedented detail. "We are starting to ask questions that we wouldn't have been able to consider before because the technology was not there," says Marko.

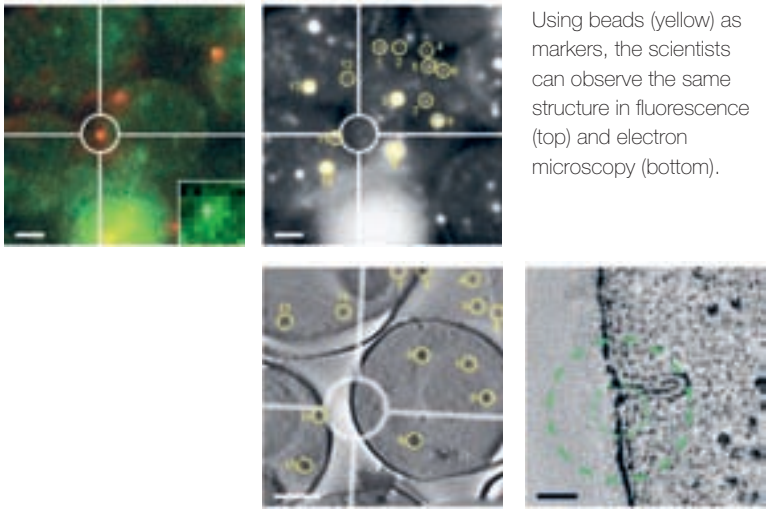
The project found its beginnings when John and Marko first met in Heidelberg. The two group leaders joined EMBL at about the same time, and had a common research interest: how the thin membrane surrounding cells bends to form tiny pouches that then seal themselves and bud off from the membrane as miniscule spheres called vesicles. Cells can make these vesicles to either secrete molecules such as hormones, in which case the vesicles form on the outside of the cell, or to import molecules from their surrounding environment, in which case they form on the inside. Studying this vesicle-formation process, known as membrane budding, is important for understanding basic cell biology. Membrane budding can also be hijacked by a number of viruses, such as the human immunodeficiency virus (HIV), to sneak into the cell as well as to release new copies of themselves.

"We are starting to ask questions that we wouldn't have been able to consider before."

John and Marko were both working on membrane budding, but were – quite literally – looking at it from different perspectives. Marko's team was using a form of microscopy called fluorescence microscopy, or FM, to study the membrane budding that cells use to import molecules, a process known as endocytosis. Working in living cells, they tagged the molecules they wanted to study with fluorescent dyes. Using a light microscope, they could then document how these molecules moved and associated with each other during the process of membrane budding. Although this gave them the "big picture" of what was happening, and allowed them to catch fleeting interactions, they couldn't see the details.

"We got real-time images and could follow these processes as they were happening," says Marko. "But we were limited by the resolution of light microscopy."

John's team was working at the other end of the spectrum. They were studying membranes using electron microscopy, or EM. Instead of using light, this microscope uses beams of electrons, which lets you see objects that are thousands of times smaller than the ones you can see with a light microscope. Although this gives fantastic detail – allowing scientists to see things less than a billionth of a metre across – it has a number of drawbacks. One is that biologists



Using beads (yellow) as markers, the scientists can observe the same structure in fluorescence (top) and electron microscopy (bottom).

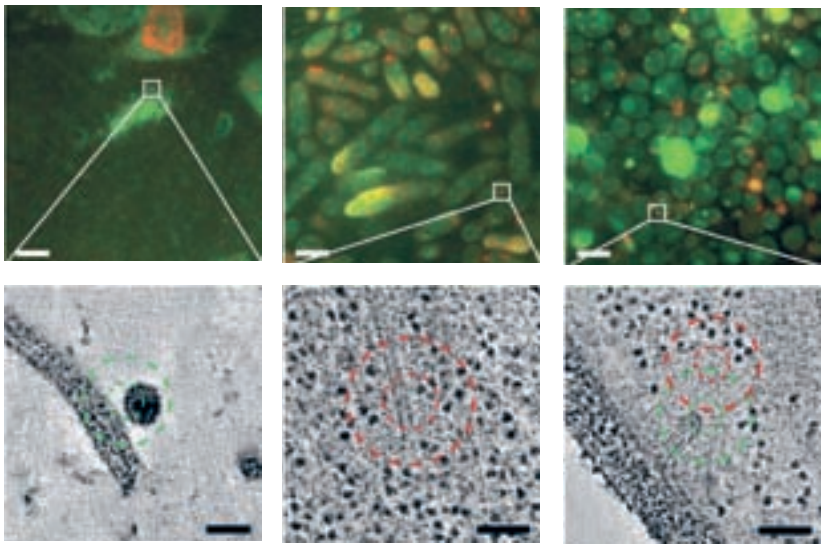
can't look at living tissue: samples have to be frozen or embedded in resin to stop them being fried by the electron beam. Another is that because EM works at such a tiny scale, the cell suddenly becomes a (relatively) huge place. Trying to track down a molecule of interest in a cell at this scale isn't so much like trying to find a needle in a haystack as trying to find it in the Atlantic Ocean. These difficulties are exacerbated in a related technique called electron tomography, which allows researchers to use an electron microscope to create a three-dimensional picture of their sample.

But the two teams soon realised that their different approaches could complement each other. "I was doing electron microscopy, Marko was doing fluorescence microscopy," says John. "It seemed a pretty obvious collaboration." It wasn't long before they started talking about finding a way to merge, or correlate, the two microscopy methods so that they could study the same process in the same cells at the same time. "At some point, we decided to develop a correlative method," says John. What they really needed was a postdoc who could work between both labs – just the kind of endeavour the EMBL Interdisciplinary Postdoctoral (EIPOD) Programme was developed to foster. "This was the ideal project for this scheme," says John. "We needed someone who would really understand the methods."

So he and Marko hired Wanda Kukulski as an EIPOD fellow. Wanda had worked with EM for a number of years, and was keen to break new ground. "I wanted to learn something new, something cell biological," she says. So John and Marko set her the challenging task of developing a method that would let them identify an interaction or process with FM, and then zoom in and build up a detailed fine-scale three-dimensional picture with electron tomography.

To make sure the method was reliable, Wanda had to ensure it met five strict conditions: the results it created had to be reproducible; it had to let scientists use EM to zoom in to the spot identified by FM to within 100 billionths of a metre; it had to be sensitive enough to detect very small numbers of proteins tagged with their fluorescent labels; scientists had to be able to use combinations of different dyes; and finally, the method should be suitable for use in a wide range of cell types and living things. It sounds like a very tall order, but Wanda wasn't fazed. "I didn't think it was easy," she says, "but I didn't worry too much." Sure enough, within a remarkably short time, she had developed something that worked.

"This approach that Wanda has developed is really quite simple," says Marko. It relies on adding the equivalent of little marker beacons on the sample to allow researchers to navigate back to the point in the cell with an electron microscope that they identified using a light microscope. The team begins by tagging their proteins of interest in cells with fluorescent dyes before either freezing them or embedding them in resin. They then sprinkle the sample with tiny plastic spheres that show up under both light and electron microscopes. Once they have found a point



With the new method, scientists can identify structures and follow their dynamics under the fluorescence microscope (top), and zoom in to see details under the electron microscope (bottom).

of interest with the light microscope, they take bearings from the nearby spheres. This gives them the coordinates they need to retrace their steps with the electron microscope.

To demonstrate its versatility, the team put their new method to the test in three different scenarios. The first, not surprisingly, was in the study of membrane budding. The team wanted to see whether they could capture and study a dynamic event called scission: the fleeting process by which a new vesicle closes off and cuts itself free from the membrane. To do this, they labelled the proteins involved in scission and used a light microscope to create a highly detailed time line of the order and timing in which these protein interactions took place. They then froze cells at specific time points and studied their fine structure with electron tomography. "We discovered that the vesicles were not round, which was a big surprise," says Marko.

Next, the team showed that their method could help scientists studying how viruses invade cells. They added HIV particles to cells in a laboratory dish and then located the viruses with both microscopes – something that is notoriously hard to do. "If you try and find them with an electron microscope you will fail," says John. But with the new method, the viruses show up as fluorescent green spots in the embedded specimens, allowing researchers to home in with EM.

The final test was to track highly dynamic cellular structures called microtubules. These form part of the cell's internal scaffold, and they are constantly lengthening or shortening at their ends. Central to understanding this process is the structure of the lengthening end: some researchers think the ends are sheet-like and roll up to form a tube, others think they are flared, like the speaker on an old-fashioned gramophone. Tracking and zooming in on the proteins involved in microtubule lengthening allowed the team to show that most of them are indeed flared.

"The three projects really show the kinds of things you can do," says John. "I think there are a lot of problems to which it would be applicable." The equipment used is relatively standard – most large EM labs will be able to reproduce it, meaning the Heidelberg team has created a new technique that will be of wide benefit to the cell biology community. The response has been very positive. "We hear feedback now from many people," says Wanda. "Lots of people want to try it!"

Kukulski W, Schorb M, Welsch S, Picco A, Kaksonen M, Briggs JAG (2011) Correlated fluorescence and 3D electron microscopy with high sensitivity and spatial precision. *J Cell Biol* **192**: 111-119

For the love of lipids

The typical high-school teen movie has many stock characters, from the popular Jocks and Cheerleaders to the quiet Nerds and shoe-gazing Loners. If the cell was a high school, proteins and DNA would be the Jocks and Cheerleaders of the biological world: they're very popular, and everyone wants to get to know them. Meanwhile, lipids — molecules such as fats and waxes — have largely been relegated, like Nerds in a teen drama, to the sidelines of the biological social scene. "They've often been seen as boring," says Anne-Claude Gavin, a biologist in the Computational and Structural Biology Unit at EMBL Heidelberg.

Yet lipids are crucial biological molecules. They serve as energy stores and form the building blocks of the biological membranes that encircle cells and divide them into internal compartments. Lipids are also involved in more dynamic processes, serving as signalling molecules that bind to proteins within the cell, and guiding proteins to various biological membranes.

To gain a better handle on how proteins interact with lipids, Anne-Claude and colleagues carried out a systematic screen of lipid-binding proteins in the yeast *Saccharomyces cerevisiae*. This screen identified more than 500 interactions between 124 proteins and 30 lipids, most of which were previously unknown. These test-tube results were then followed up with studies on live yeast cells, which largely confirmed the biological relevance of these interactions.

The team also took an in-depth look at the sequences and structures of some of the lipid-binding proteins they found. They discovered that many proteins are able to bind lipids even though their amino-acid sequence differs significantly from typical lipid-binding proteins. "By doing a more in-depth sequence analysis we discovered 'cryptic lipid-binding domains' that were overlooked by classical algorithms," says Anne-Claude. This suggests that there are numerous ways to build lipid-binding domains, which may not be predictable from sequence data alone. "We really need to measure them with biochemistry," says Anne-Claude.

The team also gained new insights into the finer details of how lipids bind to proteins, specifically a lipid-binding domain called the pleckstrin homology (PH) domain. Their studies on the three-dimensional structure of the PH domain in the protein Slm1 indicate that it can recognise and bind not just one but two lipid molecules simultaneously. This means that the PH domain can act as a 'coincident sensor' that only responds fully when two lipid signals are present, which enables different signalling pathways to be integrated. "This is an exciting finding, and may be a widespread mechanism that applies from yeast to humans," says Anne-Claude.

This project – which integrates cell biology, genetics, and structural biology – is the kind that can only be carried out at large-scale research institutions such as EMBL, where researchers can work across the boundaries of biological specialities. "We worked with colleagues in a number of Core Facilities, including Protein Expression and Purification, GeneCore, Advanced Light Microscopy, Genome Biology, and Cell Biology and Biophysics," says Anne-Claude. "It would have been impossible without them."

Gallego O *et al* (2010) A systematic screen for protein–lipid interactions in *Saccharomyces cerevisiae*. *Mol Syst Biol* **6**: 430

What have we here?

If you're wondering which proteins are in your sample, the Proteomics Core Facility in Heidelberg is the place to go. There, Jeroen Krijgsveld and his team can separate and identify proteins, and provide an estimate of the amount of each protein in the sample. The team can also see whether your protein has been modified by molecular processes such as methylation or phosphorylation.

Proteomics Core Facility

"Essentially, half of our users come to us to confirm, and the other half to discover, depending on their specific projects," Jeroen says. Confirmation comes into play in quality control, for instance when a structural biologist wants to check that the sample they intend to crystallise is pure enough, and contains the right protein – if the bacterium Escherichia coli was used to produce the protein, sometimes a bacterial protein can be extracted by mistake. In other cases, the hunt is on for which proteins interact with a certain molecule inside cells, and, having extracted them, scientists come to Jeroen's facility to identify these mystery players – the discovery aspect of Jeroen's work.

The team recently developed and implemented a new workflow that enables them to compare the amounts of proteins in different samples, so that researchers can compare how much of a certain protein is present in cells under different conditions, or see how protein interactions change over time. This new pipeline was first put to the test by a visiting scientist from the Massachusetts Institute of Tech-

Krijgsveld team

Jeroen's team also apply their techniques to their own research, which focuses on determining the amounts of different proteins in stem cells as they differentiate into other cell types, in an effort to identify the mechanisms behind that switch.

Pillai group

At EMBL Grenoble, Ramesh Pillai and his group look at Piwi proteins, a group of proteins that play an important role in the formation of sperm (see page X). They have turned to the Proteomics Core Facility to uncover how these proteins are modified during the process, and to see with which other proteins Piwis interact.

Lemke group

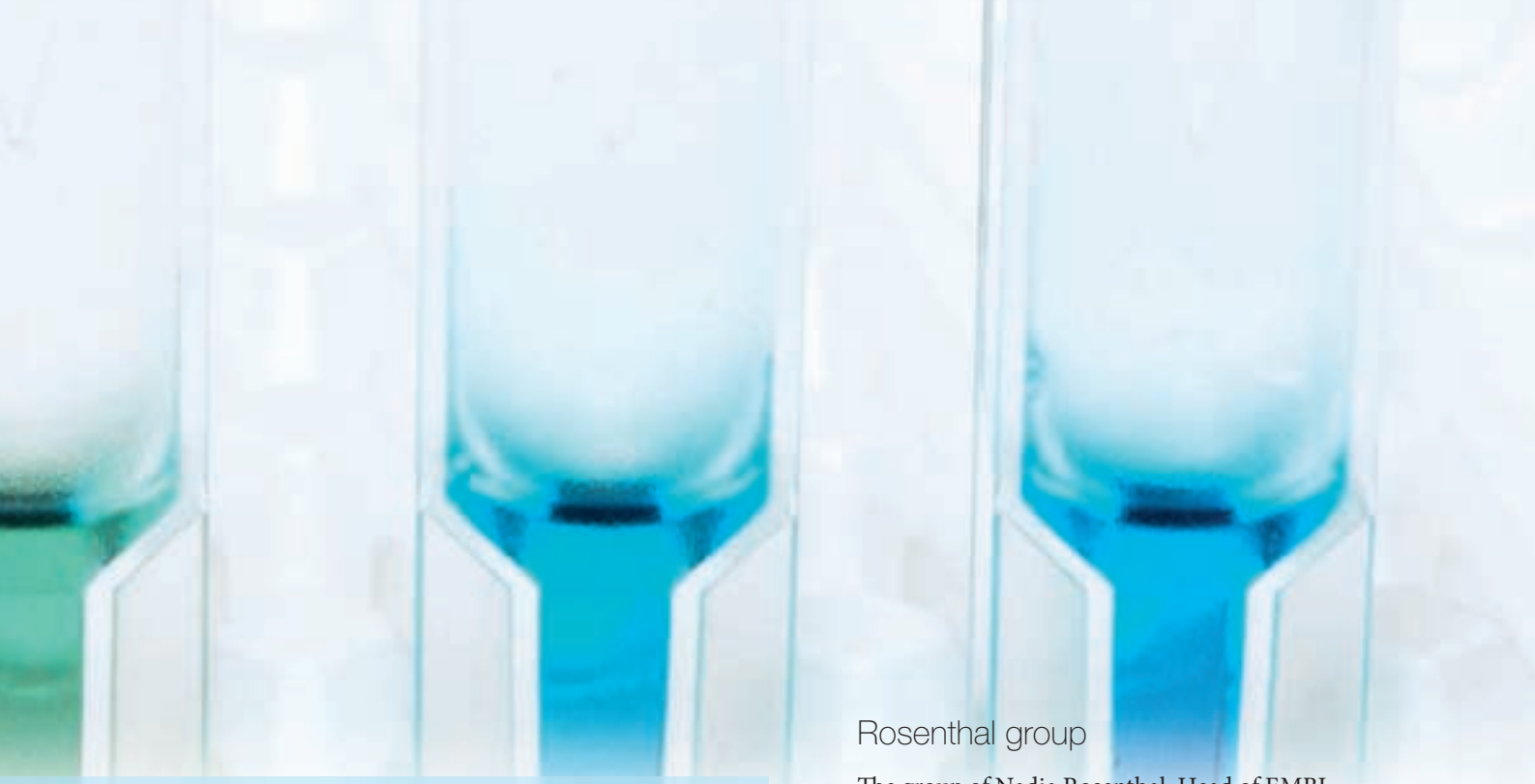
In an approach known as synthetic biology, Edward Lemke and his group produce artificial amino acids, which are versions of the building blocks of proteins that do not occur naturally in cells. Once they have coaxed the cell's machinery into replacing one of a protein's amino acids with an artificial one, the Heidelberg group ask Jeroen's facility to confirm that the artificial amino acid really has been incorporated into the protein.

Wilmanns group

The group of the Head of EMBL Hamburg, Matthias Wilmanns, studies the three-dimensional structure of proteins from the bacterium that causes tuberculosis, in an effort to aid the fight against this disease. Matthias and his group ask the Proteomics Core Facility to perform quality control on their samples, to ensure that they have the correct proteins.

De Renzis group

Protein interactions are what brings Stefano de Renzis' group to the Proteomics Core Facility. They ask Jeroen's team to uncover the identity and the concentration of the proteins that interact in the cells of a fly embryo as it develops.



nology in Cambridge, USA, whom Jeroen's team taught not only how to obtain the data but also how to interpret them. "This is something I'd really like to do more," Jeroen emphasises, "to have people come over to the lab so we can show them how we do things and teach them how the interpretation works, because then they can get the most out of it." The fact that EMBL scientists can easily come to the Proteomics Core Facility in person, to plan and discuss projects at their different stages, is a great advantage of being located on site, he adds. This proximity is also advantageous for training: Jeroen ran a practical session in the EMBL predoc course for the first time this year, which was well received and may bring him more users. Not that he really needs them – the facility already has a steady stream of users from EMBL Heidelberg, the outstations, and the wider research community. So much so, in fact, that they have to prioritise EMBL projects, and select which outside projects they can take on.

Heppenstall group

In their efforts to understand the molecular mechanisms behind the sensations of touch and pain, Paul Heppenstal's group sends samples from EMBL Monterotondo to the Proteomics Core Facility to see whether their proteins are acetylated.

Rosenthal group

The group of Nadia Rosenthal, Head of EMBL Monterotondo's Mouse Biology Unit, studies how muscles – including our heart – repair and regenerate. They send their samples to Heidelberg for the Proteomics Core Facility to identify the proteins that interact with known players in this process.

Mattaj group

Iain Mattaj, Director General of EMBL, and his group turn to the Proteomics Core Facility to separate the different proteins that form the nuclear pores they study, and which allow specific molecules into and out of the cell.

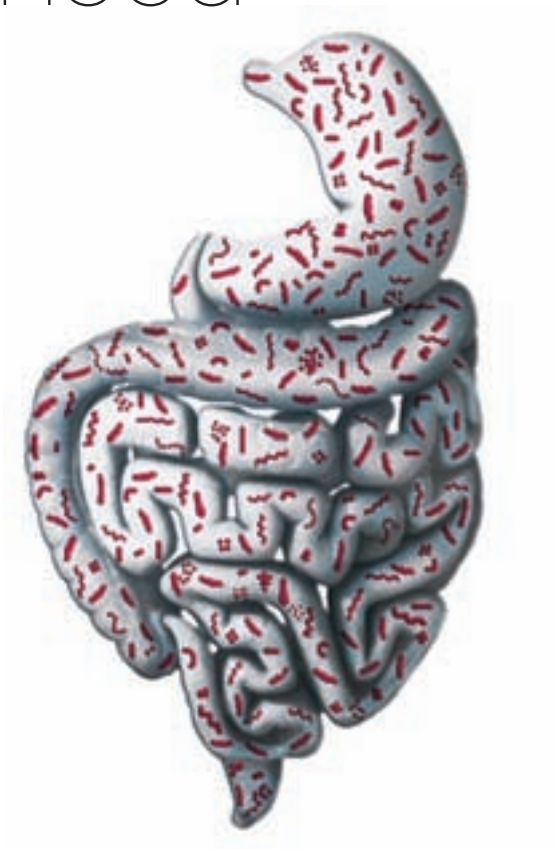
Beck group

Martin Beck and his group study how a large group of proteins called the nuclear pore complex assemble into a gateway to the nucleus. They use the facility to measure the amounts of specific proteins that make up this complex at different stages.

Köhn group

Maja Köhn and her group are working to design proteins that inhibit molecules involved in disease mechanisms. These scientists turn to the Proteomics Core Facility to confirm the identity, purity and overall quality of target proteins and their inhibitors.

In the neighbourhood



When people are looking for a new house, one of their main concerns is the neighbourhood. Virtually everyone wants to live in a nice neighbourhood, but what this actually means can vary wildly from person to person: it might be a quiet retirement village, a bustling city centre with lots of young people going out at night, or a place with lots of families so that the kids have friends to play with. And microbes, Peer Bork and his group at EMBL Heidelberg have discovered, are even choosier about with whom they share a neighbourhood.

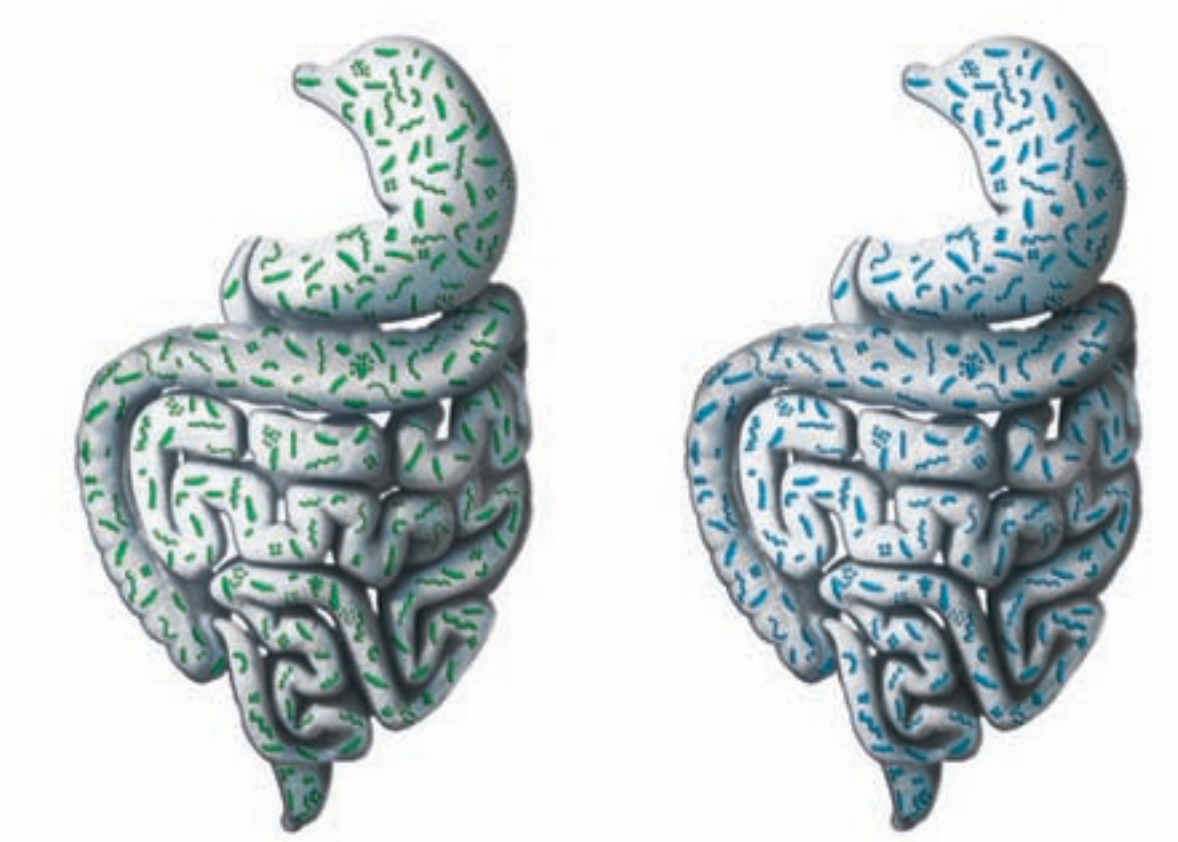
Our bodies have at least ten times more bacterial cells than human cells, and a good portion of these live in our guts. Peer and his colleagues in the international MetaHIT consortium are studying the bacteria that inhabit our digestive system. More precisely, they are looking at the genes of these bacteria. In an approach called metagenomics, they first determine the sequence of the DNA fragments present in a stool sample, and then put these puzzle pieces together to identify which bacteria they belonged to, thus cataloguing the bacterial inhabitants of a person's gut (see Annual Report 2009-2010).

A single human town can have dozens of different neighbourhoods, but the bacterial equivalent is much more select. Peer's group found that human gut bacteria seem to form three different community types. "Each community has a different combination of microbe species," Peer says, "and each person's gut has one of these three types of community. So we have three gut types, a bit like we have four major blood types." And like blood types, these gut types, or enterotypes, are independent of factors such as body-mass index, age and nationality.

Peer and colleagues analysed data from MetaHIT on gut bacteria from 39 people from three different continents (Europe, Asia and America), and later expanded the research to data from previous studies of an extra 85 people from Denmark and 244 from the USA. "Despite all the variation in sampling, which makes it a big challenge to compare the results of different studies, we still found the same three groups in all of them, which makes us confident that the results are meaningful," says Mani Arumugam, the study's first author, who worked on the project as part of his PhD in Peer's group.

Of all the different bacteria in the human gut, a group called Bacteroides are the most abundant. Nevertheless, the EMBL scientists found that one of the three gut types has many more Bacteroides than the other two. The other two gut types can be differentiated by their relative numbers of less abundant, non-Bacteroides microbes, like two suburban neighbourhoods with lots of families but whereas one also has some older couples and very few youngsters, the other has some youngsters and hardly any elderly.

The scientists don't yet know why gut bacteria form these specific communities. It could be down to differences between people's immune systems, for example, or it could be related to different physiological strategies for eliminating hydrogen. And although these gut types are independent of a person's weight, the fact that we



harbour a particular combination of bacteria in our gut could influence our body's reaction to diet and medication, raising the possibility that gut types may one day be medically relevant.

"When blood groups were first discovered, they were a curiosity with no real application, but when transplants entered the picture, blood groups became very important," Peer points out. "Similarly, knowing that we may have different gut types is an interesting starting point."

Although the overall neighbourhood of microbes in our gut doesn't seem to change with age, weight or nationality, certain bacterial genes do. The group found genes and gene networks that are linked to age, for example. Microbial genes involved in breaking down carbohydrates seem to appear in larger numbers in older people's guts, possibly because as we age we become less efficient at processing those nutrients, so to survive in the human gut, bacteria have to take up the task.

"The fact that there are bacterial genes associated with traits like age and weight indicates that there may also be markers for traits like obesity or diseases like colo-rectal cancer," Peer says.

The EMBL scientists' work proves that this kind of genetic marker can be obtained from stool samples, which – unlike blood samples and biopsies – are non-invasive and therefore easier on the patient. But before they can be used routinely in medical exams, the methods will have to be improved and simplified, as the current procedure involves a very specific, complex protocol.

If the methods can be made more tractable for general medical use, and if scientists do find bacterial genes that are typical of the guts of people suffering from specific conditions, this research could have implications for diagnostics and prognostics. When assessing the likelihood of a patient contracting a particular disease, diagnosing the disease, or predicting how it is likely to progress, doctors could look for clues not only in the patient's body but also in the bacteria that live in it. And treatment could be adapted to the patient's gut type to ensure the best results.

In short, the tenants in our gut probably play a big role in who we are, and how we react to diet and drugs. And ultimately, we could end up describing ourselves – medically, at least – based on their preferences for friends and neighbours.

Arumugam M *et al* (2011) Enterotypes of the human gut microbiome. *Nature* doi:10.1038/nature09944.


Station
Stoffwechsel
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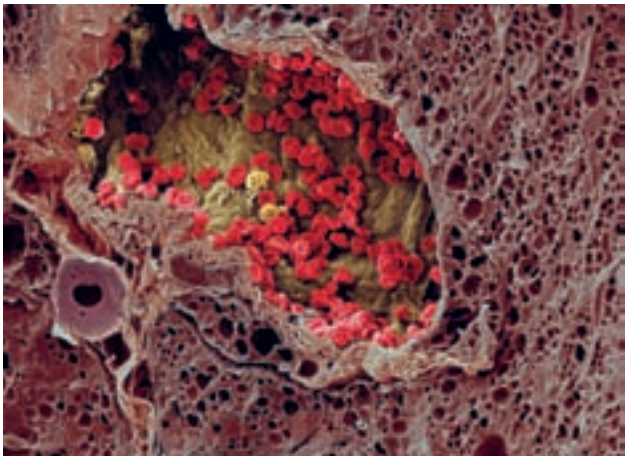
Molecular surgeries

Norma Lindemann,
Andreas Kulozik and
Matthias Hentze

On New Year's Eve 1866, Armand Trousseau came to the awful realisation that he would soon be dead. A celebrated French physician, he had, among his many contributions to medicine, noted that cancer patients often suffered from a greatly increased tendency to develop blood clots. These clots, often forming in the veins of the leg or arm, were associated with cancers of the internal organs, particularly the stomach. But on that fateful night, a mere two years after he had made his discovery, Trousseau himself developed a tell-tale blood clot in a vein in his left arm. The following day, he confided in a colleague that his symptoms left no doubt that he was suffering from gastric cancer. Six months later, he was gone.

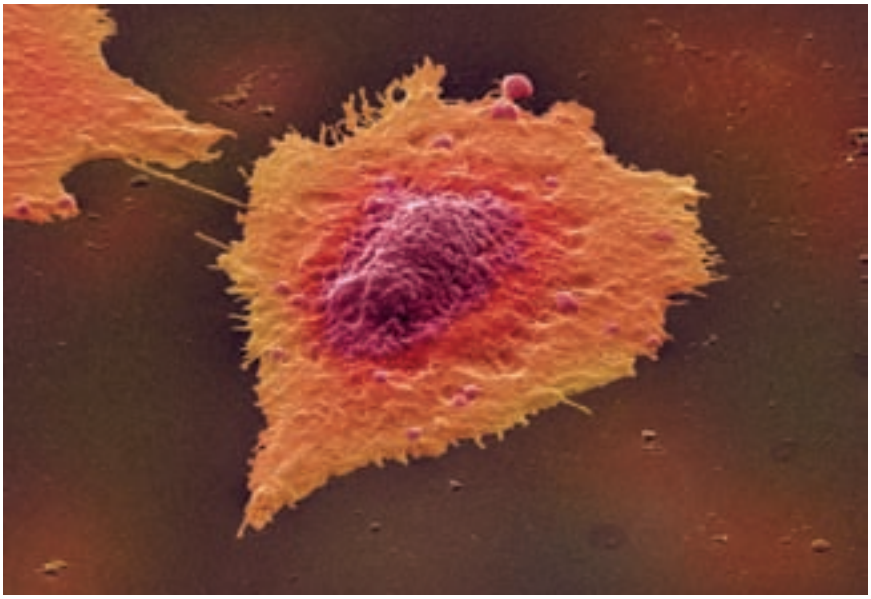
In the 150 years or so since his death, scientists have puzzled over the causes of Trousseau's discovery and even named the phenomenon after him: Trousseau syndrome. As well as being a sign of cancer, recent research has shown that people whose blood has an abnormal tendency to clot are at a higher risk of developing cancer in the first place. Intriguingly, people who take anti-clotting drugs such as Warfarin lower their risk of developing the disease. Now, thanks to research performed in the Molecular Medicine Partnership Unit (MMPU) – a partnership between researchers at EMBL Heidelberg and the University of Heidelberg – scientists have gained insight into this mysterious link. Their work also has implications for our understanding of how clotting goes wrong in conditions such as blood poisoning (septicaemia), inflammation and diabetes. And it has even uncovered a new mechanism that our cells use to control the activity of genes. "This is a prime example of how we can learn something instructive both in medical terms and in terms of basic biology, starting from a clinical observation," says Matthias Hentze, Associate Director of EMBL, who jointly heads the MMPU team with Andreas Kulozik of the Medical Faculty of Heidelberg University.



Cancer cells (brown) may produce more thrombin to drive the formation of nourishing blood vessels (red).

The story centres on a protein called thrombin, a key factor in the blood clotting process. Thrombin is like a molecular surgeon: it cuts bits off other proteins to change their shape and function. During blood clot formation, it customises another protein called fibrinogen, changing it so that it can form sticky threads that mesh together like fibreglass to form a clot. In recent years, however, scientists have realised that thrombin's role in blood clotting is merely its day job – the protein's surgical interventions are involved in other areas of our physiology, including the immune system, blood vessel development and cell growth. In addition to its involvement in cancer, it has been implicated in a wide range of common serious illnesses, such as multiple sclerosis, diabetes, stroke and Alzheimer's disease. But scientists knew little about how thrombin's activity is controlled.

Then about ten years ago, researchers noticed that there is a common mutation in the gene that makes thrombin that predisposes carriers to developing blood clots. The gene itself actually codes for a precursor of thrombin, called prothrombin. Prothrombin is an inactive form of thrombin that circulates in the bloodstream until it is needed for clotting, whereupon it is converted into active thrombin. Normally, the body only makes a small amount of prothrombin, but people with the mutation have an abnormally high level of the protein in their blood. The



Colon cancer cells seen under an electron microscope.

strange thing was, however, that the mutation didn't affect prothrombin itself. Instead, it interfered with the process that produced the protein.

This process works as follows: when a cell needs to make a protein, it begins by reading the DNA of the gene that encodes it. The sequence of letters in the DNA spell out instructions for how the cell should string together amino acids, the building blocks of the protein. The cell copies these instructions into another molecule called messenger RNA (mRNA), which then travels from the DNA to the cell's protein-making machinery. Before it can be used to make protein however, the mRNA has to be processed into the right form and adorned with proteins that control its behaviour. Unprocessed mRNA can't be used to make protein. So cells can control the amount of a protein they produce by controlling how much of that protein's mRNA is processed into a usable form.

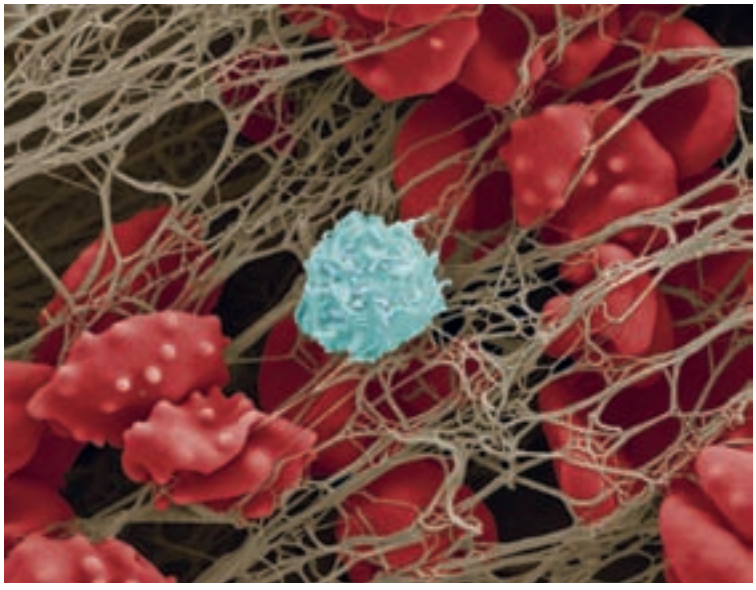
This is where the mutation that predisposes people to blood clotting comes in. It doesn't affect the DNA sequence that details which amino acids the cell should select. Rather, it is found at the end of the gene, which encodes instructions for making the tail end of the mRNA. This tail contains instructions telling the cell how to process the mRNA and provides a place for the proteins controlling its behaviour to dock. The MMPU team had previously discovered that the mutation that affected the extremity of the mRNA tail causes far more of it to be processed and used to make prothrombin protein than normal.

But although this discovery explained why people with the mutation had clot-prone blood, it raised another question. When the MMPU team looked at the end of the "normal" mRNA tail, which lacks the mutation, they realised that it would allow processing to take place so inefficiently that hardly any prothrombin would be produced. "So we asked the question: if the processing is so inefficient, why is prothrombin made at all?" says Andreas. The team took a closer look at the rest of the prothrombin mRNA tail. To their surprise, they discovered a new, extra section at the start of the tail that seemed to be responsible for boosting processing. This new section, which they dubbed the Upstream Sequence Element, or USE, had never been seen in other mRNA tails before. So why did prothrombin have such a complicated set-up? "We thought it might be a mechanism for tuning the production of prothrombin," says Andreas. In other words, the USE might allow cells to produce more or less prothrombin in response to changes in the body's physiology.

It was a promising idea: researchers already knew that prothrombin production increases when a person is under stress, such as when they are undergoing surgery. The MMPU team treated cells in the laboratory with a drug that mimics the effects of stress. Sure enough, the cells increased their production of prothrombin, but not the production of proteins whose mRNAs lacked a USE section. Infection is another trigger for blood clotting, so the team injected mice with a bacterial molecule to mimic the effects of blood poisoning. This triggered widespread inflammation and increased prothrombin production in the tissues of the mice.

But how does the prothrombin RNA detect these conditions? The team discovered that this is controlled by a signalling system called p38 MAPK. Cells lacking this signalling system cannot boost their prothrombin production in response to stress. The signal works by allowing the proteins needed for mRNA processing to dock on to the USE, which in turn increases the production of prothrombin protein from that RNA. This is the first time anyone has observed cells controlling the amount of protein produced from RNA in this way. "It's a novel mechanism of gene regulation," says Matthias.

To investigate the link with cancer, the team studied samples of invasive tumours taken from colon cancer patients. The tumours were "metastases", or tumours that had spread from the cancer's original site to other parts of the body. The team found prothrombin protein and processed mRNA at the fringe of where the tumours actively invaded healthy liver tissue. This may be linked to prothrombin's non-clotting activities: it's surgical abilities could help invading tumours hack through the matrix of proteins that surrounds cells in healthy tissues, whereas its role in blood vessel development could help tumours establish their blood supplies.



Under an electron microscope, the fibres that form a blood clot are clearly visible.

So here at last is a possible explanation for Trousseau syndrome: cancer cells increase their prothrombin production to invade tissues and grow blood vessels. The abnormal blood clotting seen in cancer patients is simply a side-effect of this increase. And now that researchers know that p38 MAPK is involved, it opens up the possibility of research into drugs to prevent the spread of cancer as drug companies are already working on p38 MAPK as a target for treatments for other diseases. "It opens up a path for future evaluation," says Andreas.

The discovery also highlights the benefits of marrying clinical and basic biological knowledge to tackle a medical problem. Andreas, an expert in biomedicine, co-directs the MMPU with Matthias, an expert in molecular biology. Both sets of expertise were vital to the success of the project. "I think this is a very good example of the overall philosophy of the Molecular Medicine Partnership Unit," says Matthias. Trousseau, who espoused breadth and artistry in the practice of medicine, would surely have approved.

Danckwardt S, Gantzert A-S, Macher-Goeppinger S, Probst HC, Gentzel M, Wilm M, Gröne H-J, Schirmacher P, Hentze MW, Kulozik AE (2011) p38 MAPK controls prothrombin expression by regulated RNA 3'end processing. *Mol Cell* **41**: 298-310

Spot the difference

Along with crosswords and Sudoku, the 'spot the difference' game is a favourite of magazine puzzle pages. The task is simple: to look at two near-identical pictures, and note the minor changes that have been made to one of them. When the print quality is poor, however, it can be hard to tell the difference between accidental smudges or printing errors and genuine, significant differences.

Biologists face a similar problem when comparing how biological systems act under different conditions: are the differences seen real and significant, or are they just noise, the equivalent of printing errors? It is a problem that Wolfgang Huber, from the Genome Biology Unit at EMBL Heidelberg, has encountered in his own studies of how the expression of genes varies between individuals. "We're looking for signal in the noise, a needle in a haystack," says Wolfgang.

The fundamental problem is statistical. Even when the measured numbers indicate that gene expression or transcription-factor binding varies across individuals or conditions, this difference might just be a chance result, reflecting random, and uninformative, variation. Deciding whether the difference is meaningful depends in part on how much random, natural variation already exists *within* groups of individuals or environments. And so the question becomes whether the variation seen *between* groups is more meaningful than the natural variation *within* groups. This is relatively easy to answer when you have large sample sizes. Yet practical constraints often mean that studies are much smaller than statistical purists might prefer. When the number of samples in each group is small, it is difficult — in fact, impossible — to reliably infer the size of the variation from the data. This makes both false positives and negatives more likely: seeing differences when none exist, and failing to spot ones that do. Inspired by discussions of these challenges with EMBL colleagues Lars Steinmetz, Eileen Furlong and Jan Korbel, Wolfgang and Simon Anders, a postdoc in Wolfgang's group, decided to tackle this practical problem.

Some computational challenges require brute force computation, but Wolfgang and Simon's solution was to work smarter, not harder. Together, they have developed *DESeq*, a bioinformatics tool that combines information about variance from many individual genes to effectively boost the sample size of the dataset. "We're safeguarding against these errors by pooling information across different genes," says Wolfgang. "Rather than looking at each gene separately, we look at many simultaneously."

Although the mathematical details of *DESeq* are complicated, it essentially gives you more analytic return on your investment of data. "It's a way of gaining statistical power without having to run larger, more expensive studies," says Wolfgang. "You're using the data in a more efficient, cleverer way." As such, *DESeq* could help identify clinically useful biomarkers to distinguish between different cancer types, or diseased and non-diseased tissue.

DESeq is open-source software, and is freely available to the research community through *Bioconductor*, a worldwide software collaboration. The software has already been used by hundreds of research groups and, says Wolfgang, "has received an enthusiastic reception among researchers around the world."

Anders S, Huber W (2010) Differential expression analysis for sequence count data. *Genome Biol* **11**: R106


XX
XY

Striking a balance

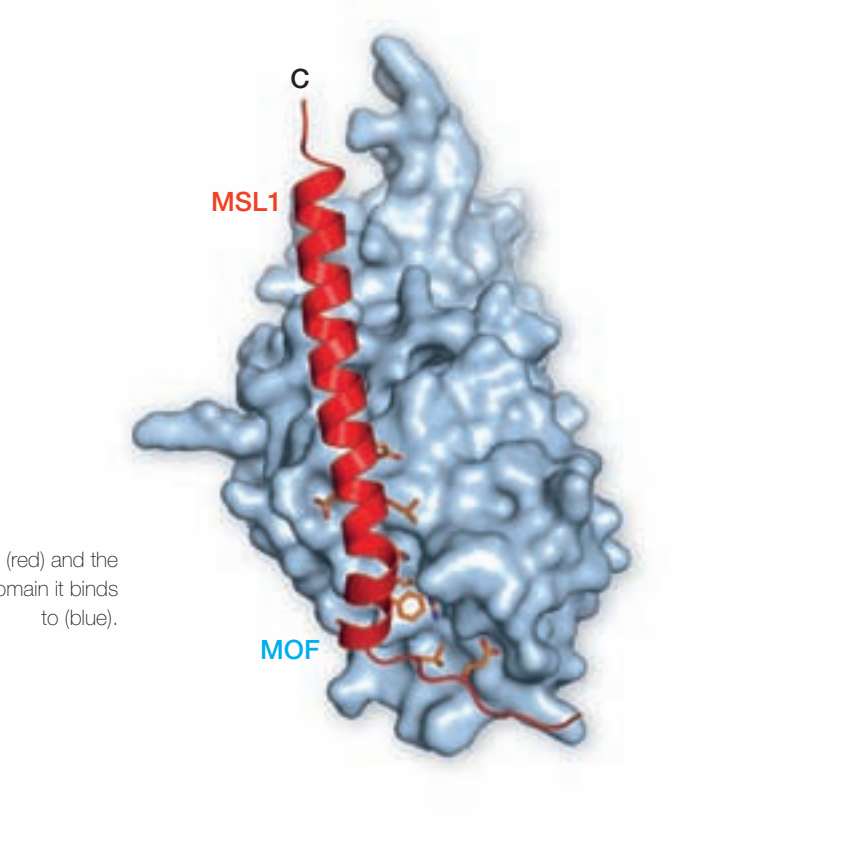
If you've ever tried listening to your favourite piece of music on a bargain-basement portable stereo, you'll know how awful it can sound: tinny and unbalanced, with the vocals and instrumentals mangled into an indistinguishable mush. Play it on a decent hi-fi system, on the other hand, and you can tinker with the graphic equaliser to alter the balance of the different frequencies in the music to your liking. For example, you can crank up the bass of a powerful Mahler symphony until the walls shake, or enhance the treble of a Handel oratorio to bring out the sopranos.

Our cells have their own equivalent of a graphic equaliser – not to get the most out of their iPods, of course, but to make sure that the proteins produced from our genes are present in the right proportions and are thus working together in perfect harmony. If the relative amounts of these proteins are thrown out of kilter, the effects can be dramatic. A person born with one extra copy of chromosome 21, for example, has an extra dose of all the genes it contains and thus makes too many of the proteins encoded by that chromosome. The consequence is Down syndrome, a congenital condition that results in a characteristic physical appearance and learning difficulties. On the other hand, if a cell in your body loses a gene or a chromosome, the loss of the proteins involved can cause that cell to become cancerous.

Given its importance, it's no surprise that cells have evolved a number of mechanisms to keep gene activity on an even keel. However the exact workings of these mechanisms are not clear. But Stephen Cusack and his team at EMBL Grenoble in collaboration with Asifa Akhtar, a group leader at EMBL Heidelberg (now at MPI Freiburg), have now determined the structures of parts of a key molecular machine, or protein complex, involved in regulating the balance of gene activity, or gene "expression", in the cell. "This gives us new insights into how the complex is assembled and operates," says Stephen.

The process Asifa, Stephen and their teams are studying is how gene expression on a particular kind of chromosome, the sex chromosomes, is controlled. In many animals, an individual's sex is dictated by the combination of sex chromosomes it inherits. In humans, these chromosomes are the X and Y: inherit 2 Xs and you become female, inherit an X and a Y, and you become male.

The issue of balance becomes clear when you consider the other non-sex chromosomes, called autosomes, that we inherit along with our sex chromosomes. Humans have 22 autosomes, which come in pairs – one chromosome of the pair is inherited from your father, the other from your mother. As each chromosome in a pair contains the same genes, we have two copies of all the genes on our autosomes. The activity of the genes on each pair is carefully balanced so that between them, they produce the right amounts of proteins.



MSL1 (red) and the MOF domain it binds to (blue).

The sex chromosomes, however, are a different story. The X and Y chromosomes are radically different from each other: the Y is a fraction of the size of the X and they share almost no genes in common. This means that females, with their two Xs, carry a double dose of the genes on that chromosome, whereas males, who carry an X and a Y, only have a single dose.

Different animals have evolved different ways of dealing with this disparity. Human females shut down one copy of their X chromosome in all of their cells. This phenomenon, known as X-inactivation, ensures that males and females both have a single active copy of each X chromosome gene. Other animals do the opposite: instead of shutting down one X in females, they boost the activity of the genes on the X chromosome in males, a phenomenon known as dosage compensation. These two processes, akin to sliding a fader up or down on a graphic equaliser, are of great interest to biologists because they allow cells to control all the genes on an entire chromosome at once.

"This gives us new insights into how the complex is assembled and operates."

Asifa's team has spent a long time studying how dosage compensation is controlled in fruit flies. These tiny creatures are widely used in biological research because it is easy to perform genetics experiments on them and also because their biology is now relatively well understood. What's more, many of the genes and proteins involved in the cell biology of flies have similar counterparts in humans. This means that flies can be used to give insights into our own biology.

Oddly enough, this work has revealed that there may be a process related to dosage compensation in humans. Even though flies and humans seem to have very different ways of dealing with their sex chromosome problem, the group of proteins used by flies to control dosage compensation has an equivalent in humans. This is rather mysterious because so far, biologists have not found any evidence that human cells boost gene activity on their X chromosome.

One possible answer to this puzzle lies in how the fly proteins are thought to work, as part of a group, or complex, called the MSL complex. This complex modifies another set of proteins called histones that make up the scaffolding of a chromosome. The DNA in the chromosome is wound around histones like thread on thousands of tiny bobbins, forming a structure known

EMBL Grenoble

as chromatin. As well as packaging the DNA and protecting it, chromatin is also involved in controlling the activity of the genes encoded in the DNA. By adding different chemical tags to histones, the cell can control how tightly they pack the DNA away. If DNA is closely packed, it can't be decoded to make proteins; if it is loosely packed, it can. In flies, the MSL complex is thought to work by altering the histones of the entire X chromosome. "Essentially, you are influencing the gene expression levels of the whole chromosome by modifying the chromatin structures," says Jan Kadlec, who works as part of Stephen's team.

Although the fly MSL complex has been studied for many years, a number of mysteries remain. Exactly how all the proteins in the complex assemble on the X chromosome and how they change its chromatin structure is not fully understood. Even more mysterious is the function of the human equivalent. Knowing more about the structure of the complex and what it looks like bound to chromatin would undoubtedly help.

But this is much easier said than done. The fly MSL complex comprises five large proteins called MSL1, MSL2, MSL3, MLE and MOF, together with two long molecules of non-coding RNA, a chemical relative of DNA. The human equivalent has a similar composition, minus the RNA. "We would like to determine the structure of this whole complex, as this should shed light on its mechanism," says Jan. "But it's very difficult, if not impossible, to do."

As a start, the researchers broke things down: they created a simpler complex between fragments, or "domains", of just two of the human proteins, MSL3 and MOF, and studied how this complex interacts with different fragments of human MSL1. To determine the structures, the team used a technique called X-ray crystallography, in which they obtained crystals of their different protein complexes, shone X-rays on them and deduced their structures from the way in which the crystals scattered the X-rays. "The flexible access to the X-ray beamlines of the European Synchrotron Radiation Facility was instrumental to this project," says Stephen.

"We are also grateful to the High-troughput Crystallisation Facility at EMBL Grenoble, which helped us to obtain usable crystals of these tricky complexes."

The structures revealed that MSL1 acts as a scaffold, attracting MSL3 and MOF to the MSL complex. What's more, it looks as though the human and fly protein structures are very similar. "We could see that similar surfaces exist on all of them," says Jan. To find out how the complex loads itself onto the X chromosome, the team went back to the fly equivalents of these proteins and mutated the key building blocks, or amino acids, they had identified from the structure as being important for the interactions between MSL1 and MSL3 or MOF.

"The flexible access to the X-ray beamlines of the European Synchrotron Radiation Facility was instrumental to this project."

This showed that by mutating particular amino acids, the team could eliminate either MOF or MSL3 from the complex. This gave them a very useful tool for dissecting the process by which the complex assembles on chromatin. By ridding the complex of either MOF or MSL3 in living cells, they were able to show that the complex behaves differently on different areas of chromatin. In the middle or at the end of genes, and in "high-affinity" areas that particularly attract the MSL complex, for example, it needs MOF and MSL3 to bind to chromatin. But in the control regions at the start of genes, MOF and MSL3 were dispensable.

"We now have a much better idea of what the core of this complex looks like and we now have the tools and first results on the recruitment and binding of this complex to the chromatin," says Jan. The next challenge is to add more proteins from the complex into the mix, to better understand how our cell's graphic equalisers work. "Now we are trying to make larger complexes," says Jan. "But the larger they get, the harder it is."

Kadlec J, Hallacli E, Lipp M, Holz H, Sanchez-Weatherby J, Cusack S, Akhtar A (2011) Structural basis for MOF and MSL3 recruitment into the dosage compensation complex by MSL1. *Nat Struct Mol Biol* **18**: 142-149

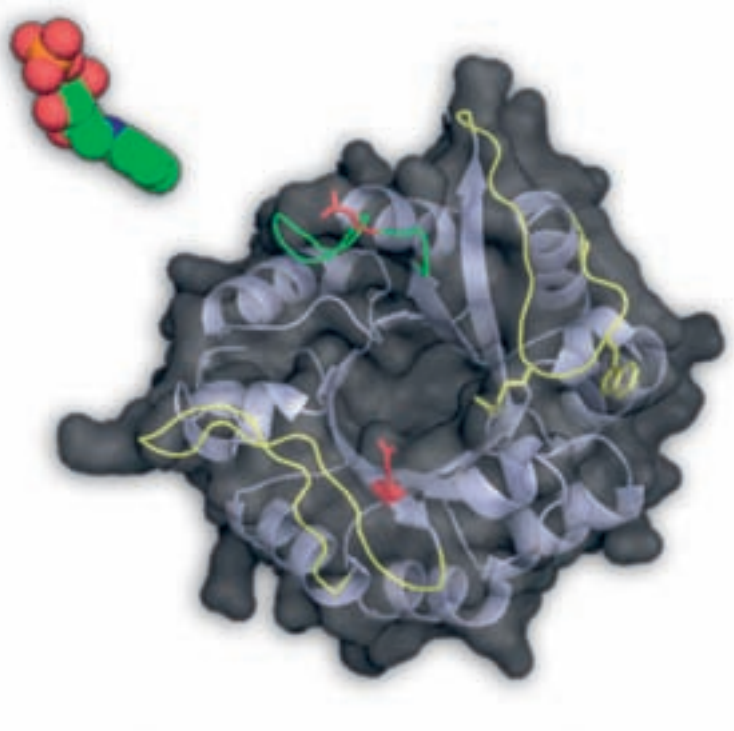
The secret double life of TB

"*Late one accursed night, I compounded the elements, watched them boil and smoke together in the glass, and when the ebullition had subsided, with a strong glow of courage, drank off the potion.*" So goes the sorry tale of the noble Dr Henry Jekyll, who transformed himself into the wicked Edward Hyde. Dr Jekyll may be fictional, but it now seems his use of a chemical to switch between diametrically different alter egos is a habit shared by a real-life protein in the tuberculosis (TB) bacterium. Matthias Wilmanns and his colleagues at EMBL Hamburg have discovered how a TB protein called PriA pulls off this trick, a finding that both solves a long-standing biological mystery and opens up a new avenue for developing drugs against this deadly disease.

PriA is an enzyme, which is a protein that speeds up a chemical reaction. Enzymes work by seizing one of the molecules involved in the reaction and changing it so that it reacts more easily. The molecule-grabbing part of an enzyme is known as its active site and for many years, scientists believed that an active site could only recognise one particular target molecule, known as its substrate. This was because the structures of the substrate and the active site fitted each other exactly, just as a key fits into a lock. Accordingly, it was thought that each reaction in the cell was controlled by a unique enzyme.

Recently, however, scientists have discovered some 'promiscuous' enzymes, including PriA, that can recognise more than one substrate and so control more than one reaction. PriA was particularly puzzling because its two substrates are so different: one is twice the size of the other. "It really was quite enigmatic," says Matthias. "We had no idea how one active site could do both things." PriA is a vital enzyme for the TB bacterium, as the two reactions it controls are essential for making two of the amino acids on which its survival depends. Most bacteria rely on two separate enzymes for this process.

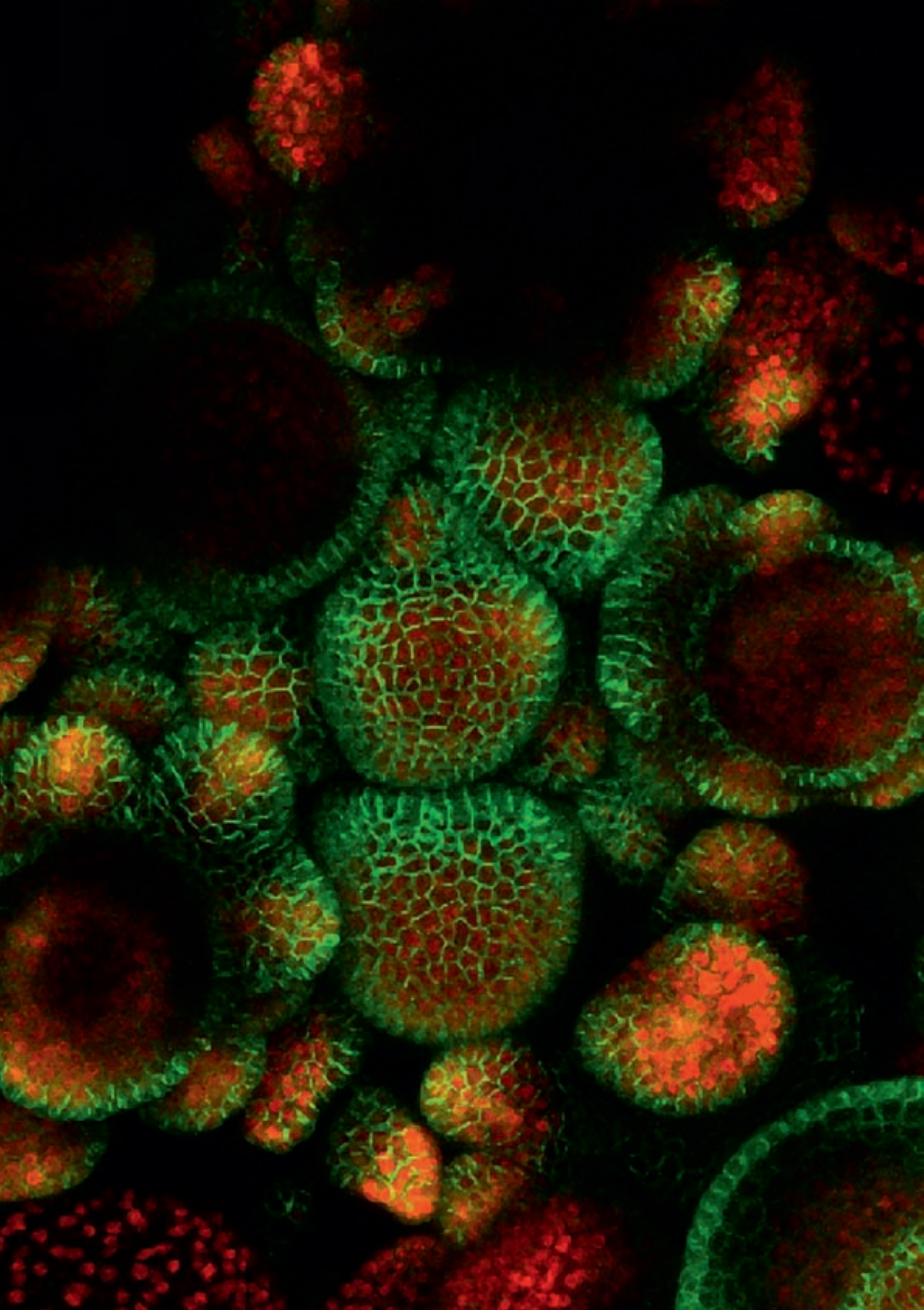
To find out more, the team turned to X-ray crystallography, a technique in which scientists determine the structure of a protein by shining X-rays on crystals of that protein. In this case, the researchers wanted to look at how PriA behaved when it interacted with its substrates. This involved mixing the enzyme with compounds that mimic one or other of the substrates and creating and studying crystals of these mixtures, with the help of the high-throughput platforms at Hamburg and the state-of-the-art synchrotron radiation facilities at EMBL Grenoble.



3D structure of *Mycobacterium tuberculosis'* multitasking enzyme, PriA.

They discovered that PriA's active site is extraordinarily flexible and that the substrates themselves mould it into the right shape, making it metamorphose from one function to the other. The team then found six compounds that bind to PriA's active site and block both of the enzyme's functions. Matthias thinks that this kind of approach – finding and targeting processes that are unique to TB – could complement more 'traditional' pharmaceutical approaches for finding much-needed new treatments. "We have to look for biology that is different in TB compared with other organisms," he says. With any luck, TB's secret double life, like that of Henry Jekyll, could ultimately lead to its demise.

Due AV, Kuper J, Geerlof A, von Kries JP, Wilmanns M (2011) Bi-substrate specificity in histidine/tryptophan biosynthesis isomerase from *Mycobacterium tuberculosis* by active site metamorphosis. *PNAS* **108**: 3554-3559



Going with the flow

In his book *River Out of Eden*, Richard Dawkins depicts the flow of genetic information from one generation to the next as a river winding through time. By following the river back to its source, we can trace our ancestry back to the beginning of life on Earth. Each of us starts our journey at a slightly different point on the river's bank, because no two people are exactly the same. These genetic differences are being catalogued in a project led by researchers at EMBL-EBI, the first results of which have now been published (page 28).

On a shorter time-scale, every cell must control the flow of molecules into and out of itself – another research group in Hinxton has begun to understand how a particular class of gatekeeper molecules selects what enters a cell (page 37). Meanwhile, researchers at EMBL Grenoble took a snapshot of the moment when a protein produced inside a cell is handed over to machinery on the cell's membrane (page 45).

In Hamburg, new state-of-the-art facilities are in place to improve the efficiency with which scientists can determine the shape of a molecule by how light flows around it (pages 46 and 48).

Paul Flicek

It takes all sorts

If you want to get a glimpse of one of the biggest challenges facing modern genetics, take a peek in any wedding album and see what family traits you can spot. The bride's immediate family might all have dark hair, but the proud father-of-the-bride might have brown eyes whereas his daughter's are blue. The groom, meanwhile, has inherited his mother's enormous nose, a fate his sister has escaped. She, however, has her father's protruding ears, artfully hidden under this season's must-have hat. The group photo of all the guests, meanwhile, is a smorgasbord of physical characteristics, from the rounded figures of the bride's drinking buddies to the towering frames of the groom's Scandinavian work colleagues.

So here's the challenge. All these people are human, meaning they – including the unrelated guests – all share almost all of their DNA sequence in common. How do you explain the sheer variety in physical characteristics and susceptibility to different diseases that you see across the human race? How are these traits transmitted (or not) to different family members? And why do some people tend to develop certain diseases, such as diabetes, whereas others are more likely to get cancer?

The short answer, of course, is that it's down to that tiny, fractional difference in DNA sequence: different people have different versions, or variants, of the genes that underlie these traits. The long answer – zeroing in on this fraction to find the genes and variants associated with these traits and work out what they do – is still very much work in progress.

Such research, however, is set to receive a major boost from work by Paul Flicek and his colleagues at EMBL-EBI. They are undertaking an ambitious project to create a definitive catalogue of human genetic variation by studying the genomes of thousands of individuals in unprecedented detail. They hope the work will accelerate research into the genetic basis of common conditions and rare inherited diseases, as well as helping scientists understand more about what determines our physical traits, from blue eyes to big ears. The team recently published the findings of the pilot phase of the project, which is already helping researchers track down the genes involved in inherited diseases. "It won't happen in every case," says Paul. "But I'm very confident that in the next two years you will regularly read high-profile papers describing genetic diseases that have had their causes found."

The project is called the 1000 Genomes Project, and is the next logical (and highly ambitious) step to further biologists' understanding of human genetics. Back in 2001, researchers announced that they had read the entire sequence of DNA building blocks, or bases, that make up the human genome, the genetic information that spells out the instructions for making a human being. Although this was truly groundbreaking, this "reference" sequence only represented one individual genome, not enough to get a handle on human variation.

The first big project to target variation was the International HapMap project. This looked for points in the genome that varied by just one DNA base between populations. These tiny variants, called Single Nucleotide Polymorphisms, or SNPs for short, gave the first overview of human variation and have proved invaluable in the search for disease-related genes. The HapMap, however, didn't give the whole picture: there are many other ways in addition to SNPs in which a gene sequence can vary, which the HapMap didn't document. And the technology used to make the HapMap didn't give the fine level of detail full genome sequencing would provide.

The reason earlier research into variation didn't use DNA sequencing is because, at that time, reading even one genome was prohibitively expensive and time-consuming. Over the past five years, however, technology has advanced with lightning speed, slashing the costs and effort involved and making the sequencing of many individuals a viable option.

So in 2007, Paul and his colleagues first mooted the idea of the 1000 Genomes Project. The idea was to sequence the entire genomes of at least a thousand individuals with a high degree of accuracy. "It was a hugely ambitious project," says Paul. "The ambition has only gone up as the project has developed." Four years ago, the plan was to sequence about six trillion bases, or six "terabases"; the team now has its sights set on 60 terabases. The number of individuals being sequenced, meanwhile, has grown to 2500. "The goal is to create, to the extent possible, a complete map of shared variation in multiple human populations," says Paul. To that end, the project will be gathering data from five major population groups: people living in or having ancestry from Europe, East Asia, South Asia, West Africa and the Americas. "The populations we have chosen represent the majority of people living in the world," says Paul.

The aim is to find variations that are shared by at least 1 in 100 different people within a population. The researchers are looking for shared variations because this will help scientists track down the genes behind physical characteristics. The more people share a variant, the more likely it is to be linked to common traits such as having blue eyes or, as many people believe, a tendency to develop high blood pressure. Rare variants are more likely to be associated with uncommon, inherited diseases that are caused by faults in single genes. Having all this information to hand would help geneticists pick out and zoom in on the genes that are most likely to be involved in the disease they are studying. If they are investigating a rare inherited disease, for example, and work out which region of the genome is harbouring their gene, the 1000 Genomes data will let them pick out the rare variants in that region for further analysis.

Given that the team was entering uncharted territory and pushing new and developing technologies to the limit, they began by performing a smaller, pilot project to test their experimental strategy. The results from this pilot, published in October last year, have not only helped the team refine their plans for the main project, but have also revealed many intriguing insights into the genetic variation that gives humanity its dazzling diversity of shapes and sizes.

The pilot project was divided into three smaller projects. The first two aimed to test how thorough the sequencing had to be to paint a sufficiently accurate picture of a person's genetic variants. The more times a particular genome is read – its "coverage" – the fewer mistakes and gaps there are in the final sequence, but the more expensive the experiment. The team compared low-coverage sequencing of 179 people from four populations with high-coverage sequencing of two families (each comprising Mum, Dad and one daughter). "The low-coverage approach turned out to be very accurate," says Paul. The family sequence work also suggested that the rate of new mutations arising in each generation was actually very low – about 30 changes across a genome of some three billion bases.

The third project targeted high-coverage sequencing to the parts of the genome that code for proteins. Proteins perform much of the biology in our cells and bodies, hence the interest in how they vary. A striking finding from this study was that each of us carries up to 300 mutations that disable proteins encoded by these genes. Between 50 and 100 of these mutations are already known to cause particular inherited diseases. In many ways, these discoveries shouldn't be too surprising, says Paul. "We all get some disease and that disease is a combination of environmental and genetic factors," he says. "There is no 'perfect' genome!" Fortunately, we have two copies of each gene in our genomes – one from each parent – and so we usually have a backup working copy of any disabled proteins.

Collecting and managing the vast reams of data for the 1000 Genomes Project is no mean feat. "We're able to do it because we work so closely with the European Nucleotide Archive team at the EMBL-EBI," says Paul. Sharing the data is also vital: the projects' salient findings will be published in the EMBL-EBI's online database Ensembl, making it freely accessible to researchers around the world.

Putting all their findings from the pilot project together, the team announced they had found 15 million SNPs, a figure that has since jumped to 25 million, more than double the number previously known. "This number will continue to grow," says Paul. What's more, the team also found a million variations that involve losing or gaining a short piece of DNA and 20 000 rearrangements of the structure of chromosomes. Most of these were previously unknown. "We now have a much more complete picture of what the variation looks like," says Paul. Helping to build that picture is work by Jan Korbel in Heidelberg, looking at large variations in the structure of genomes (page 89).

The full project is scheduled for completion in 2012, and will doubtless unveil further revelations about human diversity. Perhaps in years to come, we'll know not just what gene variants are behind the physical quirks of our nearest and dearest, but also know more about how they originated and came down to us though the generations. As Paul puts it: "A genome sequence is kind of the ultimate family history."

The 1000 Genomes Project Consortium (2010) A map of human genome variation from population-scale sequencing. *Nature* **467**: 1061-1073


The dark side
of the cell

Lars Steinmetz and Wolfgang Huber

Gazing up at the starry sky of a balmy summer's night is one of life's simple pleasures. As you do so, ponder this: there is a surprising parallel between the vast majesty of the cosmos and the inner workings of your body's cells. The universe and you share a similar scientific mystery, one that Lars Steinmetz and his team at EMBL Heidelberg are helping to solve.

Cosmologists have long sought to explain why the stars and galaxies are scattered across the cosmos in the way that they are. There simply isn't enough normal matter around to account for the gravity to explain why the universe keeps expanding. So they have proposed the existence of invisible "dark" matter, which exists in greater amounts than visible matter, to account for it. No-one has yet seen this mysterious substance, but if it does exist, much about the universe suddenly makes sense.

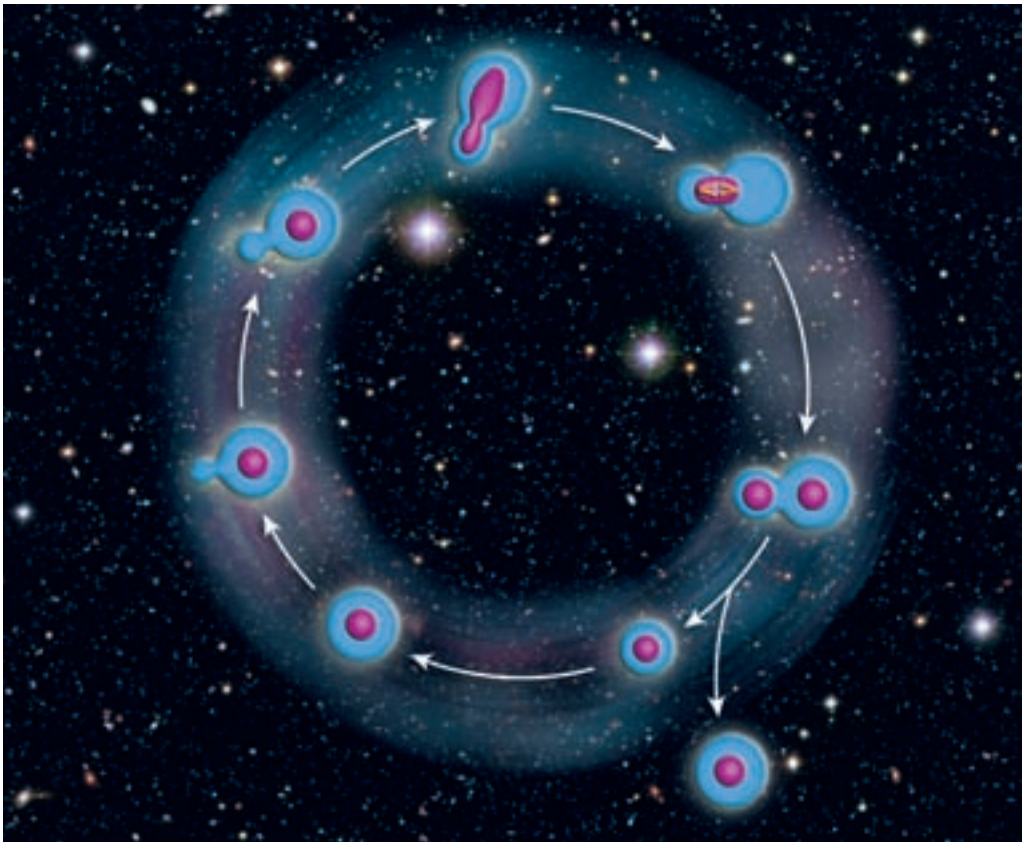
Molecular biologists have their own equivalent of dark matter to puzzle over. In many ways, their problem is the opposite of the one faced by cosmologists: the dark matter of the cell is entirely visible, yet its function is a mystery. This matter takes the form of molecules that, according to theory, really shouldn't be there. Yet they are there, in spades, and finding out what they do could plug a gap in our understanding of how our cells and bodies work.

"I hope our high-resolution 'satellite imagery' [...] will stir the imagination of scientists."

The molecules in question are RNA molecules. RNA is a large molecule that is similar to DNA and is essential to all forms of life. Historically, however, biologists underestimated the extent of the role of RNA in the cell, thinking that it acted mainly as the cellular equivalent of a courier and a bricklayer. This idea had its roots in the discovery of how genes spell out the instructions for making a protein. A gene consists of a sequence of DNA "letters" that encode instructions for stringing together the building blocks, or amino acids, that make up a particular protein. When the cell makes a protein, it begins by reading the gene and making an RNA copy of the sequence of letters. This process, called transcription, produces a kind of RNA called messenger RNA. This makes its way to the cell's protein-making factories, where molecular robots called ribosomes read the RNA and piece together the correct sequence of amino acids.

But as molecular biologists started exploring genomes, they ran into a mystery. There seemed to be long stretches of DNA that didn't seem to code for proteins at all. The sequencing of the human genome confirmed this: less than two per cent of our genome consists of protein-coding genes. The rest was apparently functionless "junk" DNA. A few years later, work from a number of laboratories including EMBL-EBI and EMBL Heidelberg, revealed that almost all of this "junk" was being transcribed into RNAs of differing lengths. Because they weren't involved in producing proteins, these RNAs were named "non-coding RNAs". As they vastly outnumbered the messenger RNAs and yet had no known function, they soon became known as the dark matter of the genome.

During the past few years, scientists have discovered that some of these RNAs – short molecules called microRNAs and small interfering RNAs – are involved in controlling gene activity. But the function of the longer non-coding RNAs remains mysterious. So Lars and his team decided to take a closer look at what happens in yeast cells. Yeast have much of their basic biology in common with our cells, but unlike human cells, they are easy to manipulate with genetics and molecular biology. Biologists can, for example, disable a single yeast gene or RNA with great precision, allowing them to work out its function.



The scientists measured all the RNAs produced during yeast's cell cycle.

Like the human genome, the yeast genome churns out vast quantities of non-coding RNA. Lars' team was the first to profile and publish the total RNA output – or "transcriptome" – of a yeast called *Saccharomyces cerevisiae*, also known as baker's yeast. As well as being used for baking and for brewing beer, this organism is commonly used in molecular biology studies. "We were very surprised because we saw all these RNAs showing up in regions where we didn't expect to see them," says Lars.

So the team took a closer look at the mystery RNAs. Some came from parts of the genome that lay in large gaps between protein-coding genes, yet showed no signs of coding for proteins themselves. Others were more mysterious still. They were produced from the same genes that code for normal proteins, but were a kind of mirror image of the messenger RNA produced by that gene.

Normally, when a cell makes a messenger RNA, it begins by unzipping the double helix of the DNA that encodes the gene. DNA is made up of two intertwining strings of molecular letters, or bases. When a cell reads a gene to make a messenger RNA for a protein, it only reads one of the two strands. This coding strand is called the "sense" strand. The opposite strand is called the "antisense" strand and until now, biologists believed that it was almost never transcribed. Lars' data, however, suggested that these mirror-image-like antisense transcripts were commonplace.

To try to get a handle on what some of these RNAs might be doing, Lars' group teamed up with bioinformaticians Peer Bork, at EMBL Heidelberg, and Wolfgang Huber, then at EMBL-EBI. With the help of the Genomics Core Facility, they measured how the production of these RNAs varied over the course of a cell's life, as it went through the repetitive cycle of growing and dividing into two new cells. This process, called the cell cycle, is fundamental to the biology of all cells. What's more, abnormalities in the cell cycle are hallmarks of a number of human diseases, particularly cancer.

If the production of certain RNAs varied over the course of the cell cycle, Lars reasoned, this would suggest that they might somehow be involved in either controlling or executing it. So the

team undertook a heroic set of experiments: to sample yeast cells every five minutes over the course of three cell cycles (each lasting an hour or more) and measure all their RNAs.

Halfway through the experiments, disaster struck. The team realised that one of the reagents they were using was creating mistakes in the data: producing "phantom" transcripts that didn't really exist in the cell. Fortunately, they devised a way to solve the problem, but they still had to repeat all their work. "It was a huge effort," says Lars. But the hard work paid off –18 months later, the team had high-quality results. "The data that we published are fresh, clean data," says Lars.

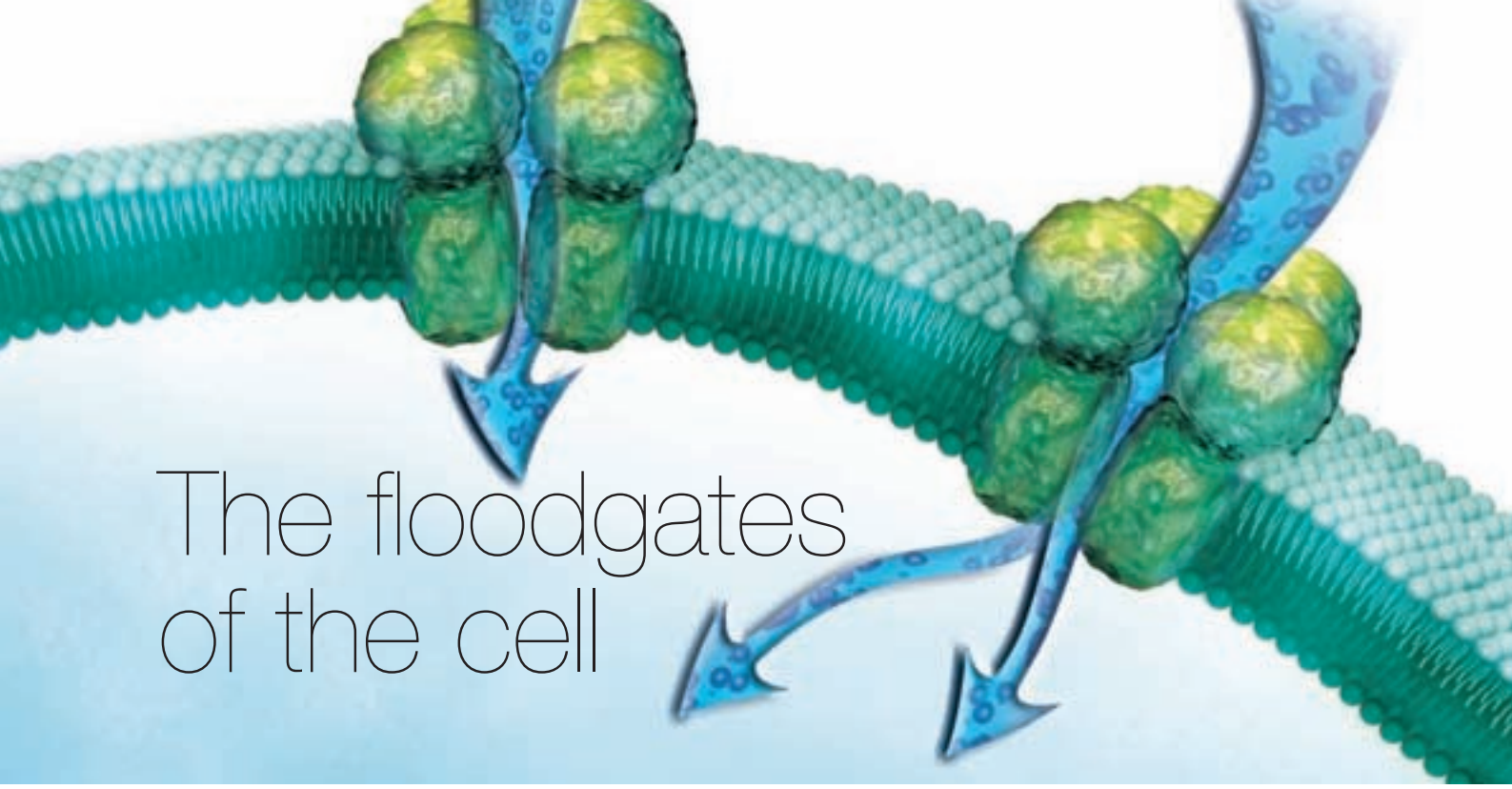
The data have resulted in a highly detailed "atlas" describing all the transcripts in yeast and how they vary during the cell cycle. Some non-coding transcripts from the gaps in between protein-coding genes were transcribed in a periodic fashion, others were not. Some antisense transcripts were periodic, as were their sense counterparts. But other periodic antisense transcripts were twinned with non-periodic sense transcripts, and vice-versa: some periodic sense transcripts had non-periodic antisense opposites. Just to make things even more complicated, many transcripts seemed to come from overlapping sections of the genome.

The big question is: what are they all doing? "These are all very hotly debated areas," says Lars. "We cannot be conclusive at the moment in saying how many of these are functional." One key argument in the debate is whether these non-coding RNAs have any function at all, or whether they are simply produced accidentally by the cell's transcription machinery being a bit "overenthusiastic". Lars is sceptical of this idea: "I am of the belief that if something happens in biology it's not just noise, there must be a reason for it," he says. He points out that the cell has to invest a lot of energy into producing all that RNA: "Transcription costs something for the cell."

The team is conducting experiments to test out their hypotheses, and have already uncovered hints that antisense transcripts could help fine-tune gene expression (see page 96). As well as revealing more about what these RNAs are doing, the atlas promises to give new insights into how the cell cycle works. "The high resolution of this dataset allows one to get a much more accurate way to model the cell cycle," says Lars. At the moment, such models are based on the behaviour of protein-coding genes. Lars' data will allow scientists to not only include the information on the non-coding transcripts, they will also be able to benefit from the more detailed protein-coding transcript data the study has provided. Another benefit is the innovation Lars and his team developed to counter the problem reagent that creates false results. Molecular biology laboratories will be able to produce more reliable results by following Lars' modified method. "I hope our high-resolution 'satellite imagery' of the global regulation of all transcripts during the yeast cell cycle will stir the imagination of scientists to further explore their favourite regulatory patches in more detail, perhaps conferring an as yet unknown functional role to the new non-coding RNA molecules we have mapped," says Marina Granovskaya, a postdoc in Lars' lab who performed the yeast experiments.

So biologists now have a starting point: the entire constellation of yeast RNAs and how they vary through the cell cycle laid out in fine detail, an atlas to help them navigate their way to a better understanding of what this mysterious cellular "dark matter" is doing. The only question that remains is whether they will beat the cosmologists to finding an answer.

Granovskaia M, Jensen L, Ritchie ME, Toedling J, Ning Y, Bork P, Huber W, Steinmetz LM (2010) High-resolution transcription atlas of the mitotic cell cycle in budding yeast. *Genome Biol* **11**: R24



The floodgates of the cell

"You make a better door than a window!" is how English people will often tease you if you're blocking their view of the TV. Rather than shuffling apologetically out of the way, here's how to tease them back. Tell them that you don't just make one excellent door, you are in fact made of millions of them: tiny molecular portals peppering every cell in your body. These doors come in a multitude of different kinds, each of which carefully selects which molecules can pass in and out of the cell. Now, EMBL-EBI Director Janet Thornton and her team have solved part of the mystery of what makes these gatekeepers so choosy.

The doors in question are proteins known as membrane channels, which poke through the fatty envelope that surrounds cells and keeps vital molecules safely inside and excludes those that are unwanted or harmful. Membrane channels ensure the right molecules pass in and out of the cell, through the tunnel-like hole, or pore, that runs down the centre of the protein. Most membrane channels will only allow one specific kind of ion or molecule, such as water, to pass through. Others will admit a select handful of molecule types. A number of human diseases, including heart disease, involve membrane channels, and they are the target of about half of all medicinal drugs under development. But although the structures of 37 of these proteins have been determined, researchers did not understand what made the channels so selective.

Janet and her team have long been interested in how these proteins work. "Membrane proteins are just beautiful," says Janet. "They simply fascinate us." They decided to focus on a particularly important type of membrane protein called aquaporins, which allow water and several other important molecules into the cell. Aquaporins come in two main types: "orthodox aquaporins", which only take in water molecules and "aquaglyceroporins", which admit water and other small molecules such as glycerol and carbon dioxide.

Tim Maiwald, a Masters student in Janet's laboratory and senior postdoc Marialuisa Pelegrini-Calace developed the software PoreWalker, which can calculate the internal shape, size and chemistry of a membrane channel's pore from its structure. Together with sabbatical visitor Romina Oliva, from Università di Napoli "Parthenope", who has a longstanding interest in aquaporins, they applied the program to the aquaporin structures and found that the different patterns of electrical charges on the amino acids lining the pores of different channels tallied with their different specificities. These charges, termed electrostatic charges, probably reflect the physics of the molecules each pore transports. Orthodox aquaporins have a greater electrostatic charge at one end of their pore, whereas the charge in the pores of the aquaglyceroporins is spread out more evenly.

Although electrostatics may only be part of a bigger picture, they do give important new insights into how our cellular floodgates control the flow of water in our cells, says Janet. Her team has now made PoreWalker freely available on the EMBL-EBI's website to help other researchers undertaking similar projects – opening the door for more revelations about these mysterious and beautiful proteins.

Oliva R, Calamita G, Thornton J, Pellegrini-Calace, M (2010) Electrostatics of aquaporin and aquaglyceroporin channels correlates with their transport selectivity. *PNAS* **107**: 4135-4140

Dónal O'Carroll

Finely-tuned machines

What do you and a rally car have in common? More than you might think. Rally cars have teams of mechanics to keep them finely tuned, so that as well as being able to drive sedately along normal roads between racing stages, they can also cope with extreme, cross-country courses without breaking down. It now seems that cells, perhaps including those of our own bodies, have their own molecular mechanics that keep them ticking over under all conditions.

Dónal O'Carroll and his team at EMBL Monterotondo study microRNAs (miRNAs), a group of molecules that help control the activity of the genes they target by shutting down the production of the proteins encoded by those genes. They are intriguing because miRNAs seem to control a huge number of genes in developing embryos and have been implicated in a range of diseases, including cancer. Yet, scientists know relatively little about how they work. Dónal's team has now found that two of them act as mechanic-style fine-tuners of gene activity in the vital process of red blood cell production.

Dónal and his colleagues previously studied a protein called Ago2, which helps to execute miRNA function. When the team disabled Ago2 in mice, they found the animals had problems producing mature red blood cells. So Dónal decided to look for the miRNAs that were missing when Ago2 was disabled. This highlighted two miRNAs, miR-451 and miR-144, that are active in developing red blood cells. "That was the clue; the way in," says Dónal. His team then removed, or "knocked-out" these miRNAs in developing mice. Surprisingly, most of the mice survived and seemed quite healthy. But appearances were deceptive: the mice did indeed have a slight problem producing mature red blood cells, but not enough to cause them a problem in everyday life. "Like a lot of things in life, subtlety is important," says Dónal.

This became apparent when the team treated the mice with a drug to induce anaemia, which they might experience as a result of disease or after losing a lot of blood from an injury. Mice lacking the miRNAs couldn't make enough red blood cells and the majority of them died, whereas their normal counterparts all recovered. "The system is fine until it's stressed," explains Dónal.

To find out more, the team compared the activity of genes in normal cells with those that lacked the two miRNAs, and discovered that tens of thousands of genes became either more or less active in their absence. To work out which of these genes are directly controlled by the miRNAs, Dónal turned to his EMBL-EBI colleague, bioinformatician Anton Enright. Anton wrote a program called Sylamer, which sifted through all the candidates, looking for a tell-tale molecular signature that shows a gene is regulated by miR-451 or miR-144. Sylamer identified nearly 600 genes, some of which are already known to be involved in red blood cell maturation. This suggests that the miRNAs are fine-tuning the activity of these genes, says Dónal. Although this work was carried out in mice, it is likely that humans have a similar mechanism to help their cells to cope when they put pedal to metal.

Rasmussen KD, Simmini S, Abreu-Goodger C, Bartonicek N, Di Giacomo M, Bilbao-Cortes D, Horos R, Von Lindern M, Enright AJ, O'Carroll D (2010) The miR-144/451 locus is required for erythroid homeostasis. *J Exp Med* **207**: 1351-1358

Microscopes on auto-pilot

"I'm running on autopilot," we say, when a task is so mundane and repetitive that we feel like our brain isn't engaged. Scientists searching for the right cells under the microscope for a particular experiment often feel this way. But now, they can put the microscope on autopilot instead.

The groups of Jan Ellenberg, head of the Cell Biology and Biophysics Unit, and Rainer Pepperkok, head of the Advanced Light Microscopy Facility, have teamed up to create a novel computer programme that can rapidly learn what a scientist is looking for and then take over this laborious and time-consuming task. Called Micropilot, the new software searches through the sample, locates the right cells and then automatically performs complex microscopy experiments on them.

"This new software brings machine learning to microscopy," Rainer says. Micropilot analyses low-resolution images taken by a microscope and, once it has identified a cell or structure of interest, it automatically instructs the microscope to start the experiment. This can be as simple as recording high-resolution time-lapse videos or as complex as using lasers to interfere with fluorescently tagged proteins and recording the results.

Micropilot generates more data, faster. In a mere four nights of unattended microscope operation, it detected 232 cells in two particular stages of cell division and performed a complex imaging experiment on them, whereas an experienced microscopist would need to work full-time for at least a month just to find the relevant cells among the many thousands in the sample. With such high throughput, Micropilot can easily and quickly generate enough data to obtain statistically reliable results, allowing scientists to probe the role of hundreds of different proteins in a particular biological process.

"This allows microscopists to do systems biology," Jan says. "It allows us to do things we didn't even consider before because it would not have been possible to put the resources together."

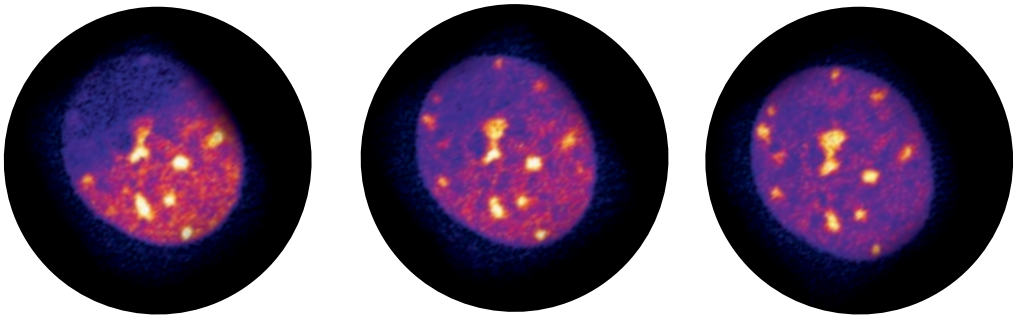
This is precisely why the software will be put to use in two systems biology projects in which Jan and Rainer are involved. Jan and his collaborators within and beyond EMBL will use it in a project called MitoSys, to find cells that are about to start dividing and then film them in high resolution throughout the whole division process. While it does so, Micropilot will also be instructing the microscope to record and measure exactly where certain proteins are and how many copies of them reside in a particular place in the cell. Thus the researchers hope to understand the role of the proteins encoded by genes that the project's precursor, Mitocheck (see Annual Report 2009/10), found were important for cell division.

In another international consortium – dubbed SystemsMicroscopy – Rainer, Jan and their teams will be using Micropilot to measure the interactions between proteins inside cells, and how these interactions fluctuate over time, resulting in dynamic proteomics information.

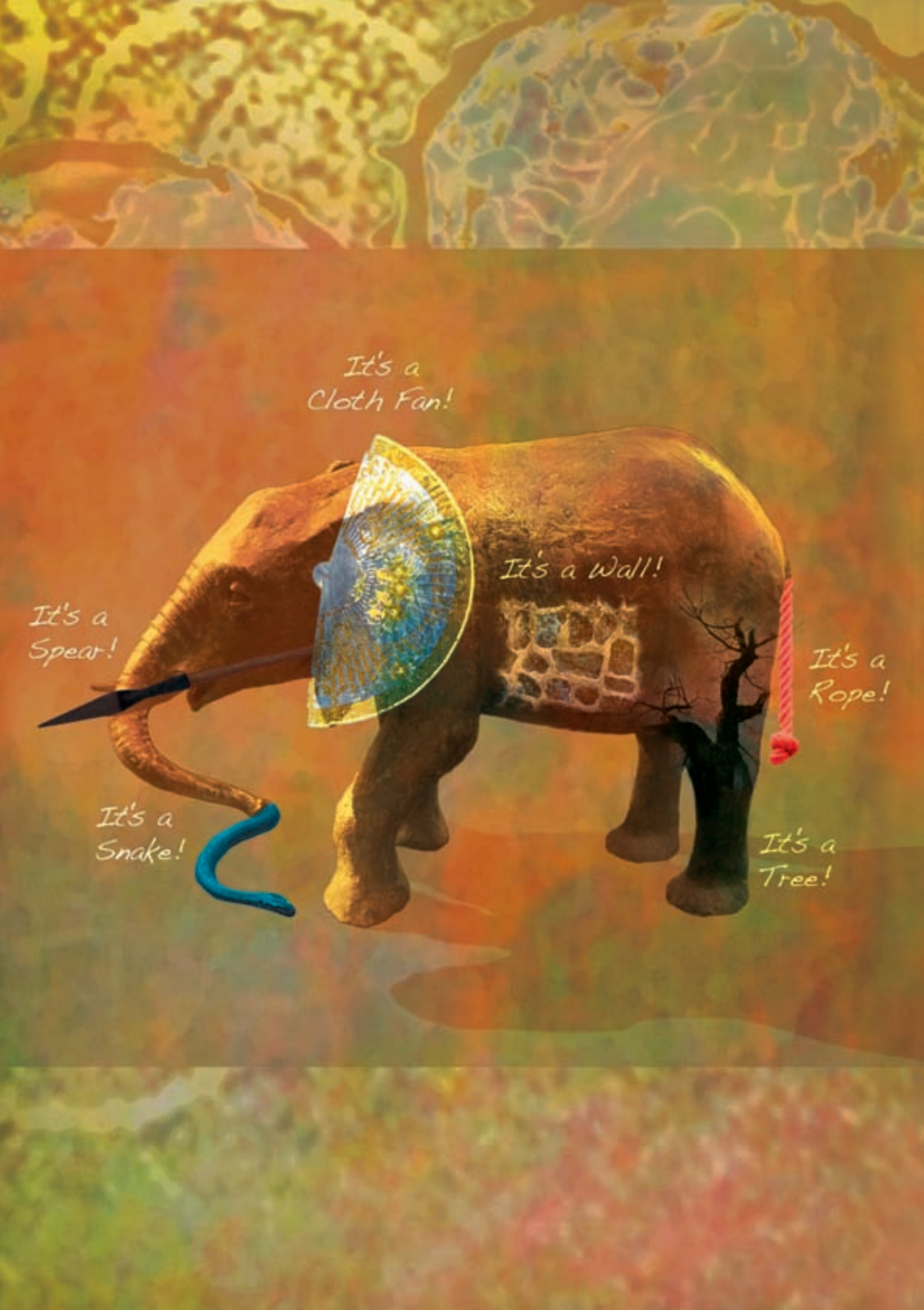
Micropilot has also already generated interest from the wider scientific community, to whom it is freely available as open-source code. But no-one need lose sleep over the thought that researchers will be replaced by machines, Jan asserts. "Programmes like this don't design the experiments, and they can't come up with the creative models that really explain things – that's what people should be spending their time on," he says. "If you want to come up with surprising ideas and hypotheses, you still need people."

Watch the video on EMBL's YouTube channel: www.youtube.com/emblmedia

Conrad C et al (2011). Micropilot: automation of fluorescence microscopy– based imaging for systems biology. *Nature Methods,* Advance Online Publication 23 January 2011.



Micropilot removed the fluorescent tag from half of this nucleus (left), and recorded what happened next.


It's a
Cloth Fan!
It's a Wall!
It's a
Spear!
It's a
Rope!
It's a
Snake!
It's a
Tree!

Imaging the elephant

In an ancient Indian tale, six blind men attempt to identify a large object by touch alone. One man believes he's touching a pillar. Another is sure he senses a hanging rope. The others feel a bare wall, a snake, a spear, a cloth fan. Only when they combine their impressions is the object finally revealed to be an elephant.

Just as each blind man contributes knowledge of a unique feature of the pachyderm, different techniques can be combined to form a complete image of a biological molecule's physical structure. One such technique, known as cryo-electron microscopy, or cryo-EM, is central to the work of several EMBL groups. Cryo-EM allows them to obtain high-resolution information about a molecule's form and, ultimately, its biological function.

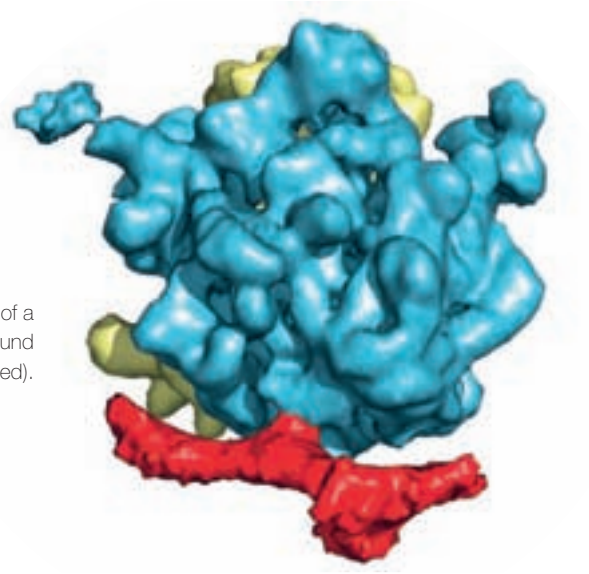
In cryo-EM, as in all types of electron microscopy (EM), a beam of electrons is focused at the specimen. Some electrons pass straight through whereas others hit the specimen and are scattered. The sample's unique pattern of interference with the electron beam reveals details of its structure.

EM allows scientists to obtain high-resolution images because the wavelength of the electrons is very short: if the wavelength of EM electrons were represented by the diameter of a football, the wavelength of visible light would be about as long as 200 football pitches positioned goal-to-goal. Both EM and light microscopy are constantly advancing, but with current EM techniques scientists can see things that are more than 1000 times smaller than what they can see with powerful light microscopy. Light microscopy can illuminate objects as small as bacteria, but some EM techniques can go as far as detecting individual atoms.

Cryo-EM is distinguished from other types of EM by its relatively less invasive method of sample preparation. In other kinds of EM samples are hardened and sliced into sections, or stained with heavy metals. But in cryo-EM, samples are preserved in or close to biological conditions. A sample is kept below freezing temperature (hence "cryo"), which holds target structures in place and preserves their form.

Trying a different angle

Christiane Schaffitzel, a group leader at EMBL Grenoble, learned of the advantages of cryo-EM while studying ribosomes during her post-doctoral research at the Institute of Molecular Biology and Biophysics at the ETH in Zürich. She had been enlisting another structural technique – X-ray crystallography – whereby the three-dimensional properties of



3D cryo-EM image of a ribosome (blue/yellow) bound to targeting proteins (red).

a molecule are obtained by analysing a solid crystal made from many copies of the sample arranged in a regular lattice. But depending on the size or atomic interactions of a molecular complex, producing crystals can be a tricky business.

"My project was to crystallise a translating ribosome, but I never obtained crystals," she says. "Still today, many years later, a ribosome with a nascent polypeptide in its tunnel has not been crystallised." So Christiane asked Joachim Frank of Columbia University to examine the sample with cryo-EM. "It didn't even take half a year. I realised this is actually a great method to solve complexes which are not very stable and which do not easily crystallise."

Christiane has since found cryo-EM to be very useful for studying how newly formed proteins are targeted to different locations in a cell, a process known as co-translational targeting. In recent research, she and her colleagues combined cryo-EM with data from other techniques to better understand this process (see page 45).

"It is like a puzzle," she says, "You take your electron microscopy data, you take your biochemical evidence, cross-links, mutations, fluorescence measurements, crystallographic data, bits and pieces, and then…put it [all] together to generate a quasi-atomic model that makes sense."

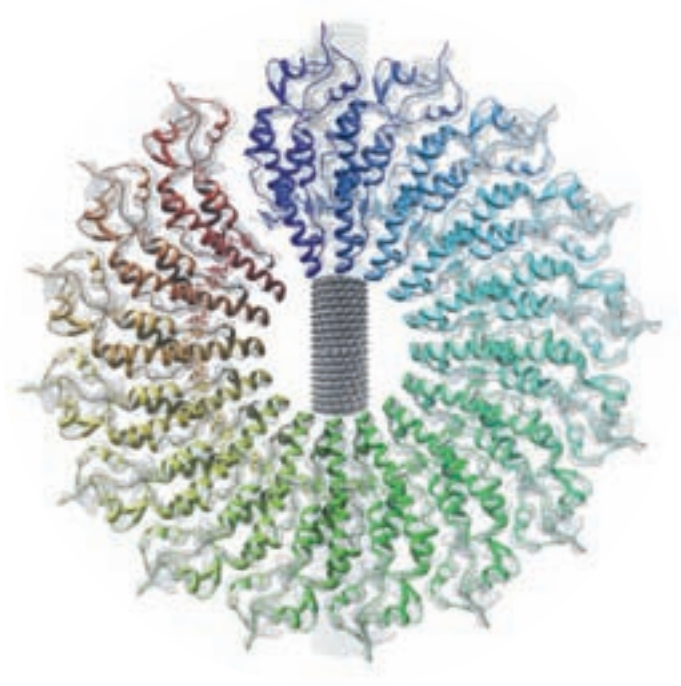
A tool in the toolbox

Christiane's group uses single-particle cryo-EM, in which multiple copies of a molecule are imaged in two dimensions. A three-dimensional model can then be created with software that combines all the images, in effect taking an average structure of all the copies.

But cryo-EM could actually be represented by two blind men in the story of the elephant. In a second approach, called cryo-EM tomography, the sample is tilted in between multiple exposures to the electron beam. A three-dimensional image can then be created from one copy of the structure.

Group leader John Briggs uses cryo-EM tomography in his work at EMBL Heidelberg. He studies how proteins induce pockets of cellular membranes before they bud off. This process is important both for the formation of vesicles – membrane-enclosed sacs that transport materials into, out of and within a cell – and for the assembly of membrane-bound viruses like human immunodeficiency virus (HIV).

"We're interested in the fundamental mechanism," John says. "How can you collect together a bunch of different proteins to turn a piece of the plasma membrane or some other cellular membrane into the membrane which surrounds a virus or a vesicle?"



Tobacco Mosaic Virus imaged by cryo-EM.

To address this question, John, like Christiane, combines cryo-EM images with data collected through other means. These include other types of electron microscopy and fluorescence microscopy, a light microscopy technique that indicates the presence and position of specific proteins.

"We've been looking at the structures of various intermediate steps between the immature and the mature HIV virus to try to understand the structural changes that occur during the maturation process," John says. "We use different types of microscopy at different stages of the project depending on what type of information we need at that particular time. We get complementary information from the different methods."

John's colleague Martin Beck also constructs cryo-EM tomography images of cellular structures. Martin, also a group leader in EMBL Heidelberg, studies the structures of large biological molecules, with a focus on nuclear pore complexes. These multi-protein assemblies dot the membrane surrounding the nucleus of a cell and help transport materials in and out of the nucleus.

"We look at nuclear pores still embedded in the nuclear membrane," Martin says. "We have determined the general structure of a nuclear pore, and now we are trying to figure out where certain modules of the complex are precisely localised."

Martin combines cryo-EM with other techniques as he moves closer to a complete structural model of the nuclear pore complex. He hopes to one day chart the structure down to the level of its component atoms. Single-particle cryo-EM, crystallography, and mass spectrometry – a broadly informative technique that measures particle mass and electric charge – will all help Martin uncover the intricacies of this "elephant" of a molecule.

The Titan Krios

Martin and John's projects will soon be accelerated, thanks to the recent addition of the innovative Titan Krios to EMBL Heidelberg's electron microscope collection. According to John, the instrument will allow for faster, more automated data collection.

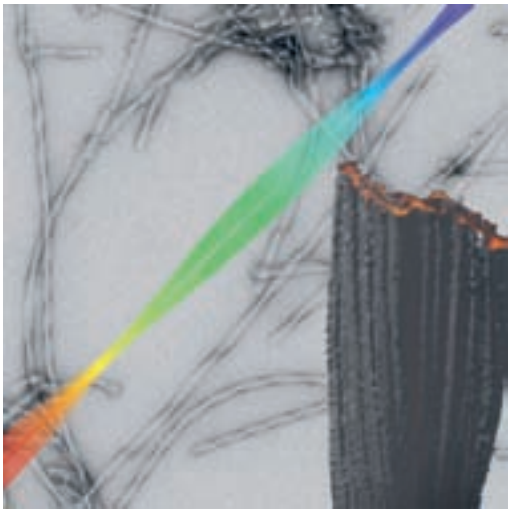
"The Titan has been used in the materials sciences, and now it has been adapted for cryo," says Carsten Sachse, another EMBL Heidelberg group leader who works with cryo-EM. "It has very good optics, and it has been shown to be quite a boost for biology in terms of resolution."

Carsten will be using the Titan Krios to investigate how protein aggregates are cleared from a cell. Abnormal protein accumulation is characteristic of neurodegenerative illnesses, including

Alzheimer's, Parkinson's, and Huntington's diseases. By studying how protein aggregates are normally removed from a cell through endocytosis, or eliminated within a cell by autophagy, Carsten hopes to better understand diseases in which these mechanisms seem to fail.

"There are clear molecular links between the two processes," Carsten says. "There's a multitude of proteins involved that are thought to function like little machines inside the cells and somehow reshape membranes. We would like to understand more closely how they work."

The Titan Krios will also benefit the research of other scientists. In one ongoing project, John and Carsten are working with EMBL Heidelberg group leader Marko Kaksonen on visualising membrane budding in yeast cells. Meanwhile, Christiane is collaborating with EMBL Grenoble group leader Imre Berger, to determine the structure of the main transcription machinery in eukaryotic cells.



Protein fibers found in Alzheimer's disease. Background: one of many cryo-EM images used for 3D reconstruction.

These scientists continue a long tradition of cryo-EM breakthroughs at EMBL. In fact, early in EMBL's history, group leader Jacques Dubochet and colleague Alasdair McDowall invented cryo-EM sample preparation. They published their method in 1981 in a brief, typewritten paper in the Journal of Microscopy, which outlines a way of rapidly cooling a sample so that the liquid solution forms a glass-like layer instead of freezing into crystals.

In the tradition of many important discoveries that are initially under-appreciated, Jacques and Alasdair's paper faced a prevailing belief that such "vitrification" of liquid water was thermodynamically impossible. Nonetheless, the validity of the method was soon evident, and formed the foundation of the cryo-EM techniques used today.

What's next for cryo-EM?

"What we hope for the future of cryo-EM is that it will be a standard technique alongside crystallography and nuclear magnetic resonance spectroscopy, a technique that can identify the components of a molecule based on their magnetic properties," Carsten says. "It's just not as mature as other techniques, and it's not a common thing that's available at every university. Cryo-EM will be quite powerful one day." Indeed, improving cryo-EM techniques was part of Carsten's development as a scientist, and he and his colleagues continue to refine the method.

In the story of the blind men and the elephant, careful study by each man allowed for insight into a bigger picture. As it improves, cryo-EM – used in parallel with other techniques – will allow for increasingly detailed insights into complex biological structures. If the blind men had put similar efforts into their own powers of examination, they might have gone on to catalogue the entire animal kingdom.

Dubochet J, McDowall A (1981) Vitrification of pure water for electron microscopy. *J Microsc* **124**: RP3-RP4.

Special delivery


Christiane Schaffitzel

In a crowded harbour, a tugboat almost looks like a toy, as it weaves through a maze of cruise-liners, ferries and cargo ships several times its size to find the vessel it is scheduled to tow, and guides it to the right dock before leaving to pick up its next customer.

Christiane Schaffitzel, a group leader at EMBL Grenoble, has taken the first snapshot of a molecule that performs a similar job inside cells, precisely at the moment when it is delivering its cargo to the dock.

Not all the proteins produced by a cell are destined to stay within it. Some have important functions to perform outside the cell, for instance in communicating with other cells. Others must be embedded in the membrane, to serve as gateways for different molecules to enter or exit the cell. If they're not recognised and ferried to the right location, such proteins can accumulate inside the cell with disastrous results. This is what happens in cystic fibrosis, for example, and failures in this process have also been linked to Parkinson's disease.

The tugboat-like molecule, called the Signal Recognition Particle (SRP), searches all ribosomes that are making proteins until it finds one that is assembling a protein that is tagged for transport. The SRP picks up the ribosome with the nascent protein attached, and carries the whole complex to the membrane, where it docks onto the SRP-receptor and hands the protein over for export or embedding. The hand-over happens quickly, and SRP leaves the scene. "Because this is a fast, transient process, it's very hard to visualise," Christiane explains.

In collaboration with Guy Schoehn at the Institut de Biologie Structurale (IBS) in Grenoble, as part of the IBS-EMBL Electron Microscopy Partnership, Christiane used cryo-electron microscopy (for details on this technique, see page 40) to determine the three-dimensional structure of SRP at the moment of hand-over, when it is bound to both the ribosome and the SRP-receptor.

This work builds on previous experiments Christiane carried out during her post-doc work at the Swiss Federal Institute of Technology (ETH) Zurich a few years ago, where she determined the structure of the SRP bound to the ribosome, and she now noticed a striking difference between the two images: when it is bound only to the ribosome, the SRP latches on to it at three different places, but when bound to both ribosome and SRP-receptor, the tugboat molecule is only attached to its cargo by one of those three bonds. "So the act of binding to its receptor triggers the SRP to start letting go of its ribosome cargo," Christiane remarks.

Curiously, having a ribosome in tow actually makes it easier for the SRP to dock onto its receptor. In a collaboration with the Shan laboratory at Caltech in Pasadena, California, the scientists found that, when the SRP is already bound to the ribosome, the bond between SRP and SRP-receptor forms 50 to 100 times faster.

Christiane is interested in how the cellular machinery identifies proteins for transport and takes them to their correct location, so she and her group are looking to get more snapshots of what happens before and after this hand-over. They hope to understand how the SRP tugboat knows which cargo to pick up and where to take it and, once the newly formed protein has been delivered to the membrane, how it is folded into the right shape to carry out its tasks.

Estrozi LF, Boehringer D, Shan S, Ban N, Schaffitzel C (2011) Cryo-EM structure of the *E. coli* translating ribosome in complex with SRP and its receptor. *Nat Struct Mol Biol* **18**: 88-90

Kings of the ring

New structural biology facility, EMBL@PETRA3

High energy, bright lights, lightning-fast reactions and specimens at the peak of physical fitness: for a ring-side seat at the world's best X-ray radiation source of its kind, you can't beat EMBL Hamburg's new structural biology facility.

In the arena of synchrotron radiation science, physics has historically been the heavy hitter: since the first synchrotron accelerators were developed in the mid-1940s, physicists have gone the distance with this powerful high-energy source.

But biology is by no means a featherweight in the field. In the 1970s, Sir John Kendrew, the first Director General of EMBL, coordinated the international use of beams at the Deutsches Elektronen-Synchrotron (DESY) in Hamburg for biological structure research. The proposal for an outstation in Hamburg swiftly followed, along with another in Grenoble, where EMBL would coordinate the biological uses of the neutron beams produced by the Institut Laue-Langevin (ILL).

As the finishing touches are made to the new PETRA III synchrotron facility at EMBL Hamburg, it's clear that life science applications continue to punch well above their weight. Conversion of the PETRA accelerator at DESY into the most brilliant storage-ring based X-ray source in the world was completed in 2009. Of its 14 beamlines, three are being designed, built, and operated by EMBL for the structural biology community, under the watchful eye of group leader Thomas Schneider.

It's a knock out

Biologists and physicists are not the only contenders rising to the challenge of creating opportunities in the field of modern synchrotron radiation. Close collaboration between instrumentation and scientific groups is required to harness the brilliant beam of PETRA III. Stefan Fiedler's team works closely with Thomas's, providing expertise in X-ray optics, precision mechanical engineering, robotics, control software and electronics. The ultimate goal is to create optimal conditions for state-of-the-art experiments in structural biology.

Hundreds of hours have gone into preparing the facilities at PETRA III. Precision engineering and sophisticated control systems are required to maintain reliable and absolutely stable beams. With positrons being accelerated almost to the speed of light in the massive 2.3 kilometre-long PETRA storage ring, producing intense X-rays 100 billion times brighter than hospital X-rays that are channelled into beams much finer than a human hair, there is no room for error. "The instruments we build are solid and robust enough to provide the necessary precision to make the best of the precious beam from PETRA III," says Thomas. "This will allow us to push macromolecular crystallography and small angle X-ray scattering beyond their current limits."

SAXS appeal

When it comes to synchrotron radiation, things move fast. Just eight months after PETRA III was officially inaugurated with the help of Professor Annette Schavan, Germany's Federal Minister for Education and Research, EMBL scientists and engineers celebrated their first milestone. Following comprehensive testing, the first beam was successfully guided into the small angle X-ray scattering (SAXS) beamline on 15 July 2010. "Not only do we have a fine radiation source, but our equipment fulfils its functions and the parts of the complex optical system are working correctly together," says Stefan.

Each of the three new beamlines has a particular function or feature. The first is dedicated to SAXS, a technique that enables researchers to study biological macromolecules and their complexes in conditions that are similar to their native environment. Scientists have been using X-rays to probe the structure of matter since the early twentieth century. X-ray crystallography was the first technique to provide detailed information about the atomic makeup of materials, but as the name suggests, it only works with crystalline solids. Many complicated biological systems, which may be flexible or dynamic in nature, can be reluctant to form crystals; for these difficult cases, SAXS is more appropriate.

In SAXS experiments, X-rays illuminate a sample in solution, and a detector registers the scattered radiation. SAXS reveals relatively low-resolution structures of biological macromolecules, yet it provides valuable complementary information on the structure of targets in solution, at variable conditions and in real time. Software developed by Dmitri Svergun, another EMBL scientist in Hamburg, has revolutionised the way scattering data are used to construct three-dimensional structural models, and has become the world's most used SAXS data analysis program, now employed in more than 1300 laboratories. With focusing abilities down to several micrometres the new beamline will allow users to perform experiments in tiny, nanolitre volumes.

Taking it to the MX

Within five months of the milestone on the BioSAXS beamline, the first monochromatic beams were achieved on EMBL's two macromolecular X-ray crystallography (MX) beamlines: MX1 and MX2. "Both beamlines 'microfocus' X-ray beams to address the most challenging crystallographic problems," explains Thomas.

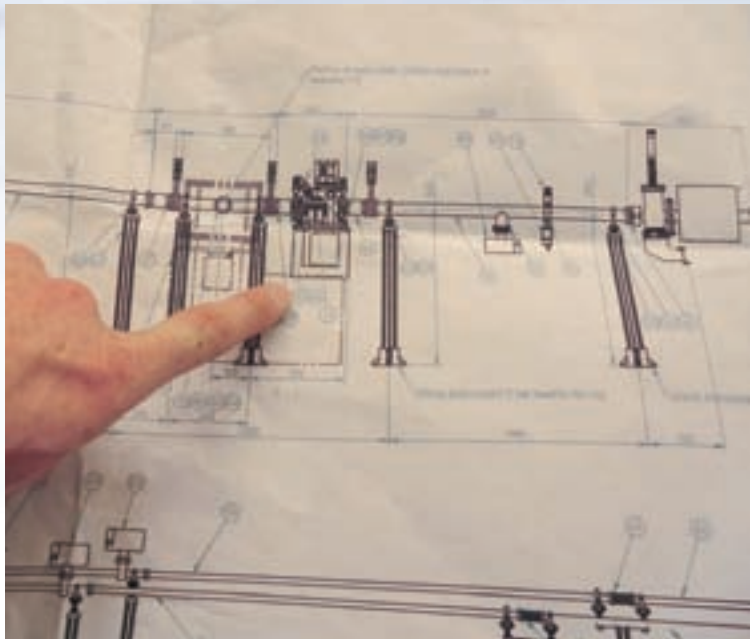
Protein molecules can crystallise under regulated conditions. In a sense, these crystals act as amplifiers: crystals are made up of multiple copies of molecules arranged in a regular three-dimensional lattice, so that scattered waves add up in phase and raise the signal to a measurable level. The X-rays deflected by atoms in the crystal lattice concentrate into sharp spots, a 'crystal diffraction pattern'. Analysis of the intensity and position of diffraction spots reveals the three-dimensional macromolecular structure.

The problem is, many protein complexes only form very tiny crystals: "It often seems as though the more interesting the system, the smaller the crystal it makes!" says Thomas. Fortunately, the microfocused MX1 beam can be used to study crystals between as little as 1-5 micrometres, and the tunable wavelength of MX2 reveals even more detail about structure and composition. Both beamlines will provide unprecedented structural insight into three-dimensional molecular information of complicated biological processes, enabling scientists to delineate the molecular origins for autoimmune diseases, cancers, and microbial infections.

Going the distance

The gloves may be off in the challenge to be 'kings of the ring', but fortunately our protagonists are trading innovation and best practice, rather than blows. "After the long phase of preparation and planning, it is very exciting to see things coming together and the beamlines and the integrated facility surrounding it taking shape," says Thomas.

The first users to benefit from the new integrated EMBL facilities at PETRA III are expected before the end of the year. Thanks to these complementary services, key aspects of research – from high-throughput protein crystallisation to sample preparation and data processing – can be carried out under one roof, enabling advancements in key areas of structural biology (page 48).



The samples' fitness centre

At EMBL Hamburg, annexed to the beamlines at PETRA III, sits a set of labs that are the domain of Rob Meijers and Jochen Müller-Dieckmann. Like exercise rooms in which athletes prepare for the next big competition, these labs provide an environment where samples are trained before entering the beamlines.

"The idea is to create a platform where even researchers who are not structural biology experts can carry out all the steps, from arriving with their sample to getting and analysing the structural data," says Rob. "We provide support along the whole pipeline, including two very important – and sometimes overlooked – aspects: quality control and sample optimisation. A few cycles of sample optimisation combined with quality control are often the essence of success."

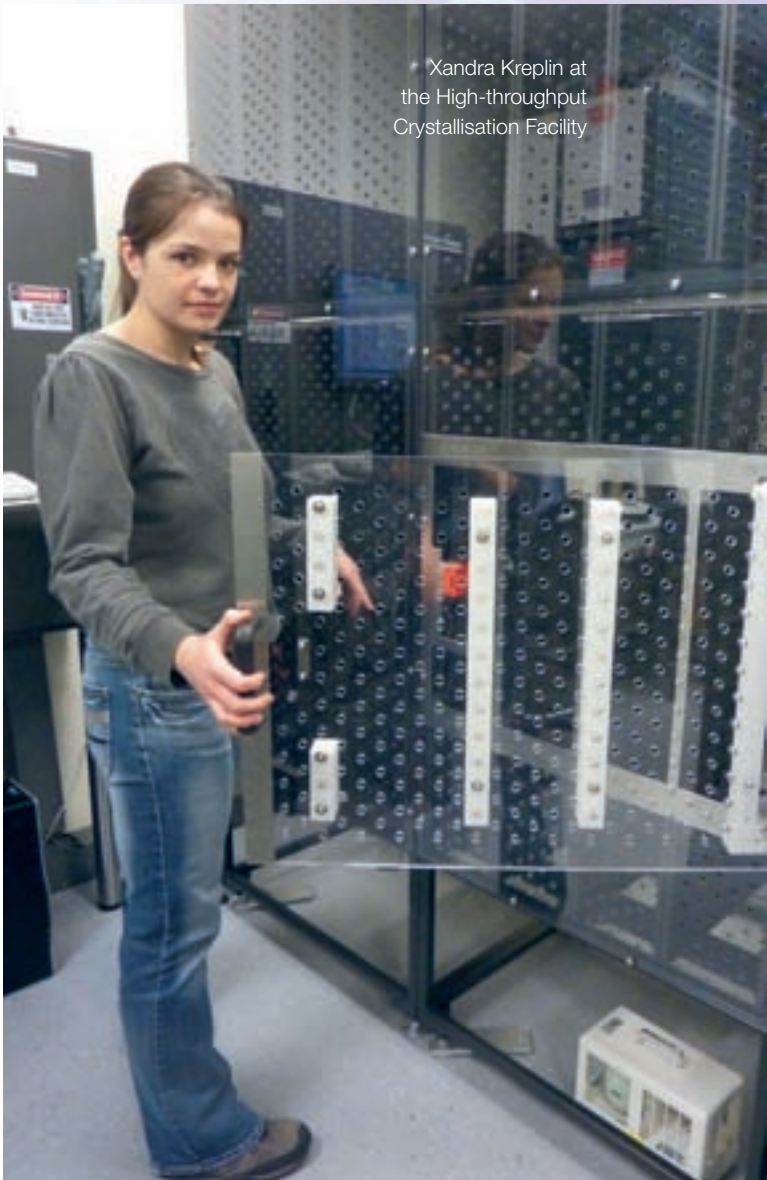
Most of the individual elements that are now under the same roof existed already, but communication between them was somewhat hindered because they were physically far apart. "Now we can interact closely with the other platforms installed here and ultimately work towards our goal of a more effective and efficient user service," says Jochen.

This is especially relevant for the small angle scattering beamline. Small angle X-ray scattering (SAXS) measurements cannot be taken accurately unless scientists know the exact concentration of a protein in their sample. Combine this with the fact that SAXS is often used for large and complex protein assemblies, and controlling the quality of the samples can be a real issue. "Scientists from all over the world come to Dmitri Svergun's Bio-SAXS facility here," says Rob, "and now that we have dedicated quality control equipment sitting literally at the beamline, we can provide them with an even better service." This proximity also allows users to obtain detailed information about their sample in real time as the SAXS experiment progresses, which means they can glean valuable quantitative data on protein interactions, for example.

Getting into shape

From the corridor, a set of double doors lead to a room almost entirely taken up by what looks like a wall-to-wall CD rack. But instead of digital compilations from Jochen's favourite musical groups, the rack holds green trays in which Jochen's team attempts to produce an entirely different kind of rock. Each of these crystallisation plates has a number of depressions, or wells, and inside each well sits a single droplet of protein, which is here literally to "shape up". The aim of the whole set-up is to coax this liquid protein into forming solid crystals, the repetitive arrangement of which will enable scientists to use the X-rays generated in the beamlines to determine the protein's three-dimensional structure. A number of different factors can influence whether a protein crystallises or not, so Jochen's team closely monitors and controls the chemical composition of crystallisation cocktails as well as the room's temperature – which is kept as constant as possible by the double doors – in an effort to make the process as reproducible as possible. They can monitor the samples' progress on site through a computer interface, which users can also access remotely.

Although it recently moved to this new location next to the PETRA III hall, the High-throughput Crystallisation Facility has been serving the general user community since 2005. In its new quarters, the facility includes another controlled-environment room, for crystallising samples in a different temperature range, as well as lab space. In total, Jochen's facility can store and image 10 000 crystallisation plates, which allow for somewhere in the order of one million experiments, fully justifying the high-throughput designation.



Xandra Kreplin at the High-throughput Crystallisation Facility

As fit as can be

Across the corridor from Jochen's racks of crystallising proteins are the laboratories where Rob's team carry out what they call sample characterisation. Here, scientists take a tiny portion of a sample that's headed for the beamlines, and give it the equivalent of a medical check-up. The team can separate proteins and measure their size, to make sure the sample contains the right molecule, and check that it behaves as expected. They can also determine how stable a protein is, and investigate ways of increasing that stability if necessary. If the sample is destined for the SAXS beamline, it will be kept in solution – dissolved in a liquid – rather than solid crystals, in which case the Sample Preparation and Characterisation Facility can also provide researchers with information on how the protein molecules behave, and how likely they are to bind to each other to form larger complexes.

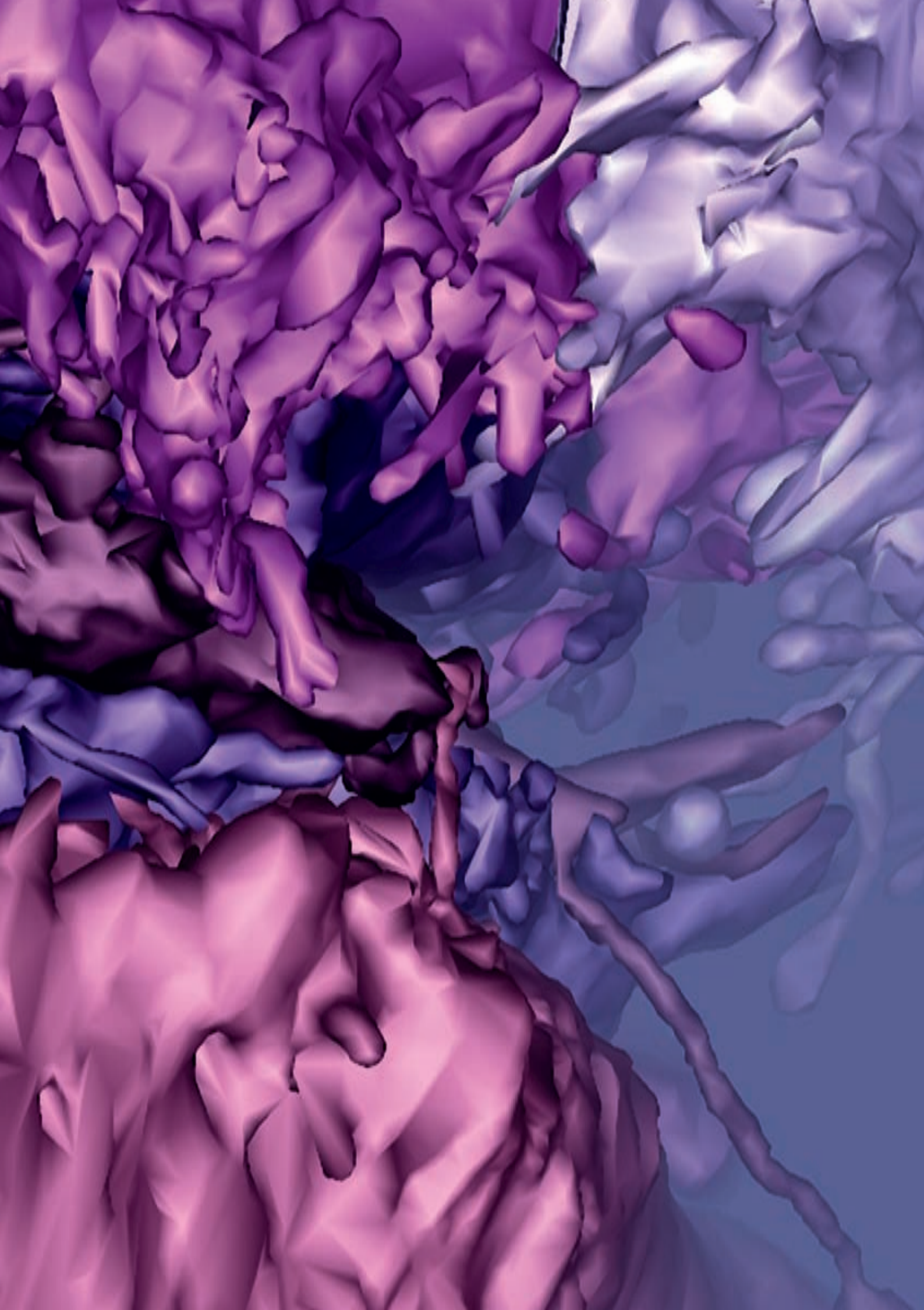
Every internal sample that enters Jochen's crystallisation facility has a minute amount removed and sent to Rob's team for analysis. "We also work closely with EMBL Grenoble, which has a similar facility," says Rob. "We use the CRIMS software that José Antonio Márquez developed for protein crystallisation, and we're hoping to extend it in a collaborative effort for sample characterisation and quality control."

By combining data from both their facilities and the beamlines, Rob and Jochen hope to one day be able to implement a system in which samples sent for crystallisation can be tested by Rob's team first, and then passed on to Jochen not only with a quality-stamp but also with the equivalent of a personalised training plan – suggestions for which crystallisation conditions might work best, along with valuable information to help interpret the structural data obtained from subsequent beamline experiments.

"These services will enrich the beamline environment and will hopefully help the user community to obtain an integrated structural view of their favourite macromolecules," Rob summarises. Together with the beamlines and computational facilities for data processing and evaluation (see page 46), the sample preparation, characterisation and crystallisation services form the new integrated facility, EMBL@PETRA3 – a concerted approach that aims to ensure that samples are at their fittest and give the best possible performance.

User access

The integrated services offered by EMBL@PETRA3 are available to the general user community. Access to the crystallisation facility is free of charge under the European FP7 initiative, P-Cube (www.p-cube.eu, see Annual Report 08/09). The newly established Sample Preparation and Characterisation facility can be reached at http://www.embl-hamburg.de/facilities/spc/index.html.



Elementary connections

"Elementary, my dear Watson," Sherlock Holmes would say to his partner, but most of the time the solution to the mystery was not so obvious to his associate. Just as it took the detective's skill to piece together the clues in the right way, so too in science it often takes dedicated detective work to uncover "elementary" connections.

Successful investigations hinge on collecting the facts, but it's not always easy to tell which facts are relevant to a case. Knowing this, EMBL-EBI redesigned its search engine to make results more meaningful to users (page 68).

Witness testimonies can be instrumental in helping detectives solve a case. With this in mind, a group at EMBL Heidelberg has developed a technique that employs genetic informants to find out when specific parts of the genome are active (page 57).

Witnesses' reactions and emotions can be as valuable to a good detective as their words. In film and theatre, to help audiences gauge characters' emotions, actors enhance their appearance with make-up. Scientists do the same within cells, and they can now highlight several structures in different colours *at the same time*, thanks to a new method developed at EMBL Grenoble (page 69).

The final ingredient in a good whodunit is chance: a twist of fate that brings all the clues together in the detective's mind. For all its meticulous planning and protocols, scientific research can also depend on chance encounters, as a pair of group leaders from different EMBL sites recently discovered (page 64).

Creative writers weave these elements into a gripping story thanks to the abilities of their cerebral cortex, which shares an unexpected history with the brain of a tiny marine worm, EMBL Heidelberg scientists found (page 60).

The Heidelberg job

Eileen Furlong,
Hilary Gustafson and
Bartosz Wilczynski

It's a classic scene in a gangster movie: a bank robber creeps up to a safe, stethoscope in hand. He slowly turns the dial of the safe's combination lock, listening intently for the faint clicks that reveal that one of the lock's pins has dropped into place. One by one, he decodes the numbers in the crucial combination, and opens the lock to reveal the riches within. Now, a team of scientists at EMBL Heidelberg has performed a similar feat, this time cracking the combination of proteins that cells use to keep genes under control. The team hopes the work will not only provide them and other researchers with the keys to unlock the codes that guard individual genes, but will also eventually reveal how they all work together across the entire genome as an embryo develops. "It's extremely complicated!" says Eileen Furlong, who heads the group.

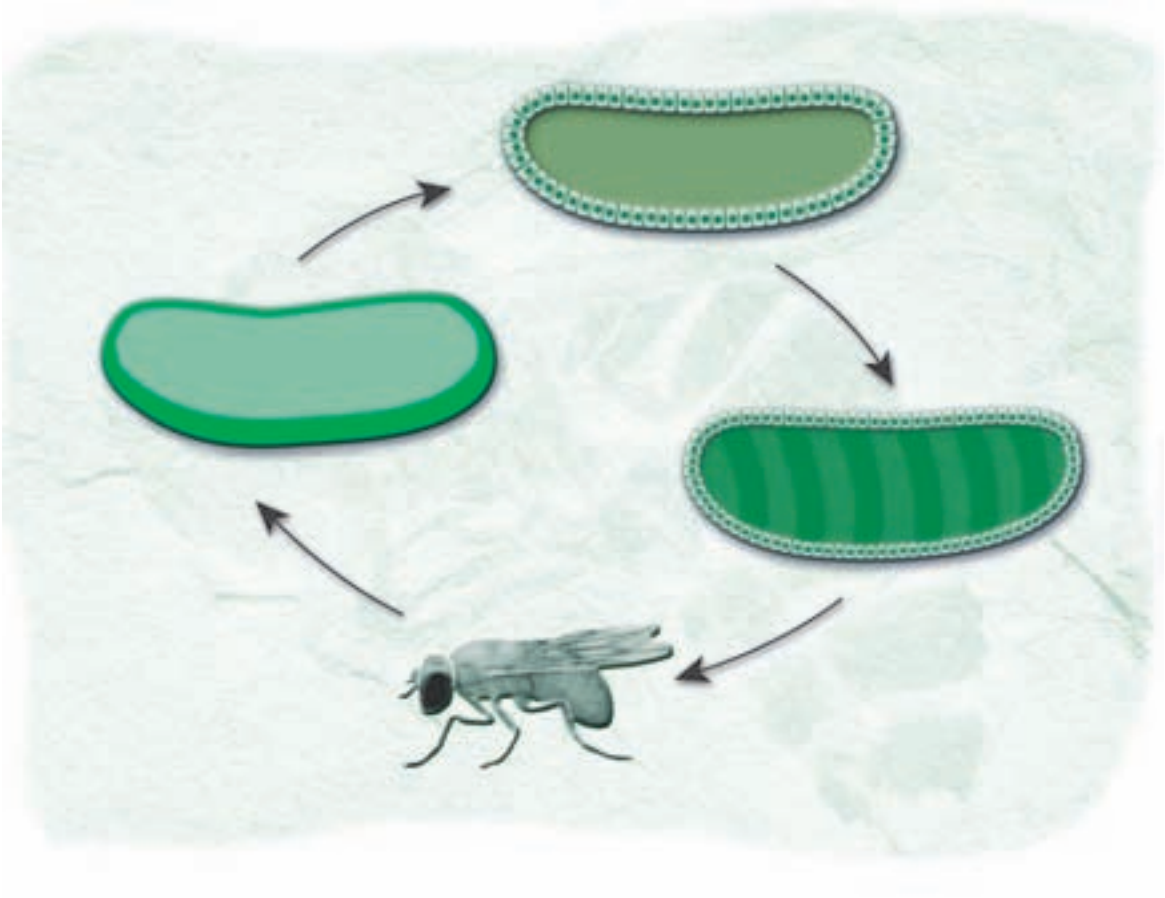
Of course, Eileen and her team are no cockney mobsters, nor are they trying to steal vast amounts of cash. The "safes" they are trying to crack contain neither diamonds nor bank notes but genes, stretches of DNA that spell out the instructions for making proteins and other vital molecules that build a developing embryo. But there is more to a gene than just the instructions for making a protein. Other instructions that detail when and where a protein should be made are contained in stretches of DNA called enhancers, which are scattered throughout the genome and can be either near to or far away from the gene itself.

Enhancers are important for the first step in making a protein, a process called transcription. During this step, the cell makes a copy of the gene using a chemical relative of DNA, called RNA. This RNA is then sent to the cell's protein-making machinery, where it is used to make the protein in a step known as translation. This whole process, from reading and copying the gene to making the protein it encodes, is called gene expression, and biologists have long been trying to understand how the cell "knows" when and where this expression needs to be turned on.

This is where enhancers come in. These stretches of DNA act rather like the barrel of a safe's combination lock: the receptacle for the right combination of pins. The pins in this case are proteins called transcription factors. Only when the correct combination of different transcription factors drop into place on the enhancer can the cell "open" and read the gene. Different genes need different combinations of transcription factors to be active, and when any of these factors leaves the enhancer, the gene is "closed" again. Biologists have a fairly good idea of how this mechanism allows embryos to control where genes are expressed: by making sure that transcription factors are only produced in the required locations in the embryo.

But although this helped explain how gene expression is controlled in space, it didn't really explain how it was controlled in time. The same gene can be switched on or off many times over the course of an embryo's development. What's more, the proteins made by these genes interact with each other to drive the process of development. This means these individual genes can be seen as part of larger "networks" of genes controlling development. Eileen and her team wanted to find a way of exploring and documenting this hugely complex, ever-changing process. "How an embryo develops is highly dynamic," she explains. "We know that it's controlled by transcription, or transcriptional networks."

To dissect something as complex as development is not easy, so the team turned to that commonly used laboratory animal and long-time ally of developmental biologists, the fruit fly *Drosophila melanogaster*. Fruit flies might seem an odd thing to study, but because they



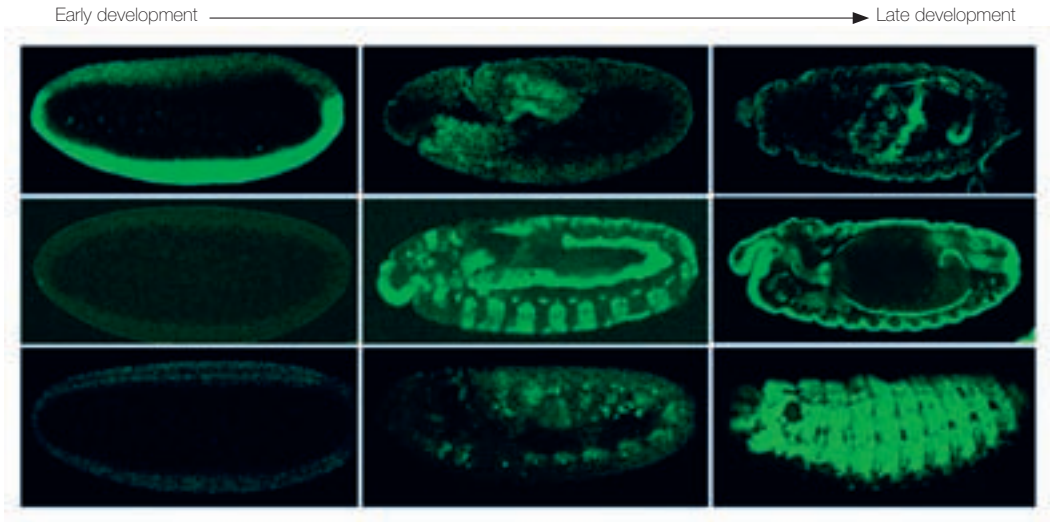
As a fruit fly embryo develops, different genes are turned on in different tissues.

reproduce quickly and are easy to use for genetics experiments, they are an ideal choice. What's more, biologists have studied how their embryos develop in great detail, and have described many of the genes involved in creating particular tissues. "We know development is under very tight transcriptional control, and we know, from genetics, a lot of the key players involved," says Eileen. "We have been focusing on one system that has been very well characterised genetically, which is the specification of the mesoderm." The mesoderm is a layer of cells present in very young embryos that goes on to form the animal's muscles and some of its internal organs.

Developmental biologists had already identified the transcription factors involved in mesoderm development, and described when and where they were expressed. However, these studies only looked at one particular point in time, and therefore only gave a brief snapshot of what was really going on. What's more, biologists had generally assumed that if a transcription factor was present in a cell, it would be bound to its target enhancer and it would be active. But some studies suggested that this might not always be the case, so Eileen and her postdoc Bartek Wilczyński decided to investigate further.

They began by collecting thousands of fruit fly embryos at different stages of development and, with the help of the Genomics Core Facility, studied the behaviour of four different transcription factors in the mesoderm at each stage. Unexpectedly, the team found that the transcription factors bound to their enhancers in a very dynamic manner, with only about half of the enhancers being occupied all of the time, and the remaining half occupied only at either early or late stages in development. "They bind to different sets of enhancers which have different sets of target genes, therefore allowing a specific gene expression programme to run at different stages of development," says Eileen.

To see the effect of this binding, Eileen's team studied the expression of the genes controlled by these dynamic enhancers. Sure enough, these genes did indeed show dynamic expression patterns. For example, genes whose enhancers bound transcription factors early in development were expressed early, whereas those that bound late caused their associated gene to be expressed later. "When the transcription factor is on, the gene is coming on, when the transcription factor is off, the gene goes off," says Eileen. It all points to a highly dynamic kind of lock, one whose combination is controlled by when its "pins" drop into the barrel as well as



A gene called rosy is turned on at early stages of *Drosophila* development, in developing muscle cells. Later, the gene fasIII is turned on in the fly's muscle, and at late stages CG5080 is turned on, but only in somatic muscle.

where. But if a transcription factor is present in a cell, what tells it to bind, or not to bind, to its enhancer?

One possibility is that other proteins might be needed to help the transcription factors bind to their respective enhancers. These proteins, called cofactors, would only be present for limited time windows – just enough to allow a transcription factor to bind and open a gene at the right moment. To find out more, Eileen and her postdocs Paulo Cunha and Thomas Sandmann looked at another pair of mesodermal transcription factors, called Mef2 and Lmd. The curious thing about these transcription factors is that if either of them is missing, the embryos have exactly the same physical defect: their muscles fail to develop properly. This suggests that they are both involved in the same developmental process, although it wasn't clear how they interacted with one another.

Further experiments showed that Lmd was behaving like a cofactor: it was expressed in the same cells as Mef2, but in a briefer time window. It bound to a subset of the enhancers bound by Mef2, whereupon it seemed to dictate the effect the enhancer had on its target gene. Rather than simply helping Mef2 to activate, or "open" the gene in all cases, Lmd sometimes caused the gene to close down. "That was unexpected," says Eileen. "This is another layer of complexity." It seems as though the function of a transcription factor – whether it acts to switch a gene on or off – depends on its context, for instance on what other transcription factors are present.

Although it seems mind-bogglingly complex, Eileen says the work offers a glimmer of hope that biologists will be able to work out whether or not a factor is active at a particular binding site. She hopes that her team's method of analysing how transcription-factor binding changes over time could ultimately be used to understand the control of gene expression at the genome-wide level. "This could be a very nice way to decode the network itself," says Eileen. "That's the big picture from my whole lab's research – to eventually get to the point of making a predictive network of the whole system."

The next challenge for the team is to explore their other hypotheses about what helps transcription factors bind to their enhancers at the right time. One of these is whether the physical structure of DNA and its associated proteins, known as chromatin, is involved. One thing is for certain – breaking into the vault of even the biggest bank is child's play compared to unlocking the secrets of gene expression. It's a challenge that will demand input from a wide range of disciplines, says Eileen. "We need to integrate genomics, genetics and bioinformatics to crack it."

Wilczynski B, Furlong EE (2010) Dynamic CRM occupancy reflects a temporal map of developmental progression. *Mol Syst Biol* **6**: 383

Cunha PM, Sandmann T, Gustafson EH, Ciglar L, Eichenlaub MP, Furlong EE (2010) Combinatorial binding leads to diverse regulatory responses: Lmd is a tissue-specific modulator of Mef2 activity. *PLoS Genet* **6**: e1001014. doi:10.1371/journal.pgen.1001014


François Spitz

Vital information

The most (in)famous informant ever –in the Western world at least – is probably Deep Throat, who in the 1970s provided journalists with the information that uncovered the Watergate scandal, and ultimately caused President Nixon to resign.

At the Developmental Biology Unit in Heidelberg, François Spitz is using a different kind of informant to study a mechanism that can also have dramatic results.

The informant that François and his group are using is a sequence of DNA known as a jumping gene. Jumping genes can move from place to place within a cell's genome. When this extra genetic material is inserted into an important gene, it can disrupt it and thereby have a detrimental effect. But, the EMBL scientists realised, the ability of the jumping genes to move around could also be harnessed to gather information about what's happening in many different places in the genome.

So they developed a new technique, which they named after another infamous character: Gromit, the inventive dog from the Aardman Productions cartoon series. GROMIT enables researchers to systematically explore the large part of our genome that does not code for proteins. This non-coding DNA is involved in controlling when, where and to what extent genes are turned on, or expressed. Understanding how it does so could help uncover what makes each of us unique.

François and his group engineered a jumping gene to react to the presence of regulatory elements, and devised a method to control when it jumps to a different location in a mouse's genome. Through selective breeding, the scientists generated lines of mice with the jumping gene in many different places. In each of these lines, the jumping gene provided information about the regulatory activity happening in the area of the genome in which it was sitting.

"Our findings change how we think about gene regulation, and about how differences between individual genomes could lead to disease," says François. Until now, scientists thought that regulatory elements essentially controlled a specific gene or group of genes. But François' group discovered that the genome is not organised in such a gene-centric manner. Instead, it seems that each regulatory element can potentially control whatever is within its reach. This means that mutations that simply shuffle genetic elements around (without deleting or altering them) can have striking effects, by bringing genes into or out of a specific regulator's zone of influence.

The EMBL scientists also discovered that many of these regulatory elements act in specific tissues, which suggests that the expression levels of every gene, even those that are active all over the body, are fine-tuned at the tissue level.

"This new technique is easier, faster, less invasive and more efficient than previous approaches," François emphasises. "We don't have to go through the complex and time-consuming process of engineering embryonic stem cells to create a mouse; with GROMIT, we only have to mate the mice." Researchers can also use GROMIT to easily delete or re-shuffle areas of the genome. This allows them to create mouse models for human diseases like Down syndrome, in which part or all of chromosome 21 is repeated.

In using them as an informant and a targeted disruptive force, François and his team have put the destructive potential of jumping genes to good use.

Ruf S et al. (2011) Large-scale analysis of the regulatory architecture of the mouse genome with a transposon-associated sensor. *Nat Genet* **43**: 379-386

Zip up your genes

Anyone who has suffered the indignity of unwittingly walking around with a trouser fly that has slipped undone will attest to the importance of reliable clothes fastenings. According to Thomas Surrey and his team at EMBL Heidelberg, something similar is true of our own cells. They rely on a zip-like structure to ensure that chromosomes are distributed properly in dividing cells, and Thomas's team has now unveiled some intriguing insights into how the zip automatically keeps itself done up correctly to keep the cell's genetic material intact.

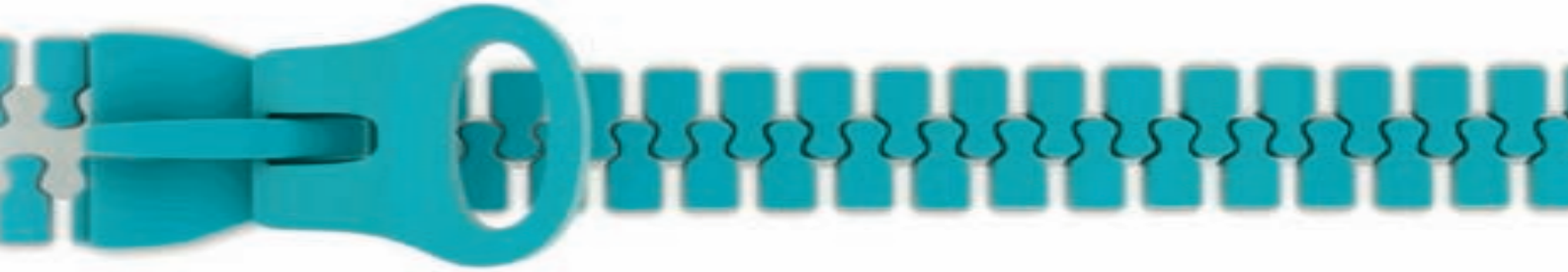
> "In principle, you can use this test for any protein that binds DNA and also binds something else."

When cells prepare to reproduce themselves, they grow bigger and make copies of all the DNA in their chromosomes. As a result of the copying process, a chromosome and its copy remain joined at the middle until the cell is ready to divide into two new cells. At this point, the paired chromosomes peel apart. But its here that the cell faces a problem: how can it ensure that each of the two new cells receives the correct number of chromosomes?

This is where a structure called the spindle comes in. It is a machine made from hundreds of molecular ropes called microtubules. The tips of the microtubules from either end of the cell overlap alternately at the centre of the spindle midpoint, rather like the teeth in a zip. The copied chromosomes line up perpendicularly to the microtubules right down this area, called the midzone, in a stage of cell division known as metaphase. Microtubules from one side of the cell lash themselves to one copy of the chromosome, while microtubules from the other side attach themselves to its joined copy. When the time is right, the microtubules suddenly shorten, yanking the copied chromosomes apart and into opposite ends of the cell in a stage called anaphase. Finally, the cell cuts itself in half down the middle, leaving two "daughter" cells with the right number of chromosomes.

"The spindle is essential for the proper division of the genetic material," explains Thomas. If this distribution is faulty, it can trigger diseases such as cancer, in which the normal control of chromosomes and gene behaviour breaks down. If it goes wrong during the production of eggs and sperm, it can result in miscarriages or in developmental problems such as Down syndrome. This is why biologists are so keen to understand how the spindle is made and how it divides the duplicated chromosomes.

A key question is how the duplicated chromosomes make their way to the midzone in metaphase. Biologists knew that a group of proteins called kinesins somehow pushed them there. Kinesins are the haulers of the cell: their ability to drive other molecules along microtubules and other parts of the cell's internal scaffolding, the cytoskeleton, has earned them the name "motor proteins". But researchers didn't know how many kinesins were involved, or exactly how they worked together to shift chromosomes.



To find out more, Thomas and his team developed a way of sticking chromatin to glass slides to create a flat, chromatin-coated surface. The chromatin the team used was extracted from frog eggs, and so already had the motor proteins bound in the correct proportions to the chromatin. They then added microtubules to the slides and used a light microscope to see how the motor proteins pushed the microtubules around.

Thanks to their new test and some further experiments, the team showed that two kinesins, called kinesin-10 and kinesin-4, were the only motor proteins attached to the chromatin that interacted with microtubules. Kinesin-10 binds to microtubules strongly, but moves the chromosomes slowly, whereas kinesin-4 binds more weakly, but moves faster. Combining forces, the two chromokinesins ensure that the chromosomes bind well to the microtubules and move at an appropriate rate. "This is interesting for the field, because few studies look at the combinatorial effects of motor proteins," says Thomas. What's more, the new method his team has pioneered will find broader applications within cell biology. "In principle, you can use this test for any protein that binds DNA and also binds something else," says Thomas.

Because the spindle has to pull the duplicated chromosomes apart during anaphase, the cell has to ensure that the alternate overlaps of the microtubule ends are exactly right. At this point kinesin-4 switches roles and, together with another protein called PRC1, plays a part in regulating the all-important overlaps. "If you don't keep the spindle intact in anaphase, the chromosomes could start to mix again," explains Thomas. "And the only thing that keeps it intact is the central part of the spindle." The challenge for the cell is that it has to keep the microtubule ends in the midzone stable, while still allowing other parts of the spindle microtubules to change so they can keep pulling the duplicated chromosomes apart.

Working with microtubules and purified proteins on glass slides, Thomas and his team found that PRC1 can bind to the alternating ends of the overlapping microtubules, bundling them together in the midzone. PRC1 then attracts kinesin-4 to the overlapping ends. Here, kinesin-4 ensures the overlap is the right size, by blocking the growth of the microtubule ends. "The goal is to produce an overlap size of a certain length," says Thomas.

The ingenious thing about this process, he adds, is that it regulates itself. When the overlaps are too short, less kinesin-4 can bind, meaning that its ability to block microtubule growth is reduced. Consequently, the overlap ends grow until enough kinesin-4 binds to make them stop. "If this is happening in living cells, it's a clever way of self-regulation," says Thomas. Sadly, no-one has yet invented a trouser zip that can automatically self-regulate to spare its wearer's blushes.

Bieling P, Kronja I, Surrey T (2010) Microtubule Motility on Reconstituted Meiotic Chromatin. *Curr Biol* **20**: 763-769

Bieling P, Telley I, Surrey T (2010) A Minimal Midzone Protein Module Controls Formation and Length of Antiparallel Microtubule Overlaps. *Cell* **142**: 420-432

Detlev Arendt

Bookworms

In the famous *Dune* universe created by novelist Frank Herbert, denizens of the desert planet Arrakis worship colossal sand worms called Shai-Hulud. These tough, tunnelling creatures live for thousands of years, and a major rite of passage for the desert-dwellers is to learn to summon and ride atop the massive invertebrates.

Although worm-worshippers are surely a minority here on Earth, humans may now view some worms with more reverence, as a result of recent work performed by scientists at EMBL Heidelberg. They have found evidence that two different structures in the worm and mammalian forebrains arose from a single brain structure in a common ancestor 600 million years ago.

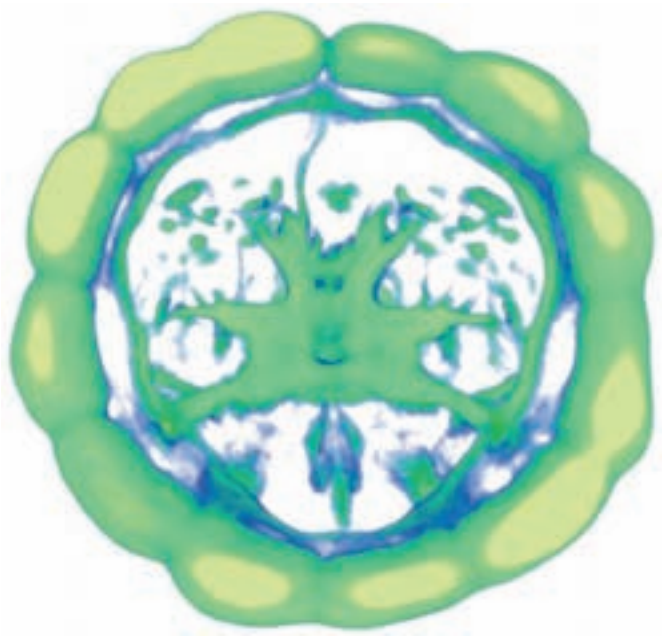
Without the region of the brain known as the cerebral cortex, Herbert – and every other novelist – would never have been able to create such imaginative tales. The cerebral cortex is a neuron-packed, complex part of the forebrain, also referred to as the pallium, or the mantle layer of the brain. All vertebrates use the pallium to process olfactory information, but humans and other mammals also depend on the cerebral cortex for many additional functions, including learning, memory, language, and advanced motor skills.

The importance and complexity of the mammalian cerebral cortex make it an intriguing area of study for biologists. Many scientists have examined its formation by altering its development in controlled experiments. But some researchers have turned to evolution to better understand how the cerebral cortex came to be.

EMBL group leader Detlev Arendt and his team investigated the evolution of the vertebrate pallium by looking in what might be considered an unexpected place: the brain of a marine *in*vertebrate. Specifically, they studied the worm *Platynereis dumerilii*.

Platynereis is classified as an annelid, as are common earthworms and leeches. Like insects and other worms, it possesses neural structures called mushroom bodies – named for their distinctive, fungal shape. "The function of the mushroom bodies is to integrate information from different senses – primarily chemical or visual information – into movement," Detlev says. "The sensory information is gathered and translated into locomotor output."

Scientists have long been aware of a resemblance between mushroom bodies and parts of the vertebrate pallium: they share similar anatomy and function. However, the vertebrate and annelid evolutionary lineages have long been independent, so researchers had assumed that mushroom bodies and the pallium evolved separately, and converged upon the best anatomy to carry out their common tasks. Work by Raju Tomer, a postdoc in Detlev's group, now challenges this view, and indicates that the mushroom bodies and the pallium actually arose from the same ancient structure.



This virtual *Platynereis* brain was created by averaging microscopy images of the brains of 36 different individuals, viewed from inside the larva, at 48 hours old.

"Most people thought that invertebrate mushroom bodies and the vertebrate pallium had arisen independently during the course of evolution, but we have proven this was most likely not the case," says Raju. Detlev adds: "The evolutionary history of our cerebral cortex has to be rewritten."

These findings are based on molecular evidence obtained with a new imaging technique developed by Raju.

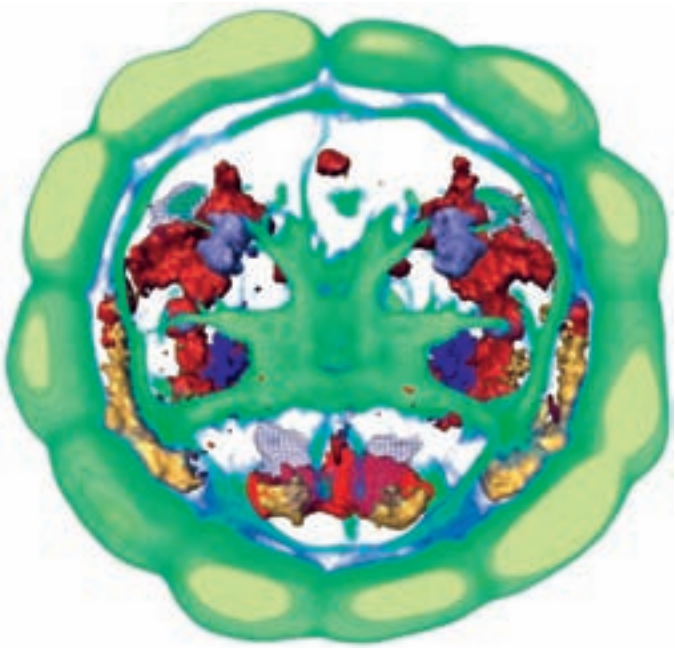
To see which genes are expressed – that is, turned on – in an organ like the brain, standard techniques involve introducing specific fluorescent labels into the relevant cells. A microscopic image of the tissue reveals labelled, glowing regions that show where the gene is turned on. With current technology, though, this can only be done for one or two genes at a time.

Raju overcame this problem through a "divide and conquer" strategy. He imaged one or two genes in one worm, another one or two in another, and so on. And he did this at different stages of development, examining more than 150 genes at each developmental stage and analysing each gene in multiple worms, to ensure that the results represented what happens in most animals and were not individual flukes. Raju then aligned the images he had collected for each stage, using the scaffold of axon tracts and nerves as a landmark. Thus, for each stage of *Platynereis* brain development, the scientists created a three-dimensional, multicoloured map showing where and when each of the 150-plus genes was turned on in the worm's brain.

"It became clear that they are too similar to be of independent origin and must share a common evolutionary precursor."

Raju's method is called Profiling by Image Registration (PrImR), and is the first technique to allow scientists to study the neuron type-specific expression of a large number of genes simultaneously in a compact brain. Now, instead of just using shape and location to determine the brain's different cell types, scientists can use gene expression. "For us, this is much more telling than any physiological or morphological feature, where you never know whether this was independently evolved or whether it's meaningful or not," Detlev says. "The molecular fingerprint is a new tool to compare cell types even between species that split long ago in evolutionary history."

The genes examined in *Platynereis* were not chosen at random. Each one is known to play a role in the development of the mammalian cerebral cortex. Detlev and his colleagues examined



Gene activity mapped onto the virtual *Platynereis* brain.

the annelid PrImR images and compared the gene expression patterns with those of the developing mouse brain.

They found that the vertebrate pallium and the mushroom bodies develop from regions with very similar gene expression patterns. They also noted that the structure that develops into the mushroom bodies gives rise to neurons similar to those of the vertebrate pallium.

"Comparing the molecular fingerprints of the developing ragworms' mushroom bodies to existing information on the vertebrate pallium," Raju says, " it became clear that they are too similar to be of independent origin and must share a common evolutionary precursor."

What could have been the nature of this 600 million year-old ancestral brain structure? Detlev says that it was most likely a group of densely packed cells that received and processed information about smell. It probably directly controlled locomotion in response to olfactory information, perhaps enabling our ancestors crawling over the sea floor to identify food sources, move toward them, and learn from their previous experiences.

Although they share basic similar functions, it is unlikely that this ancient structure looked like either the pallium or the mushroom bodies. Instead, it probably had a simpler shape that then evolved as our ancestors gained the ability to integrate different kinds of sensory information into more and more complex motor output.

"Two stunning conclusions emerge from this finding," Detlev says. "First, the pallium is much older than anyone would have assumed, probably as old as higher animals themselves. Second, we learn that it arose as an adaptation to early marine life in Precambrian oceans."

As one of the first writers to popularise ideas about ecology, Herbert would probably have thought it fitting that his skill in creating *Dune*'s giant sandworms shares a history with a tiny marine worm's ability to swim towards interesting smells.

Watch the video on EMBL's YouTube channel:

www.youtube.com/emblmedia

Tomer R, Denes A, Tessmar-Raible K, Arendt D (2010) Profiling by Image Registration Reveals Common Origin of Annelid Mushroom Bodies and Vertebrate Pallium. *Cell* **142**: 800-809

Teresa Carlomagno
and Bernd Simon

Instant recognition

When Ramesh Pillai, a group leader at EMBL Grenoble, visited EMBL Heidelberg to give a talk, he had no idea he was about to make a chance encounter that would change the course of his research. His team works on proteins that help control the expression of our genes, keeping them stable and healthy. But the team was faced with a mystery: how did these proteins "know" how to recognise and interact with the correct molecules to carry out their function? The researchers had tried to look at the proteins' structure to understand how they worked. But try as they might, the proteins resisted all their efforts to study them with a method known as X-ray crystallography.

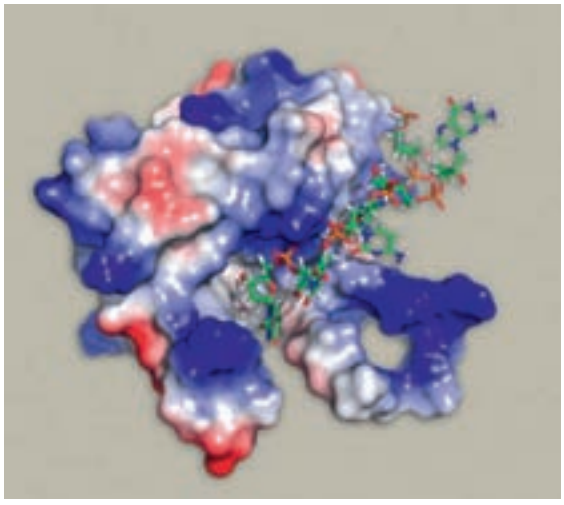
Sitting in the audience of his talk, unbeknownst to Ramesh, was a researcher who could help solve the problem. Teresa Carlomagno, a group leader at EMBL Heidelberg, realised that the structural biology technique her team uses, called nuclear magnetic resonance spectroscopy, or NMR, would probably work on Ramesh's proteins. What's more, her team was already interested in the biology of proteins that are involved in similar processes to those studied by Ramesh. So she approached Ramesh after his talk and offered to collaborate with him. Two years on, the collaboration has not only solved the original problem, but has grown and is starting to address new ones. The two group leaders have now created an EMBL Interdisciplinary Postdoctoral (EIPOD) position to carry on with the work. "This is a beautiful example of how joining expertise can really work out," says Teresa.

The proteins Ramesh studies are involved in keeping a lid on a kind of genetic parasite that we all have in our genomes. These parasites, called transposons, are short lengths of DNA that can cut themselves loose from one part of a chromosome and insert themselves in another. This ability to hop around the genome like so many tiny fleas has earned transposons the nickname of "jumping genes". "Transposons are dangerous for the genome because they have the ability to move from one location to another," says Ramesh. This means they can jump into functional genes, either disabling them or triggering harmful mutations. Having lots of transposons hopping around the genome can cause it to become unstable – a key factor in the development of cancer. What's more, mice that lack the ability to suppress their jumping genes are sterile, possibly because when transposons are released from their bonds and jump *en masse* into new regions of the genome, they can cause massive, irreparable damage to the DNA. This, in turn, can prevent the cell from copying its DNA, a key step in the production of eggs or sperm.

So it's no surprise that cells have evolved a mechanism to disable transposons. This suppression process begins in developing eggs and sperm, when the cell allows transposons to become active. When activated, each transposon is copied by the cell into a molecule called RNA, which is similar to, but distinct from, DNA. RNA molecules derived from regular genes are typically used as a guide for making the protein encoded by that gene. But when a transposon

is copied into RNA, the cell uses an unknown machinery to cut it up into lots of tiny pieces called piRNAs. These piRNAs are then loaded into proteins called Argonautes that shut down, or "silence" transposons, making it impossible for them to be active and mobile. piRNAs act as guides, enabling Argonaute proteins to approach and act on transposons. Thus the act of producing piRNAs destroys the initial transposon RNAs while at the same time retaining a snippet as a memory for future silencing. "It's important to understand how these guides are made and how they function together in a complex with the proteins," says Ramesh.

There are several different kinds of short RNA molecules milling around the cell, all doing various jobs. Interacting with each kind is a dedicated type of Argonaute protein. Although different Argonautes interact with different RNAs, their structures are very similar, and biologists have deduced the structures of many of these proteins while they are bound to, or "complexed" with their target RNAs. A key exception, however, is the type of Argonaute protein that binds piRNAs. These are called Piwi proteins, and relatively little is known about their structure. Ramesh's team wanted to know more about the structure of Piwi proteins to understand how they were able to specifically recognise piRNAs. This was something of a mystery because of the unique structure and chemistry of piRNAs. Unlike other small RNAs, they have a chemical tag added to one end. Ramesh's team wanted to know whether this chemical tag could act like an identity badge for piRNAs, allowing the cell to recognise them and load them onto the appropriate Piwi proteins.



The piwi protein's PAZ domain bound to the RNA.

When an Argonaute protein and its RNA guide meet, the RNA slots snugly into a cleft in a section of the protein called the PAZ domain, like a key fitting a lock. The tag on the end of the piRNAs makes them larger than regular small RNAs, so scientists expected the cleft in the Piwi PAZ domain to be somewhat bigger. The mystery was that, at first sight, the sequence of building blocks, or amino acids, that make up the cleft of the Piwi PAZ domain is very similar to that of the other Argonaute proteins, suggesting that the clefts are a similar shape and size. The most prominent difference is that two of the building blocks in the Piwi PAZ domain are different from those in the other Argonautes. Even so, these amino acids are chemically very similar, so how could they make such a big difference? Only determining the structure would tell.

But that turned out to be harder than expected. Ramesh had tried to use X-ray crystallography to study the structure of the Piwi PAZ domain while it was bound to its piRNA partner. This technique involves crystallising the molecule of interest and shining X-rays on to the crystals. The manner in which the atoms in the crystal scatter the X-rays allows scientists to deduce the structure of the molecule in it. Unfortunately, Ramesh had been unable to make crystals of the Piwi PAZ domain bound to a piRNA – probably because the complex isn't stable enough to crystallise.

Teresa's team works with a different method called NMR, which involves placing a molecule in a strong magnetic field. Atoms in that molecule absorb energy from the magnetic field in a characteristic way, allowing researchers to work out what the atoms are and how they are

arranged within the molecule. Although NMR only works on molecules below a certain size, scientists don't have to crystallise their samples: they can use solutions of their molecule instead. "For this size of complex, NMR is a great alternative," says Teresa.

So the team turned to EMBL's new in-house NMR machine, which arrived less than three years ago. The new model is a "high field" NMR machine, and is more powerful than its predecessor. It can resolve more atoms in a structure than the machines previously used at EMBL Heidelberg. "It means you can look at bigger molecules," says Teresa. The other advantage is that the machine is more sensitive, making it easier to study biological samples, which tend to contain low concentrations of the molecules of interest. "It can make the difference between seeing something and not seeing it," says Teresa. "It's a very good machine and we are very happy to have it."

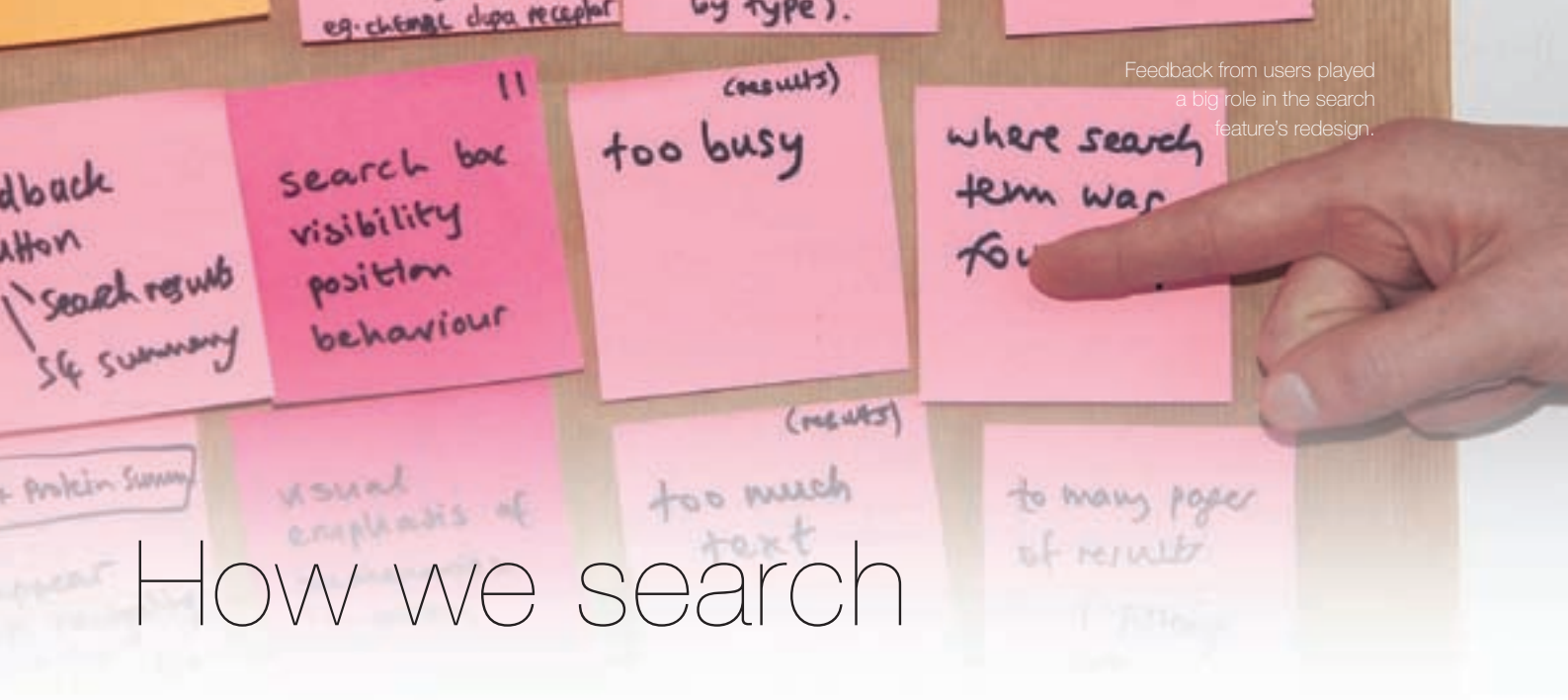
Ramesh Pillai in Grenoble.

Another advantage of having the machine in-house is that the researchers didn't have to transport their fragile, unstable samples very far, says Bernd Simon, NMR Facilities Manager at EMBL and a member of Teresa's research group. "We could get data directly next to the lab," says Bernd. "We can work much more easily than before."

With the help of the NMR machine, Ramesh and Teresa's teams were able to determine the structure of the Piwi PAZ domain. They found that two amino acids allow one "wall" of the RNA-binding cleft to swing up, creating the extra space needed for the piRNAs' chemical tag. Ramesh and Teresa suggest that these amino acids make subtle changes to the domain, making it physically more stable when it swings "open" in this way. By contrast, the amino acids in domains that recognise non-tagged RNAs make them most stable when their clefts are closed. "It's quite amazing how these subtle mutations in the sequence of this one single domain can regulate its specificity," says Teresa. "It's very impressive to see how nature can fine-tune things with these changes in sequence."

Having solved their original problem, however, Teresa and Ramesh are not content to sit on their laurels. They plan to continue their investigation into how the PAZ domain works, and also to study other aspects of Piwi protein biology. "This collaboration with Ramesh has been very fruitful," says Teresa, "and promises to continue to be fruitful in the future." Ramesh agrees: "It shows the synergy that can occur between a biologically orientated lab and a structurally orientated lab," he says.

Simon B, Kirkpatrick JP, Eckhardt, S, Reuter M, Rocha EA, Andrade-Navarro MA, Sehr P, Pillai RS, Carlomagno T (2011) Recognition of 2'-*O*-Methylated 3'-End of piRNA by the PAZ Domain of a Piwi Protein. *Structure* **19**: 172-180



Feedback from users played a big role in the search feature's redesign.

How we search

Bioinformatics is no longer a niche discipline. Clinicians, pharmaceutical researchers, plant breeders, environmental scientists and many others routinely draw on large, public datasets in their work. Nevertheless, many researchers find it difficult to navigate the complex landscape of biological databases and are often unaware of the powerful tools at their disposal.

EMBL-EBI's databases and tools span all the major molecular domains, which poses a unique set of challenges when it comes to serving users. Over the past few years, EMBL-EBI has strived to enable discovery by creating a single interface that invites researchers to explore this diverse set of resources.

The new search facility, launched in January 2011, provides an entirely new experience for molecular biologists. Informed by extensive user research, it draws on biologically aware search methods to present information in a clear, targeted and navigable way. The search indexes and updates more than 300 million entries a day, and serves as a gateway to the major EMBL-EBI data collections.

The process of reinventing the search service began with a consultation with users. Jennifer Cham, user experience analyst at EMBL-EBI, interviewed predocs, postdocs and clinicians all over Europe to find out where and how they discover information they need for their research. "I met people who would rather read papers for a week than use databases for an hour," she said. "These are the people the new search is really targeting. It's designed to be accessible to people who are not currently benefiting from our services."

The current design is the result of several cycles of user observation and redesign. Now, when you enter a search term you have a simple, tabbed summary showing gene expression (including a picture of where it is expressed in the body), gene and protein function, 3D protein structure, orthologues, SNPs, literature, patents and much more.

"This approach has revolutionised the way we approach our users," explained Ewan Birney, a Senior Team Leader at EMBL-EBI. "In the past we assumed that we knew what the users needed, and tended to build features that we ourselves would like to see. But after having worked with Jennifer and so many user groups, I can really appreciate the value of this kind of research, and the power of taking a methodical approach to understanding the user's experience."

"It was really rewarding to see that people had emotional responses to the new features," Jennifer said. "People would click on the gene expression tab and their face would light up when they saw the pictures from the Gene Expression Atlas. It's really nice to see in practice how a change in the design can affect usability in sometimes quite dramatic ways."

There is a growing enthusiasm for user experience design at EMBL-EBI, which serves an incredibly diverse community of users. The team leaders of EMBL-EBI's core resources, led by Associate Director Graham Cameron, were deeply involved in the project, as integrating information is key to the EMBL mission.

"The new search mainly supports a 'genomes, genes and products' mindset, which is arguably the most natural integration axis for EMBL-EBI data," Graham explained. "The next phase, which is already underway, will expand its capabilities to support, for example, disease or chemically oriented exploration of the data. This development includes more resource teams, and a wider range of usability techniques."

EMBL-EBI's search can be accessed from the homepage: www.ebi.ac.uk.

Not just a pretty face

In Chinese operas, the audience can discern the personalities of the characters – and even guess their fate – just by looking at their faces, thanks to their distinctive and elaborate traditional make-up. A red face means someone is loyal and brave, a black one stands for valour, yellow and white for duplicity, and so on. Accents, lines and details add other elements such as mood and feelings, so that actors often appear to be wearing delicately painted masks.

Scientists studying cells under the microscope use fluorescent labels in a similar way, to make certain features stand out. And, just as elaborate face-painting can take hours to complete, labelling a cell's components in different colours can also be a laborious, time-consuming process. Until now.

Imre Berger, a group leader at EMBL Grenoble, and colleagues have created the equivalent of a one-touch make-up brush that highlights different cellular features simultaneously, in different colours.

"The method is simple – good science is often simple – but it's a big deal conceptually," says Imre.

The new technique is called MultiLabel and it is based on the same principles as MultiBac, a method Imre developed a few years ago to produce several proteins at once in insect cells. Imre teamed up with Philipp Berger (no relation) from the Paul Scherrer Institute (PSI) in Villigen, Switzerland, and for the first time adapted this technology concept to mammalian cells like our own.

Previously, scientists who wanted to study several proteins simultaneously in a cell – for example to see where they interact – would have had to introduce each gene separately, which limited them to two or three labelled proteins at a time. Each gene would be contained within a separate plasmid, which is a loop of DNA that can be introduced into the cell and which commandeers the cell's machinery to manufacture the protein encoded by the DNA. Instead of creating several plasmids, Imre and Philipp built a plasmid containing all the genes for all the proteins of interest lined up one after the other, like carriages in a toy train, and thus were able to insert all the genes at once. To date, the scientists have successfully delivered up to 15 genes this way. The protein encoded by each gene can carry a fluorescent label, so scientists can then put the cells under the microscope and see where these proteins are, simply by looking for the different fluorescence signals. And because the plasmid contains all the genes of interest, each gene is present in the same ratio in each cell – a feat that has never been achieved before.

The ability to insert several genes into a cell at the same time is useful for more than just labelling. It could also be used, for example, to improve the efficiency of reprogramming cells into stem cells, as this procedure entails inserting four genes into a cell and turning them on at the same time.

"MultiLabel could also help make drug development and screening considerably faster," Imre points out, "as it allows us to label many cellular components involved in a given disease process and follow them all at the same time." Accordingly, the technique has already raised significant interest among pharmaceutical companies.

In the meantime, Chinese opera actors have no such luck: they still have to apply their tell-tale make-up one step at a time.

Watch the video on EMBL's YouTube channel: www.youtube.com/emblmedia

Kriz A, Schmid K, Baumgartner N, Ziegler U, Berger I, Ballmer-Hofer K. & Berger P (2010) A plasmid-based multigene expression system for mammalian cells. *Nature Communications*, Advanced Online Publication 16 November 2010

THE DIFFERENCE BETWEEN THE

SEXES

FROM BIOLOGY TO BEHAVIOUR

Battle of the sexes

A quick scan of the countless bestsellers, discussion forums and magazine articles that claim to reveal differences between men and women might lead you to the conclusion that we know little for certain about the way the two sexes think and behave. Yet away from the sexual politics – and polarised claims of us either being all alike or beings from distant planets – there is a significant amount that we do understand. And grasping this has important implications for areas as diverse as medicine, law, policy and human rights.

Such issues were the focus of this year's annual Science and Society Conference, 'The Difference Between the Sexes: from Biology to Behaviour', held at the EMBL Advanced Training Centre in Heidelberg. It was the 11th in this series of conferences, which take place over two days and aim to bring topical and cutting-edge science to the attention of the public. It delivered this objective, with over 350 people filling the auditorium to hear speakers from a broad range of disciplines expound on some of the most important themes in modern biology.

Across four distinct sessions, experts discussed research relating to issues such as evolution, sexual development, the benefits and limitations of animal models and rethinking our concepts of 'maleness' and 'femaleness'. It set the scene for comprehensive and lively debates, in which social, cultural, environmental and political factors were juxtaposed against the latest scientific findings.

"This topic is perfect for something called science and society," said David Bainbridge, a clinical veterinarian anatomist at the University of Cambridge, UK. "You have sex defined or undefined by basic biology and then gender is everything that is loaded on top by the society and culture in which people live. There has to be an uneasy part in the middle where the two meet and that is what makes us all so interesting."

Bainbridge, who is also a popular science writer, assessed the development of sex determination – why a foetus ends up as male or a female – which formed one of the major topics debated at the event. "For the first time we are really starting to understand how all this works – and, importantly, why it works," he said.

Keynote speaker Donald Pfaff, a Professor of Neurobiology from Rockefeller University in New York, USA, stressed the importance of studying the impact and role of a large number of components simultaneously to better understand how men and women think and behave differently.

"Our field of research reveals neuroscientific evidence for sex differences in behaviour, but how extensive are the social implications?" he asked. Pfaff explained there is enough science to lay to rest contentious issues such as whether males are better at mathematics (the evidence

suggests not), or whether cultural factors alone can explain why girls are more likely to play with dolls and boys with toy cars (they cannot).

The importance of such a holistic rather than reductionist approach was emphasised by a number of other speakers, to address what many saw as misrepresentations of the extent to which our phenotype – our observable characteristics or traits – are genetically or environmentally determined.

Anne Fausto-Sterling, a Professor of Biology and Gender Studies at Brown University in Providence, USA, called for a 'dynamic systems' approach to understand key areas of difference. For instance, biologists have recently shown that factors that determine one's sex – such as hormones and genes – take part in complex interactions, with implications for both brain and behaviour. A key challenge lies in understanding such relationships. "It is time to stop framing the question of sex differences in terms of nature versus nurture," she said. "We have to be much more careful in the details of the arguments that we make, and subtle in the claims that we make."

Donald Pfaff

Youthful fields of science such as epigenetics – which has shown that genes can be modified or affected by experience in the environment – underline the importance of a multidisciplinary approach to research. Eva Jablonka, a Professor of Genetics at Tel-Aviv University, Israel, explained that interactions of biology and the environment are integral to living organisms. The challenge, she said, is in making meaningful assertions about their impact. "Everything we do changes us biologically, but how long-term is it? What are the effects? Some changes are easy to measure, others are not."

A number of speakers also pointed to some limitations. For instance, although we know there are structural differences in the brain between males and females, little is known about how this translates into behaviour. Others questioned the suitability of animal studies – which have reshaped our thinking on behaviour – in modelling human behaviour. But such research is also opening up opportunities to learn more about why men and women experience different vulnerabilities in conditions such as mental illness, learning difficulties, and chronic disease, participants heard.

Many areas of research could also have important implications for social policy. Susan Pinker, a child psychologist and writer based in Canada, explained that often there is no easy answer. "It is very rare that science tells us what we should do. We have to make a clear distinction between what is and what should be. But we should not be afraid about looking at the data, or evidence, in order to have an open discussion."

The presentations sparked lively debate in the afternoon panel discussions, drawing questions and comments from the audience that reflected the immense significance that the issues have in everyday life. Topics ranged from the nature of gender roles to personalised healthcare, with people from a variety of backgrounds voicing their opinions.

"The interchange tells us how complicated these issues are," said Melissa Hines, a Professor of Psychology at the University of Cambridge, UK. "There is a great diversity – as the basic research has shown us – and multiple ways for the brain, behaviour and body to become one

The presentations sparked lively debate.

gender or the other. Because of this we are all complicated combinations of masculinity and femininity."

Participants included people from 35 countries among them around 20 journalists reporting on the event for international, national and local media, ensuring that the discussion continued far beyond the plenary hall. A number of school groups attended, including students from Limassol, Cyprus, who produced artwork for display at the event. A feedback survey indicated that the conference was highly appreciated by the audience.

In his closing remarks, EMBL Director General Iain Mattaj congratulated the speakers, participants and conference organisers for delivering lively, informed and productive discussions: "I do not think we have had a science and society meeting where the sessions ranged so widely and produced so many interesting questions."

EMBL's Science and Society initiative

Back in the days when Isaac Newton was pondering the universe in his orchard, scientists often convinced one another their results were legitimate in ways that might be considered somewhat unorthodox today. "Decisions made in science are not something dropped down from heaven," said Jed Buchwald, a professor of history from the California Institute of Technology in an EMBL Forum lecture this year. "People need to be convinced that you should do things a certain way. That alternatives were discarded over time does not mean that they are necessarily bad, and that is true of a lot of things in science – it evolves."

EMBL's Science and Society initiative makes use of a number of innovative platforms to consider such relationships between science and wider society. The EMBL Forum lectures – a long running series of seminars that seeks to raise awareness of the impact that research is having in society – has this year seen experts speak on hot issues such as scientific integrity, complex systems and the placebo effect.

Other parts of the programme bring science directly to public auditoria, such as the Heidelberg Forum on Biosciences and Society (a joint venture by EMBL, the German Cancer Research Centre and the Medical Faculty of the University of Heidelberg) and the EMBL–EBI Science and Society symposium, which this year focussed on the challenges and threats facing our natural world. Another highlight was a special mini-symposium in Heidelberg, looking at the evolving relationship between art and science.

The initiative is consistently pushing boundaries with a varied programme of events across EMBL sites throughout the year, seeking to engage scientists and the public in the development of a shared understanding of science.

Growing strong

From Popeye to parental advice, green vegetables and other iron-rich foods are said to help children grow up strong and healthy. But inside our cells, too much iron can be a bad thing, and scientists at EMBL Heidelberg have discovered why (page 88).

As we grow, the bogeymen of our childhood are replaced by new terrors, and the way we react to these fears changes. How adult mice respond to frightening situations is determined by a specialised group of neurons, scientists at EMBL Monterotondo have found (page 76).

Communication and comprehension is an important part of every child's development, but with such varied vocabularies, alphabets, styles of reading and writing the world over, it's amazing we are ever able to make sense of each other. Like some languages, the DNA sequences inside our cells can be read backwards, and researchers at EMBL Heidelberg are uncovering how this helps fine-tune when and where genes get turned on (page 96).

Growth can also come with its own set of problems. With the advent of next-generation sequencing technologies, the amount of data produced in biological sciences is growing so fast that the resources for storage, access and analysis can't keep up. ELIXIR, a Europe-wide venture in which EMBL-EBI has a central role, is gearing up to cure these growing pains (page 90).

Cornelius Gross

A neural switch for fear

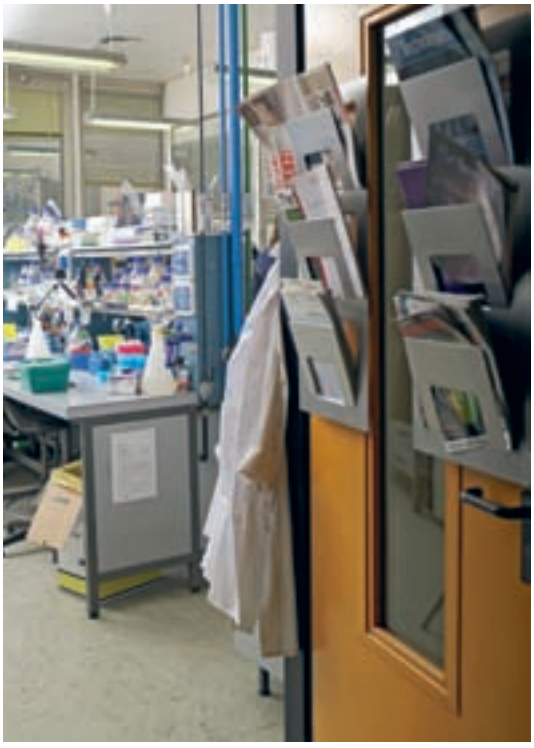
To flee, fight, or freeze? For an animal overcome with fear, that is the essential question. The answer often depends on the amygdala – a major emotion-processing hub nestled deep in the brain. In both mice and humans, it mediates behavioural responses to certain types of fear, and helps to form long-term memories of frightening experiences. However, very little is known about how cells in the amygdala communicate with other neurons to produce specific fear-induced behaviours.

Cornelius Gross and his group at EMBL Monterotondo are beginning to fill this knowledge gap through an innovative approach. By using several new techniques to map the brain circuits involved in how mice react to fear, they have identified a switch that toggles between two different responses. In the course of their work, they also discovered that there's an alternative to fighting, fleeing, or freezing: the fourth option is active risk assessment using behaviours like rearing, digging, and exploring.

If a mouse associates a sound with an uncomfortable electric shock, it will freeze as soon as it hears that sound, even if it doesn't get a shock. Scientists know that a group of neurons in the amygdala, called type 1 cells, are involved in this freezing response because when type 1 cells are inhibited, mice no longer freeze in fear. But Cornelius and colleagues have discovered that type 1 neurons are more than just an on/off switch.

In a pioneering approach employing both pharmacology and genetics, the EMBL scientists engineered mice to produce receptors for a specific drug only in their type 1 cells. When the mice were injected with the drug, it bound to those receptors, setting off molecular signalling pathways that disrupted the cells' electrical charge. Thus, these neurons could no longer send electrical signals to surrounding brain regions. Mice whose type 1 cells had been blocked in this way were then subjected to the tone they had been conditioned to fear.

"When we inhibited these neurons, I was not surprised to see that the mice stopped freezing because that is what the amygdala was thought to do. But we were very surprised when they did a lot of other things instead, like rearing and other risk-assessment behaviours," says Cornelius. "It seemed that we were not blocking the fear, but just changing their responses from a passive to an active coping strategy. That is not at all what this part of the amygdala was thought to do."



The entrance to Cornelius' lab.

To better understand the brain circuits involved in this switch from passive to active coping strategies, Cornelius's group teamed up with the group of Angelo Bifone at GlaxoSmithKline in Verona, Italy. They used a type of brain scan called functional magnetic resonance imaging (fMRI) to see which regions of the brain were active. In small animals like mice, fMRI measures local blood volume as an indicator of neural activity: the more blood there is in a particular area of the brain, the more active are those neurons. This study marks the first use of fMRI to map neural circuitry in mice, using a new technique developed by the GlaxoSmithKline team.

The brain scan also yielded another unexpected result. Scientists previously thought that the amygdala managed fear behaviours by simply relaying information to the brainstem, which links the brain to the spinal chord. But Cornelius, Angelo and colleagues found that in mice whose type 1 cells had been blocked – the mice that would assess risk instead of freezing – the outer layer of the brain, called the cortex, was unusually active, indicating that it too plays a role in determining how mice react to fear. The scientists also observed activity in a brain region called the cholinergic basal forebrain, which is known to influence cortex activity.

Like all brain scans, fMRI requires the subject to remain very still, so it can only be performed on mice that have been anaesthetised. As they were not able to observe brain activity while the mice were awake and therefore capable of reacting to fear, the scientists took the reverse approach to confirm the role of the cortex in this process. They used the drug atropine to block cortex activation in mice whose type 1 cells were also blocked, and found that the animals again showed freezing behaviour and no longer showed any risk assessment behaviours.

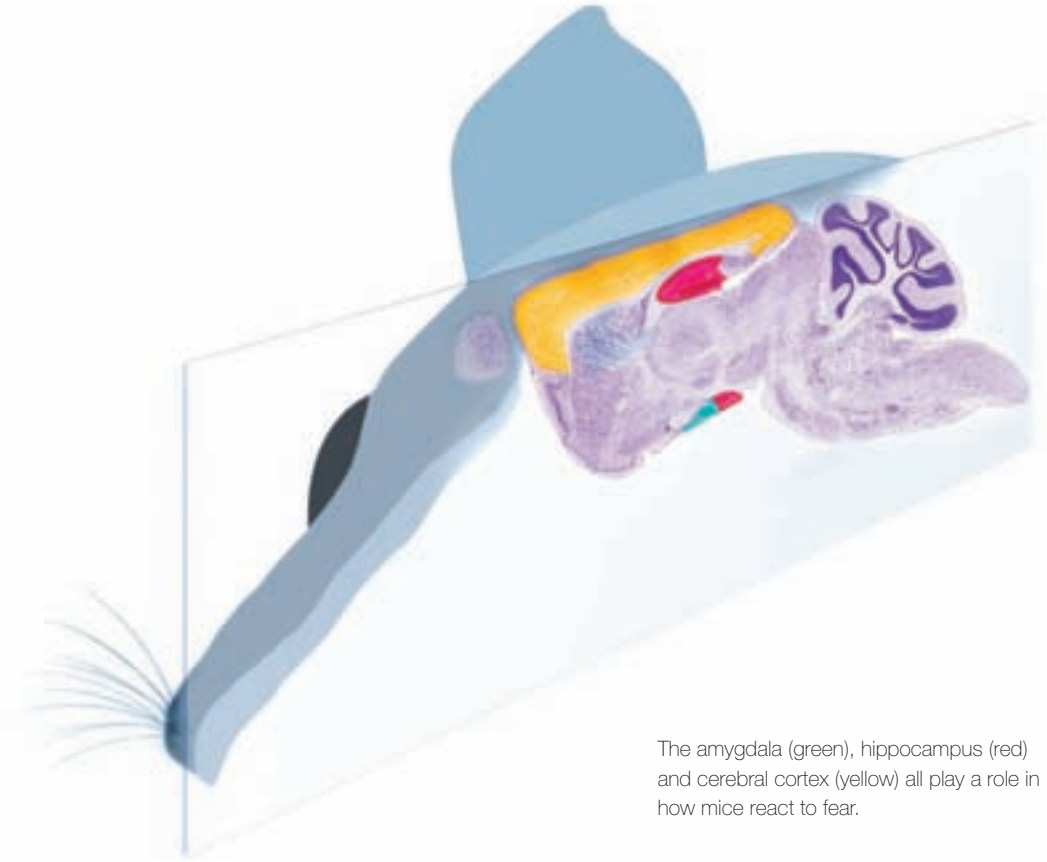
Thus, the scientists infer, type 1 cells in the amygdala normally inhibit the cholinergic basal forebrain, signalling the brainstem to initiate the passive fear response: freezing. When type 1 cells are inhibited, however, the amygdala releases its hold on the cholinergic basal forebrain, leading to cortex activity and an active reaction to fear: risk assessment.

Taken together, these results indicate that the amygdala plays a more complex role in fear processing than previously thought. Instead of merely passing on information about external threats, the amygdala makes decisions about how to respond.

It is important to note that the type of fear explored in this study – conditioned fear of a painful shock – is very specific. The results cannot necessarily be extrapolated to describe decision-making about behavioural responses to other types of fear.

"There are multiple, parallel fear circuits that handle different types of fear information. For example, one part of the brain is often used to process fear of a predator, such as a cat, while another part usually responds to an aggressive animal of the same species," Cornelius explains. "We thought there was a simplistic fear circuit that is either on or off, but that doesn't seem to be true."

Also, scientists do not yet know the circumstances under which wild mice use this circuit to promote an active coping strategy in response to threatening stimuli. Type 1 cells were



The amygdala (green), hippocampus (red) and cerebral cortex (yellow) all play a role in how mice react to fear.

artificially inhibited in this study, and there may or may not be situations when the neurons would naturally be inhibited, leading the mouse to engage in investigative behaviours to learn more about a perceived threat.

If the active response is found naturally in mice, what kinds of external sensory cues are necessary to activate it? While previous studies have shown that animals located farther away from a perceived threat are more likely to freeze in fear rather than run or fight, scientists cannot yet say whether the use of an active risk assessment response is a function of distance. Cornelius emphasises that it's important not to assume that a risk assessment response to fear would be used in place of freezing in a situation perceived as less threatening.

Nonetheless, this study has significant implications. The pharmaco-genetic and fMRI techniques that the scientists used will likely prove invaluable in many other studies of brain circuits in mice. Indeed, Cornelius and his team have already used a pharmaco-genetic approach to reveal cells that act as an input for another brain region, the hippocampus. These cells relay information that enables a mouse to gauge an appropriate level of anxiety in an uncomfortable situation.

Furthermore, we humans also show freezing and risk assessment responses to fear. We possess a region of the amygdala that is analogous to the one housing the active/passive switch in mice. Patients who have suffered lesions to this region are unable to develop conditioned fear responses, though they have normal reactions to fear in other situations. Thus, it is likely that the results of this study could apply directly to humans, Cornelius says.

Though much remains to be discovered about how humans process fear in different situations, studying fear brings scientists ever closer to developing more effective treatments for fear-related illnesses – such as anxiety and post-traumatic stress disorders. In the words of the Nobel Prize-winning chemist Marie Curie, "Now is the time to understand more, so that we may fear less."

Gozzi A, Jain A, Giovanelli A, Bertollini C, Crestan V, Schwarz AJ, Tsetsenis T, Ragozzino D, Gross CT, & Bifone A (2010) A neural switch for active and passive fear. *Neuron* **67**: 656-666

In the spotlight

Biological research and *haute couture* may seem worlds apart, but there's one thing they have in common: models. But whereas top models showcase unique designer creations, model organisms exhibit general characteristics shared by many species in a group, and thereby can serve as representatives of that group. Used to address a variety of biological questions, model organisms are usually small, develop rapidly and are amenable to observation and experimentation.

They also have some things in common with their *haute couture* namesakes: model organisms are cast into specific roles, there's a backstage team bustling with activity and catering to their every need, and these models regularly show off their attributes – and the knowledge they've brought to the scientific community – not on runways and photoshoots, but in scientific papers, posters and conferences.

Casting: The biological question determines the model organism

In molecular biology's early days, researchers had only a few models in which to study biological phenomena, such as the bacterium *Escherichia coli*, the yeast *Saccharomyces cerevisiae*, the worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*.

Thomas Hunt Morgan was the first to introduce the fruit fly as a model organism at the start of the 20th century. Using this insect, he showed for the first time that genes are located on chromosomes, and that they constitute the basis of heredity. *Drosophila* has been the classical animal model for genetics ever since. In the late 1970s and early 1980s at EMBL Heidelberg, Christiane Nüsslein-Volhard and Eric Wieschaus were able to identify the master genes that control *Drosophila* development, in work that earned them the Nobel Prize in Physiology or Medicine in 1995, and many groups at EMBL still use this insect to study both genetics and development, and the links between them.

For instance, the body axes that define a fruit fly's front, back, top, bottom, left and right, as well as the arrangement of its body segments – head in front of thorax, and so on – all begin to be determined before its parents have even mated, in the egg cell produced by the mother fly. They are defined by specific proteins that are present only in particular areas of the egg cell. After the genes that encode these proteins have been transcribed into RNA molecules, these templates are transported to where the protein is needed, and only there are they translated into protein. The group of Anne Ephrussi, Head of the Developmental Biology Unit in Heidelberg, is investigating this mechanism. "We're deciphering what ensures that these RNA molecules are only translated into proteins once they reach the right spot in the cell, how they get there in the first place, and how all this is coordinated to happen at the right time," Anne explains. "The *Drosophila* oocyte and its localised RNAs are a paradigm for the study of RNA

transport and localised protein production – processes that occur in many other cells and circumstances, too."

Since Morgan's day, new questions have arisen and new techniques have been developed, so scientists have gradually introduced additional model organisms. With a number of options available today, each scientist has to choose which model organism is best suited to address his or her specific research topic, like a designer casting the top models with the best figures to showcase his or her creations.

Group leader Darren Gilmour at EMBL Heidelberg, for example, is interested in how cells move inside a developing body. He realised that zebrafish enable him to visualise individual organs and cells as they develop because they lay their eggs in the water and the transparent embryos develop outside the mother. By placing them under a microscope, Darren can easily observe how they develop into swimming fish, and even track individual cells. "A pair of zebrafish can generate up to 300 or 400 eggs every week," he says. "It's great to have a lot of material to work with."

Another classical model organism is the mouse. Like humans, it is a mammal, and therefore is similar to us in a number of ways – on both a morphological and a molecular level. These features make the mouse an ideal model of disease. But that's not all, as group leader Cornelius Gross explains. "At EMBL Monterotondo the six groups are pursuing research in very diverse fields, all using the mouse." These areas of research range from muscle regeneration to pain perception, via gene regulation and Cornelius' own research interest: the study of anxiety. Cornelius and his group are trying to understand the underlying mechanisms of anxiety behaviour, studying them in the mouse to gain insights into how the human brain functions (see page 76).

When looking for a model organism in which to study the evolution of the vertebrate body plan, Detlev Arendt from EMBL Heidelberg fell upon a very different animal: the marine ragworm *Platynereis dumerilii*, a sea-dwelling relative of the earthworm. For the past 600 million years, the body structure of *Platynereis* has remained essentially unaltered, making it what scientists call a living fossil. The ragworm is therefore an ideal model to answer evolutionary questions, as it provides a glimpse of what our ancestors may have looked like.

Backstage: Like a huge pet shop

To control all possible variables and enable approaches like genetic studies, most model organisms are kept and bred in the laboratory. To that end, scientists have to identify everything that makes an organism happy, from its favourite food to its preferred housing, as that is the surest way of guaranteeing that it will reproduce.

In fact, two of the reasons the fruit fly was immediately such a popular model – alongside its tractability for genetic studies – are that it is small and has an uncomplicated diet, so it has a

generation time of only two weeks and is easy to grow in the laboratory. In the fly room in Heidelberg, thousands of *Drosophila* are kept in a collection of little plastic tubes with specially prepared food in the bottom.

Raeka Aiyar, from Lars Steinmetz's group in Heidelberg, works with a microscopic organism: yeast. Tiny, but very robust, yeast cells don't need much space and survive in what we would consider very harsh environments.

"We store them in the freezer at minus 80°C," explains Raeka. "You just have to mix them with some glycerol, and then they stay quite happy in there for, as far as we know, years at a time. When we actually want to work with them, we just take them from the freezer, and streak them out on an agar plate." These agar plates contain all the nutrients the yeast cells need to survive and reproduce. Put them in an incubator at their ideal temperature of 30°C, and the cells will do the rest.

Larger organisms like fish need more spacious rooms. The zebrafish at EMBL are kept in many small aquaria, and each tank houses one family. Each family has been genetically manipulated and selectively bred to have a special trait. Some fish have long fins, for instance, and the "Leopard" family have dots on their flanks instead of stripes. "If we were to put all those fish families together and mate them in one big tank, it would be chaos. So we have to keep lots of families, and that's why we have lots of tanks," explains Darren. Originally from the Ganges river, the zebrafish is accustomed to warm regions, so the fish room is kept at a constant 26°C. The fish's daily food portions consist of algae that are grown in big vessels inside the fish facility.

Another organism that feeds on algae is *Platynereis*, which is kept in a mixture of natural and artificial seawater. This is only one of the peculiarities of the *Platynereis* facility. "Maybe you won't notice at first, but there is a moon in our worm rooms, which is only on when there is a real full moon outside," says Detlev. "*Platynereis* needs the lunar information for breeding." When the moon shines, both males and females know that the time has come to mate. They perform a nuptial dance, swimming in spirals, and release their eggs and sperm in the water at the same time, to increase the chances of fertilisation. Thus, a new life cycle can begin.

The catwalk: Show what you've found

Platynereis' features are so ancient that Detlev has compared it to vertebrates and has come up with a proposal for what our last common ancestors, which swam the oceans 600 million years ago, looked like. "We are at the moment reconstructing the nervous system that was in place at this time and in these ancestors, by comparing neuron types in *Platynereis* to vertebrates," explains Detlev. He and his group recently found that certain structures in the worm's brain, called mushroom bodies, seem to have evolved from the same ancestral structures as the cortex of vertebrates, which most people didn't expect (see page 60).

Another body structure essential for human life is muscle. But how does it form? In the young *Drosophila* embryo, a network of genes is responsible for telling a few cells to develop into different kinds of muscle cells. Eileen Furlong and her group at EMBL Heidelberg are trying to

understand the regulatory networks that make this possible by controlling the genes involved at different times and in different parts of the embryo (page 52).

Yeast, by contrast, doesn't have any organs, because each individual is made of only one cell. Nevertheless, the simplicity of yeast has made it an attractive model organism to develop a variety of modern technologies, as achieved by Lars' group. And yeast can teach us about human diseases too. Raeka studies mitochondria, the components of a cell that produce energy. Because their role is so crucial to all cells, the mitochondria of yeast, plants and animals are very similar, and yeast can therefore be used as a model for human mitochondrial disease. In this type of disease, the DNA in the mitochondria is mutated. Currently, yeast is the only organism in which such mutations can be engineered. Raeka and colleagues produced such 'diseased' yeast, and then screened for drugs that would restore the cells to their healthy state. In subsequent tests, some of the drugs have proven to be effective in cells derived from human patients.

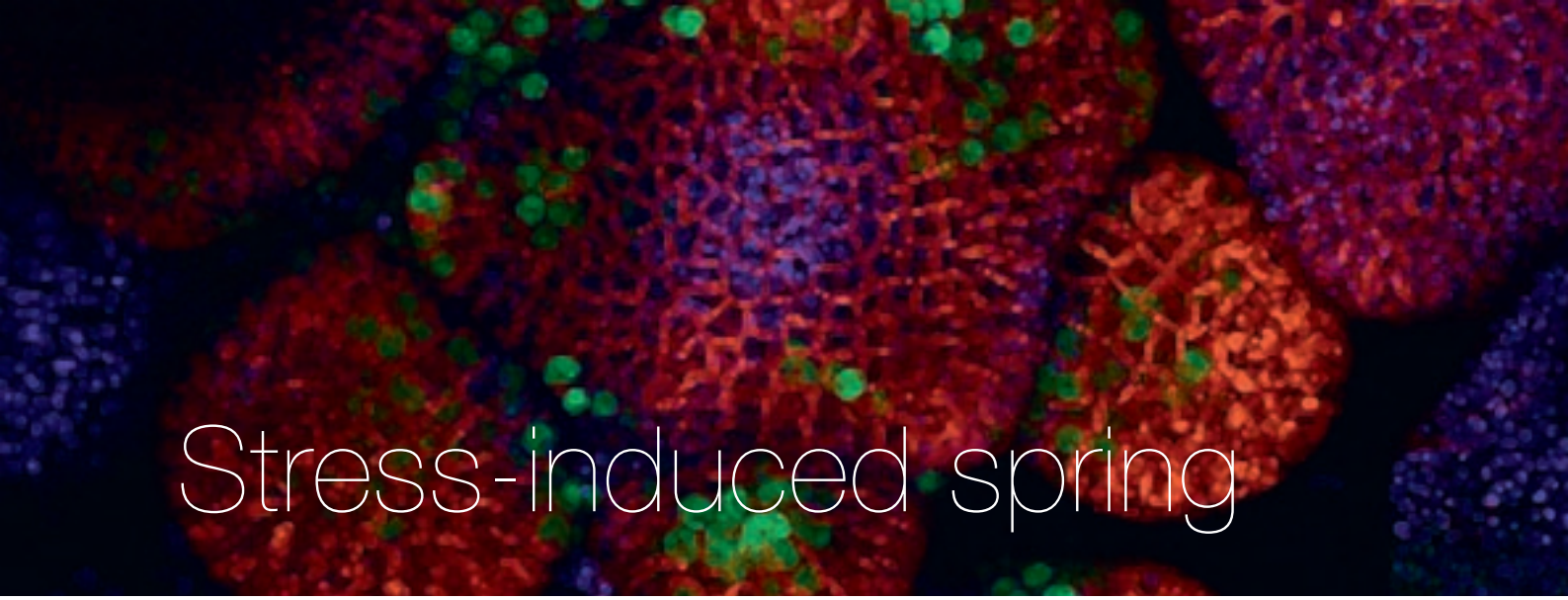
EMBL's new recruits

As researchers with different interests come and go, so do the model organisms housed at EMBL. In the late 1990s, Antony Hyman's group at EMBL Heidelberg was among the first to use information about the DNA sequence of an animal – the nematode worm *C. elegans* – to systematically search for genes involved in different aspects of cell division. When the group moved on to the Max Planck Institute in Dresden in 2002, the worms went with them.

A decade later, another group leader brought a different model organism with him. With Marcus Heisler's arrival at Heidelberg, plants were introduced as a model at EMBL for the first time. Marcus focuses on *Arabidopsis thaliana*, a small flowering plant that has one of the smallest plant genomes. Although a newcomer to EMBL, *Arabidopsis* has been the plant model organism of choice for over 100 years. A reason for its popularity is that a seed can grow to an adult plant, which gives rise again to a crop of seeds, in only six weeks. Marcus and his group are studying how plant organs such as flowers and leaves develop (see page 85).

The newest member of EMBL's animal community is the lancelet, *Amphioxus*, which is a fish-like creature that has a spinal cord but no true brain. Like *Platynereis*, it lives in seawater in Detlev's facility. As a species, *Amphioxus* is probably as old as the ragworm, but it is more closely related to vertebrates than *Platynereis*, so Detlev hopes that it will provide a link between the two.

Often with new scientific findings, more questions arise. Depending on the nature of such questions, scientists may investigate them in these model organisms, or turn to other species. Thus, we await EMBL's next selection round for new recruits.



Stress-induced spring

Every year, the spectacle of spring blooming forth inspires artists, poets and laymen alike. All around, everything seems to turn green, as countless forms of plant life develop and grow. At the cellular level, however, the sprouting greenery that makes for relaxing walks among the flowers is driven by stress. Not the stress that has become part and parcel of our fast-paced lives, but mechanical stress – in this case, physical strain on the plant cell wall, as EMBL Heidelberg group leader Marcus Heisler discovered.

Flowers, leaves and stems all develop from shoots. In the walls of a shoot's cells, cellulose fibres act like the metal hoops used to reinforce wine barrels. This orientation of cellulose determines the direction in which the plant's tissues will grow: cells tend to take the path of least resistance, and grow perpendicular to the orientation of the cellulose fibres. At the cellular level, there are two different mechanisms involved in growth. First, microtubules – protein fibres that in plant cells mainly function as a transport network – control the direction in which cellulose is deposited in a particular section of cell wall, guiding the direction of growth. Second, a plant hormone called auxin plays a role in where and when tissues grow, by "turning on" genes involved in growth. During his postdoctoral work at CalTech in Pasadena, USA, and in collaboration with colleagues in the Universities of Lyon, France, and Lund, Sweden, Marcus was the first to show that, in plant shoots, these two mechanisms are linked.

Auxin exits plant cells through a molecule called PIN1, which sits on the cell membrane and acts as a gateway. Studying the model plant *Arabidopsis thaliana* (see page 80) Marcus noticed that microtubules align in a circle around the site where flowers begin to form and, at the same time, PIN1 accumulates in the regions of the cell membrane parallel to the microtubules. By disrupting each in turn, Marcus and colleagues discovered that these two processes are independent. "Even if microtubules aren't aligning properly, PIN1 still accumulates at the same points on the membrane, and vice-versa," Marcus says.

If neither of these processes is driving the other, but they seem to be synchronised, could they both be caused by some other underlying factor? Marcus and his collaborators had previously found that microtubule orientation can be modulated by applying mechanical stresses to the cell wall. Now, the scientists were able to show that both PIN1 polarity and microtubule orientation respond similarly to such perturbations. They did so by introducing chemicals that weaken a cell's wall, thereby changing the mechanical stresses that the wall is under.

Based on their findings, Marcus and colleagues now believe that the concentration of auxin in a cell controls the mechanical properties of that cell's walls. Changes in auxin concentration can therefore change the stress distribution within the tissue. In turn, these variations in stress regulate microtubule orientation and PIN1 polarity. As PIN1 is responsible for transporting auxin out of the cell, this leads to localised changes in auxin concentration, creating a feedback loop that ultimately controls growth.

In Heidelberg, Marcus and his group are expanding on this work, taking full advantage of EMBL's collaborative environment. "I have an EIPOD fellow working in mine and François Nédelec's group, looking at the microtubule aspect of patterning," he says, "and in general in my lab we're looking at how several different patterning processes are connected, and how they're regulated by mechanisms like gene expression." The work will be aided by the young investigator grant Marcus has received from the European Research Council, and it should ultimately bring us closer to understanding the magic of spring.

Heisler MG, Hamant O, Krupinski P, Uyttewaal M, Ohno C, Jonsson H, Traas J, Meyerowitz EM (2010) Alignment between PIN1 polarity and microtubule orientation in the shoot apical meristem reveals a tight coupling between morphogenesis and auxin transport. *PLoS Biol* **8(10)**:e1000516.

An eventful year

When the new EMBL Advanced Training Centre officially opened in March 2010, it marked the beginning of an exciting new era in EMBL's long tradition of hosting world-class conferences and courses at the main Laboratory in Heidelberg.

Since EMBL opened its doors in 1974, advanced scientific training has been one of the cornerstones of its overall mission to promote scientific excellence in the life sciences throughout Europe, and provide valuable services to its member states and the international scientific community.

EMBL has extensive expertise in organising and hosting advanced courses, conferences and workshops, but its previously limited facilities meant that up to a third of prospective conference attendees and as many as 80% of course applicants had to be turned down.

The solution? To create a new central European hub for advanced training in the life sciences. The EMBL Advanced Training Centre brings together many facets of EMBL's training activities under one roof, and provides close-to-perfect facilities for courses and conferences – the benefits of which were immediately evident in its successful first season.

Firm foundations

At nearly 80 000 cubic metres, the EMBL Advanced Training Centre building is unique in both architecture and design. It was originally the concept of local physicist and philanthropist Klaus Tschira, whose foundation provided a generous donation for the construction of the building. The work, which began in October 2006, involved the excavation of 50 000 cubic metres of earth and the laying of 10 km of cooling pipes and 20 km of electricity cables, with up to 120 people working on the site at any one time.

Inspired by the structure of the double helix, the main building hosts state-of-the-art training facilities for practical courses, a 466-seat auditorium, exhibition space for over 300 posters, teaching labs for 100 participants and a 36-seat computer teaching laboratory, not to mention several seminar and meeting rooms. The large foyer, together with the rooftop terrace and the lounge, offers space for social events and informal scientific exchange in a relaxed atmosphere.

The higher capacity of the EMBL Advanced Training Centre allows more scientists to benefit from EMBL's training activities, with the number of course and conference participants more than doubling in its first season. Most importantly, however, the new venue enables EMBL to explore new forms of training and to build on the quality of existing events.

Setting the stage

Capitalising on the EMBL Advanced Training Centre as a novel platform for life science learning and conversation, exciting new conferences and events have been added to the EMBL calendar.

On 28 April 2010, Nobel Laureate David Baltimore, Professor Emeritus at Caltech in Pasadena, USA, drew a record audience to his inaugural 'Vision 2020' lecture – the first in a series of forward-looking scientific talks by world-leading life scientists. For this series of lectures, each speaker is invited to share their vision of the future of their field with an audience of scientists and interested members of the public. Vision 2020 speakers to date include Mario Capecchi, Harald zur Hausen, Susumu Tonegawa, Phillip Sharp, and Christiane Nüsslein-Volhard.

Launched in June 2010, the new joint EMBO|EMBL Symposia aim to put Europe more strongly into focus in the world's scientific community as a place for high-quality research and exchange of ideas. EMBL and EMBO have a long tradition of cooperating to provide top-quality meetings for the benefit of the scientific community. The joint symposia, which began with 'Human Variation: Cause and Consequence', provide a platform to exchange ideas on forward-looking topics and new developments, and complement the courses and conference programmes of both EMBO and EMBL.

EMBL Advanced Training Centre

35 conferences and meetings

26 courses

5 Vision 2020 lectures with approximately 1800 participants

Close to 7000 delegates, organisers, speakers and exhibitors

70 organisations gave support and sponsorship, 48 of which exhibited

Looking ahead

Since the EMBL Advanced Training Centre's official opening on 9 March 2010, 61 events have brought together nearly 7000 delegates, organisers, speakers and exhibitors in the auditorium, teaching labs, computer training rooms and meeting areas.

Courses and conferences are an integral part of the EMBL International Centre for Advanced Training (EICAT), which coordinates integrated training activities for scientists and future scientists at all levels, inside and outside EMBL. To this end, and within less than a year of its opening, the EMBL Advanced Training Centre has already enjoyed more attention as a state-of-the-art venue that serves all of Europe, the EMBL member states and beyond than was realistically expected.

EMBL remains committed to offering a steadily improving portfolio of advanced training opportunities in the future.

Find out what's coming up at www.embl.org/events

Parental control

It's a familiar scene at the family dinner table: a small child making faces at a plate of spinach or broccoli, while a parent coaxes them, in vain, to "eat their greens". It's all in the child's best interests, of course, as green vegetables contain nutrients such as iron that are vital to health. But as parents around the world fret about getting enough iron into their toddlers, EMBL scientists have been worrying about the next step: what happens to iron once it gets into the body's cells, and why is it so important? Now, the group of EMBL Associate Director Matthias Hentze has discovered how cells make sure they can supply enough iron to the tiny power plants that create the energy they need. "It's uncovered an important aspect of cell biology," says Matthias.

As any anxious parent will tell you, achieving the right body-wide balance of iron levels is crucial: too little iron causes anaemia, whereas too much overloads vital organs. Having too much or too little iron within cells also causes problems: the cells usually die. Abnormalities in cellular iron levels have also been found in diseases such as the neurodegenerative condition Friedrich's ataxia. However, scientists weren't sure why. "What we didn't know was: when you make a cell iron-deficient, where does it get hit?" explains Matthias.

His team focused on two key proteins, called IRP1 and IRP2, that are involved in controlling cellular iron levels. These regulate the production of other cellular proteins that import, store and export iron. Matthias has been interested in IRP1 and IRP2 ever since he discovered the mechanism they use to control protein production back in the 1990s. He and his team, led by Staff Scientist Bruno Galy, wanted to find out what would happen to cells if they disabled IRP1 and IRP2, thereby starving the cells of iron.

As iron is vital for life, the team couldn't simply create mice lacking the IRP1 and IRP2 genes – such mice die before birth. Instead, with the help of the EMBL Animal Facility, they used state-of-the-art genetics techniques to disable IRP1 and IRP2 only in the livers of developing mice. The results were dramatic: the mice died within two weeks after birth from catastrophic liver failure. In collaboration with colleagues at the Heidelberg University Children's Hospital, the team took a closer look at the liver cells and found that their mitochondria – tiny structures that generate energy for the cell – were badly damaged. "It's the mitochondria that really suffer," says Bruno.

This made sense because in addition to their energy-generating role, mitochondria also build vital cellular parts called cofactors, which are essential for the function of certain proteins. Some of these cofactors contain iron, for example haem, which is part of the haemoglobin protein that carries oxygen in the bloodstream. Other iron-based cofactors are needed for the proteins involved in mitochondrial energy production, and without them the mitochondria fail. "That is why the cell basically goes to pot," says Bruno.

It's likely that human cells have the same mechanism in place, which leads to an intriguing – even ironic – thought: even as grown-ups, we still have the cellular equivalent of two fussing parents, IRP1 and IRP2, watching over us and making sure our cells use up their iron properly.

Galy B, Ferring-Appel D, Sauer SW, Kaden S, Lyoumi S, Puy H, Kölker S, Gröne HJ, Hentze MW (2010) Iron Regulatory Proteins Secure Mitochondrial Iron Sufficiency and Function. *Cell Metab* **12**: 194-201

Our cut-and-paste genome

One of the biggest mysteries in biology is how to explain the huge variety in physical characteristics we see in human beings. We all have nearly all of our DNA sequence in common, but key differences in this sequence underlie why, for example, some people have pale skin and others dark, or why some people are more prone to developing certain diseases than others, even when lifestyle and environmental factors are taken into account. Now, research by an international consortium led by Jan Korbel at EMBL Heidelberg has produced a detailed map of the variations in the physical structure of the human genome. The work provides an invaluable starting point for researchers hoping to answer this mystery.

To understand how the human genome sequence varies from person to person, scientists are sequencing the genomes of thousands of people from different populations around the world, in an initiative known as the 1000 Genomes Project (see page 28). As part of the initial phase of this project, Jan led research by the Structural Variation Subgroup, which aims to discover relatively large variations in the structure of a person's genome. These variations include deletions, where a chunk of DNA is lost, and insertions, where a new piece of DNA hops into the genome. Until recently, most research into variation has focused on changes in single DNA letters, or bases. Jan's team, however, looked for changes that are more than 50 bases long, almost all of which were previously unknown.

The project benefited from a DNA analysis technique that Jan co-developed prior to joining EMBL, called paired-end mapping, which lets researchers scan DNA for structural variation without having to sequence entire genomes, and saves time and cost. At EMBL, Jan and his colleagues also created new software that allows them to pinpoint the locations of the variants at single-base resolution. "The challenge is really to analyse and interpret the millions of reads generated in these experiments properly, and identify places in the genome that vary from person to person," says Jan.

Together with teams led by Matthew Hurles at the Wellcome Trust Sanger Institute in Cambridge,UK, Evan Eichler at the University of Washington, Seattle, USA, and Charles Lee at Harvard Medical School in Boston, USA, Jan's team scanned the genomes of 185 individuals. They identified more than 22 000 deletions and 6000 other structural variations and mapped their locations on the genome. More than a thousand of these variants disrupted the function of genes and might therefore be promising leads for researchers trying to track down the genes behind certain diseases.

The team also determined the biological mechanisms behind the structural variations. Some, for example, were caused by mistakes made by the machinery that repairs DNA damage. "We did this very comprehensively and generated a map that shows how often certain parts of the genome change," says Jan. This allowed the researchers to locate 51 "hotspots" in the genome where some of these events are particularly likely to occur. Some of these regions were already known to be associated with genetic conditions such as the Miller-Dieker syndrome, which is an infant brain disease caused by large DNA deletions. Intriguingly, the hotspots that Jan and his colleagues found could also be the nurseries of new genes, creating the raw material for the evolution of yet more variation in humans.

Mills R *et al* (2011) Mapping copy number variation by population-scale genome sequencing. *Nature* **470**: 59-65

Jan Korbel

Janet Thornton

EMBL-EBI Director Janet Thornton discusses ELIXIR

ELIXIR has been described as 'a European research infrastructure of global significance'. Can you tell me a little bit about what it is, and how it fits into the innovation economy?

Access to large, public datasets is allowing life science researchers to explore information in creative ways, and has fundamentally changed the way we do research. Some of the most interesting and innovative work in recent years has come out of close collaborations between experimental and computational biologists, and we are keenly aware that unimaginable leaps forward are in store. Undoubtedly, we will need to capture, store, analyse and integrate all these data.

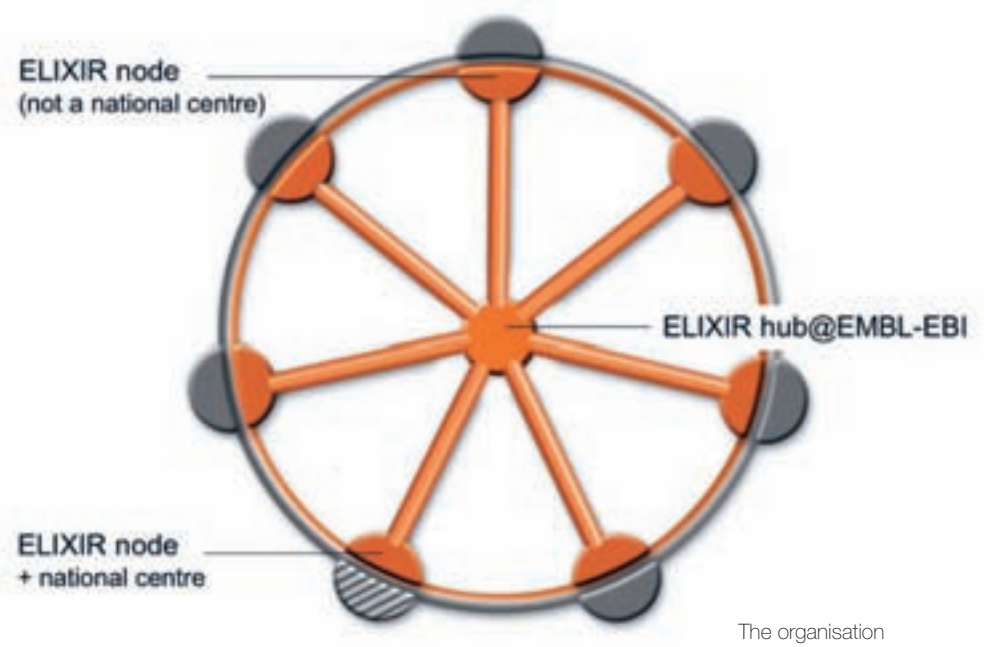
Over the past decade, European funding agencies have invested heavily in research, increasingly motivated by concerns about the security of our food supply or an ageing population. All of these funders, and the people they represent, are eager to see that maximum value is being extracted from the data that are generated, and that they are safeguarded well into the future. That's where ELIXIR comes in.

The purpose of ELIXIR is essentially to upgrade Europe's bioinformatics infrastructure so that we can continue to provide life science researchers with seamless access to biological information in a sustainable way. To do this, we need to define a coherent strategy for data and integrate the resources of life science laboratories and data centres throughout Europe. The task is simply too large and complex to be handled by any single organisation or nation, and what we have now is too fragmented to support the science of the future.

Why now? What has changed?

I'm not sure that ten years ago anyone could have foreseen that the growth in genomic data would outstrip the growth in storage and processing capacity so dramatically. Next generation sequencing machines produce billions of bases of nucleotide data per experiment, so what used to take years of painstaking and expensive research now takes minutes and costs relatively little.

So what we have is a disruptive technology: it is so much better than what we had before that the uptake is skyrocketing and both the users and the informatics infrastructure have trouble adapting to it. And because innovation breeds innovation, we expect to see these technologies being somewhere between a thousand times and a million times more productive over the next ten years. If you take the physical sciences as an example, that might be like running several experiments on the Large Hadron Collider every day.



The organisation of ELIXIR.

How can we manage all of that growth and expanding diversity?

So far, the challenge of handling Europe's core data resources – for example genome and proteome databases – has been met mostly by EMBL-EBI, funded by EMBL's 20 Member States. But with a doubling of data every five months, maintaining a single centre to address this challenge is not sustainable.

ELIXIR is helping the scientific community to define how Europe will distribute the management of its biological data. It is a coordinated, pan-European effort and investment in bioinformatics services. This is not a simple thing – it means creating robust, sustainable and distributed structures for handling data, tools and analysis as well as coordinating training and standards development.

All of these things are constantly in flux. One reason it can be so difficult to talk about research infrastructures is that if they work properly, they are largely taken for granted. They simply provide the stability you need to innovate and adapt. ELIXIR, for example, is not a new company, network or product. It is a monumental undertaking to collectively define a structure for handling game-changing developments in the life sciences.

EMBL-EBI has around 64 databases that I know of – are there a lot more being used in Europe now?

We did a survey of biological databases in Europe and identified around 500 that are in regular use. These range from major core datasets, like the vertebrate genomes in Ensembl, to very small specialist collections that are overseen on a part-time basis by individual researchers. An effective data infrastructure will encompass all of these, but also tie them in rationally to the tools used to access and interpret the data they contain.

How fast are the data growing? Is computer storage and processing speed improving quickly enough to absorb the data challenge?

You may have already seen this picture of Moore's Law, which shows how storage and processor capacity double every couple of years. Against this backdrop we see the growing volume of

biological data, which is doubling every five months or so and getting faster. This means that we need more and more storage – but you can't just keep adding servers and directing more power to a few data centres. This is a very real and serious challenge for Europe's bioinformatics infrastructure.

However, storage is only one part of the equation. Perhaps even more important is the need to integrate the growing variety of data in meaningful, research-supportive ways. Many projects today look at different biological problems from many perspectives, using several different technologies. It should be simple to draw on several powerful data resources to answer complex questions, and to move seamlessly from one to the other.

The physical sciences compute architecture has been optimised to address compute-intensive problems. But in biology we run data-rich, massively parallel queries, which present a different set of challenges. Without an exponential increase in both storage and processing power, we won't be able to cope with the new data, which could have serious implications for the scientific record, if nothing else. ELIXIR will take this on as a matter of priority.

There is so much on offer that it's hard for a regular wet-lab biologist to know which database has the information they need, or even whether one exists at all. How can ELIXIR help users?

At the moment we have a plethora of databases scattered across the bioinformatics landscape. This is indeed confusing to the majority of potential users.

ELIXIR is going to radically enhance Europe's data infrastructure, and make it more accessible. Part of that means presenting users with a single, transparent interface to a world of resources that might in fact be widely distributed. It also means fully integrating the growing variety of data and resources so that we can gain tangibly from our expanding informatics capacity. Of course, to do this we have to establish universal principles. For example, we need to have clearly defined standards for data storage and access.

Once everyone sees all of these resources in one place, do you think they might be overwhelmed? How are researchers going to keep up with all this?

Access to public biological data has become as fundamental to modern research as access to peer-reviewed literature. In modern collaborations, experimental and computational biologists work together from the outset to define and carry out a research project. So the user base has grown and diversified to include not just bioinformatics-aware researchers but also clinicians, pharmaceutical experimentalists, plant breeders, environmental scientists and so on.

Naturally, as the demand for bioinformatics rises, so does the need for training. At present the training on offer – not just at the EMBL-EBI but everywhere – cannot meet this rising demand. We risk a bottleneck in the use of all these data unless we begin to make adequate user training available throughout Europe. ELIXIR will make it easier to bring together the training community, so that users at all levels can find the guidance they need to explore the data. This will benefit new accession states in particular.

Is ELIXIR going to replace what we already have?

ELIXIR will be built on existing data resources and services; it won't replace them. It follows a hub-and-nodes model, with EMBL-EBI as the hub and the nodes distributed throughout Europe. The expectation is that it will be persistently funded by European Member States as well as regional and international agencies. The model is scalable, so that new nodes, services, resources and tools can be added and integrated as the infrastructure grows. This is the most cost-effective solution.

ELIXIR will complement EMBL-EBI and the candidate node organisations. The UK has earmarked funding that we hope will help us build a new technical hub in Hinxton, and will go towards upgrading the ELIXIR data centres. The new building will house ELIXIR staff and training facilities, which will make it easier for us to deal effectively with the many technical and administrative challenges that come with a distributed infrastructure. But the majority of this funding is needed for enhancing and upgrading the storage and compute equipment over the next decade – not to mention the energy costs that go with that.

The goal is to ensure the data are kept safe and made easily accessible. If data disappears, experiments will have to be re-run, and if there's nowhere to centrally store data, researchers won't know about it and may repeat experiments. These are just a couple of examples of how the costs of not building a realistic infrastructure for biological data are many hundreds of times higher than whatever the cost of ELIXIR. A sound biological data infrastructure is probably the best, and cheapest, insurance policy any government or agency can make to ensure continued benefits from its investments in research.

What's next for ELIXIR?

In summer 2011, we hope to see a Memorandum of Understanding signed by EMBL and candidate node countries. This is the final year of ELIXIR's preparatory phase, and we are very excited to see the construction phase taking off in 2012. The first nodes should come online in 2013.

What drives ELIXIR is the desire to empower researchers in academia and industry to solve some of society's most pressing problems. Our vision is to offer researchers seamless access to biological information on an unprecedented scale, which will go a long way to facilitating discovery. At the same time, ELIXIR will help us translate these discoveries into innovations in a host of important sectors, from medicine to agriculture and the environment. And that is a very exciting prospect indeed.

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www.elixir-europe.org

www.ebi.ac.uk/ena/

www.ebi.ac.uk/chembldb

Whether we consider the world's first public database of nucleotide sequence (ENA) or one of the EMBL-EBI's newest public databases (ChEMBL), users' needs evolve continually and it's vital that the data resources keep pace.

The European Nucleotide Archive

In May 2010 EMBL-EBI launched the European Nucleotide Archive (ENA), which consolidates three major sequence resources into a single access point to freely available, globally comprehensive DNA and RNA sequence information. ENA now holds more than 20 terabases of nucleotide sequence that, combined with the valuable information added during annotation, occupies more than 230 terabytes of disk space.

"The launch of ENA reflects our continuing commitment to promoting scientific progress by providing global access to nucleotide sequence information," says EMBL-EBI Associate Director Graham Cameron. "This has been central to EMBL's mission since the 1980s when we launched the EMBL Data Library."

Carefully annotated and cross-linked sequence records from the EMBL Nucleotide Sequence Database (EMBL-Bank) form the backbone of the ENA. The archive also provides direct access to raw sequence data, for example in the European Trace Archive, which contains data from electrophoresis-based sequencing machines, and the Sequence Read Archive, a repository for raw data from next-generation sequencing platforms.

ENA team leader Guy Cochrane explains that ENA improves access to annotated and raw sequence data using the same user-friendly interface, which provides graphical browsing, web services, text search and rapid sequence similarity search. It also features over 190 million cross-references with records in other life science data resources.

ENA is funded by EMBL, the Wellcome Trust and SLING, which is a Framework Programme 7 project coordinated by the EMBL-EBI and funded by the European Commission.

ChEMBL: A new drug discovery resource

ChEMBL, a vast and freely available online database of information on the properties and activities of drugs and drug-like small molecules and their targets, was launched by EMBL-EBI in 2010. The data on millions of compounds – and their effects on biological systems – will help translate information from the human genome into new therapies in the clinic.

ChEMBL was transferred from Galapagos NV, a biotech firm, in July 2008 through a £4.7 million Strategic Award from the Wellcome Trust. This unique resource focuses on drug discovery: records include information about how small molecules bind to their targets and how these compounds affect cells and whole organisms, as well as information about their absorption, distribution, metabolism, excretion and toxicity.

"We are pleased that there has already been a big demand for ChEMBL data – not only from large pharmaceutical companies but also from academic institutions and small companies who will particularly benefit from free access to the data," says ChEMBL team leader John Overington. "The human genome sequence has provided a molecular 'parts list' for a human being, comprising all the genes and proteins that are encoded by our genetic blueprint. In order to develop new medicines, it is important to catalogue how each of these 'parts' interacts with drugs and drug-like molecules. ChEMBL brings together information from the interface of the genome with chemistry into a set of 'chemogenomic' databases that can be used to help determine whether a particular molecule has the right properties to make an effective drug."

ChEMBL has become a major resource for medicinal chemistry and drug development in Europe and internationally.

Making sense of antisense

We all need a bit of peace and quiet from time to time. Now we can get our desired silence wherever we like thanks to noise-cancelling headphones, which work by sampling the ambient sound entering the headphones (the annoying hum of a fridge, say), and then generating an 'anti-noise' soundwave that interferes with, and cancels out, the incoming sound.

Nature has hit on an analogous mechanism for regulating gene expression. Ordinarily, genes are read by transcription factors that scan along the 'sense' strand of DNA, producing sense RNA molecules that guide the construction of the protein encoded by the gene. During the past 15 years, however, biologists have discovered that genes can also be read from the opposite 'antisense' strand. This generates an antisense RNA molecule that can selectively interfere with the expression of the same gene, just as 'antisound' cancels out ambient noise.

Yet the precise function of these antisense mechanisms, how they work, and how widespread they are in the genome remain unclear. "These issues are not really understood," says Lars Steinmetz, a geneticist in the Genome Biology Unit at EMBL Heidelberg. So Lars, working with six other members of the Genome Biology Unit, set about finding out.

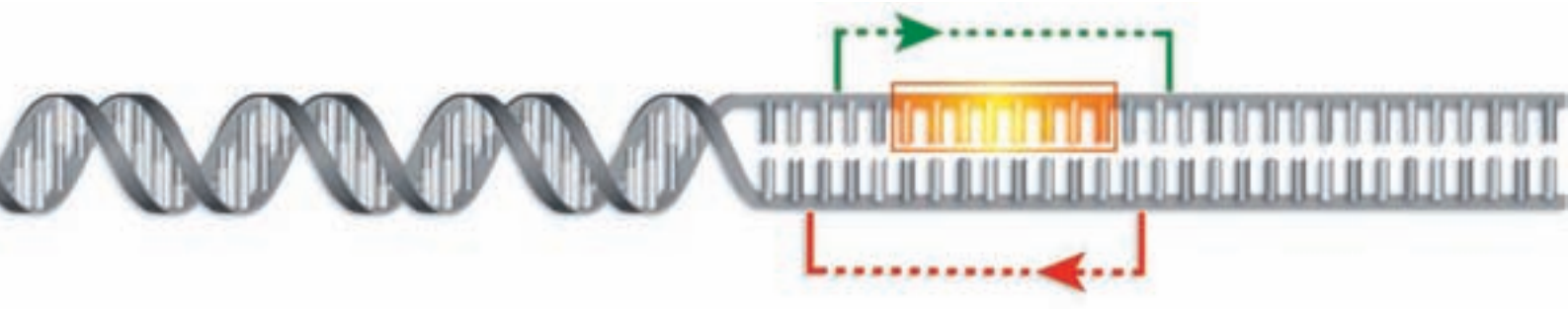
To do so, the team carried out a genome-wide screen of antisense transcripts in the yeast *Saccharomyces cerevisiae* under a variety of environmental conditions to see how the repertoire of expressed antisense molecules changed.

This screen produced two key findings. First, genes that need to be switched off under some circumstances but switched on under others — such as those encoding proteins that metabolise certain nutrients whose availability fluctuates — tend to show more antisense expression. This suggests that in addition to being under the control of transcription factors these genes also regulate their expression through antisense mechanisms, which Lars says allows for the fine-tuning of gene expression.

The second finding is that genes that express antisense RNAs also tend to have their activity linked to that of other genes. In earlier work, Lars and colleagues found that in the densely packed genome of yeast, a promoter that regulates the expression of a downstream gene often sits immediately after the protein-coding region of an upstream gene. Producing antisense RNA from the downstream gene's promoter means reading the DNA in an upstream direction, and so can interfere with the expression of the upstream gene. "So you get an interlinking of regulation between neighbouring genes through non-coding antisense RNAs," says Lars.

Although the underlying mechanisms for these two findings remain unclear, the work of Lars and colleagues underscores the widespread importance of antisense-based regulation of gene expression. A better understanding of these processes could shed light on how evolutionary changes in animal design are generated, which largely occur through altering patterns of gene expression during development. The results of Lars's study also point to the need to rethink the classical gene concept, which usually denotes the protein-coding region and the upstream promoter while ignoring downstream elements. "The importance of downstream elements that affect the expression of upstream genes means that these should be part of an expanded concept of the gene," says Lars.

Zhenyu X, Wei W, Gagneur J, Clauder-Münster S, Smolik M, Huber W, Steinmetz LM (2011) Antisense expression increases gene expression variability and locus interdependency. *Mol Syst Biol* **7**: 468



François Nédélec

Model behaviour

Imagine a building that could assemble itself and, once erected, maintain its structural integrity even while its walls, floors, supporting beams and foundations are periodically replaced. This is roughly what a cellular structure called the meiotic spindle has to do and recent studies led by François Nédélec, a physicist in the Cell Biology and Biophysics Unit at EMBL Heidelberg, have illuminated how it does it.

The meiotic spindle is involved in one of the most fundamental biological processes in sexually reproducing organisms: the formation of gametes. When cells divide to produce egg or sperm cells, the double set of chromosomes in the parent cell line up along the meiotic spindle, ensuring that each daughter cell receives exactly the right number of chromosomes. Mistakes at this stage are often profound, particularly when a gamete receives extra chromosomes — a situation known as aneuploidy, which underlies conditions such as Down's syndrome.

An enormous structure by cellular standards, the female meiotic spindle that François studied is made up of long protein filaments called microtubules and hundreds of other molecules. Yet while the spindle looks like a stable structure that just needs to be built and put in place, it is actually in a dynamic steady state: microtubules grow at one end, they shrink at the other end and at the same time, they also slide past each other in the direction of the spindle axis. Individually, these motions would be expected to either extend or shorten the spindle, but in reality the different contributions exactly cancel each other out, as the length of the spindle remains constant.

Biologists have known about the key elements that go into making spindles for a while, François says that until now there have been "no models of spindle formation that could account for its observed steady nature." So François – working with Rose Loughlin, a visiting PhD student from the group of Rebecca Heald at the University of California, Berkeley – set out to build a computer simulation that would. The team wanted to improve on earlier models by including something crucial that had so far been left out: the assembly dynamics of microtubules. "We wanted to get insights into the dynamic nature of this structure – how things move around, and in what way," he says.

François and colleagues' *in silico* simulation included many of the well-established components of the meiotic spindle, such as microtubules that shrink, grow and move past each other, and several other proteins that are important for building the spindle. These elements were programmed to function similarly to real biological molecules, mostly based on data from wet-lab biology. The resulting simulation not only generated spindles that resemble those seen in the cell, but they also elucidated how the different processes work together to maintain the constant length of the spindle.

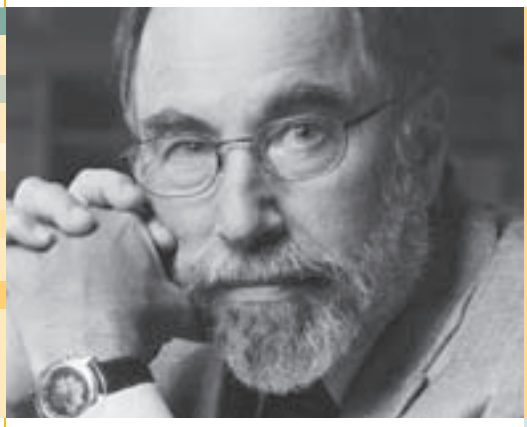
In short, the new model provides a coherent picture of the processes that combine to produce steady-state, but dynamic, spindles. "This is a big step for us," says François. "We've tried many times in the past to make a reasonable model, and now we have." And while this model, like most, omitted some fine detail, François says it will now be possible to add elements that were neglected to make it more realistic, and to further explore the dynamics of spindle creation.

Loughlin R, Heald R, Nédélec F (2010) A computational model predicts *Xenopus* meiotic spindle organization. *J Cell Biol* **191**: 1239-1249

A year in the life of EMBL

April

Looking to the future



To celebrate the inaugural year of the EMBL Advanced Training Centre and to set the stage for decades of exceptional scientific presentations, EMBL hosted a unique series of forward-looking scientific lectures by world leaders in their fields: Vision 2020. Several Nobel laureates accepted the invitation to share their vision of the future and their thoughts on the exciting new developments and possible breakthroughs in their scientific fields within the next ten years with an audience of scientists from different areas of the life sciences and interested members of the public. Caltech President Emeritus Professor David Baltimore opened the lecture series on 28 April to talk about microRNA control of inflammatory and immune processes.

Israeli get-together

On 27 April, EMBL hosted a group of 15 students from Rehovot, Israel. They were welcomed by Head of Communications Lena Raditsch and heard talks by PhD students Ioannis Legouras and Xavier Heiligenstein. The day was rounded off with a visit to the Laboratory and a tour through the EMBL Advanced Training Centre. This event was the first in a series of international visits in 2010 that included groups from France, Spain, Belgium, and the United States.

Beauty in unexpected places

Five years after the last science and art special event in July 2005, the Science and Society committee organised another Art & Science festival on 30 April. Art historian Martin Kemp from the University of Oxford, one of the world's leading authorities on Leonardo da Vinci, explored the connectivity and kinship between art and science in 'Splashing around: some structural intuitions in art and science'. The lecture was followed by a panel discussion, a musical interlude and a production by the Thalia Theatre Club. The last item on the day's programme was the opening of the exhibition 'Beauty in Science', comprising 20 scientific images selected for presentation on panels in the ATC from a pool of images submitted by EMBL scientists.

May

Happy anniversary ELMI!

On 18-21 May more than 300 participants gathered at EMBL Heidelberg for the 10th International European Light Microscopy Initiative (ELMI) Meeting. The EMBO Workshop on 'Advanced Light Microscopy Techniques and their Applications' was also held in celebration of the tenth anniversary of ELMI, which was founded at EMBL by Rainer Pepperkok, Tommy Nilsson and Christian Boulin. Several major industry partners have been on board since the beginning, and the meeting demonstrated the strong links between European scientists working in light microscopy and the manufacturers of equipment.

2010

ELLS angels at the EMBL-EBI

The European Learning Laboratory for the Life Sciences (ELLS) team's first foray into bioinformatics at the EMBL-EBI in March met with much enthusiasm from the 20 teachers in attendance. It was the first ever ELLS Learning Lab not to involve wet-lab techniques and was held with the help of scientists and staff from the EMBL-EBI and EMBL. Since its creation in 2004, the mission of ELLS has been to bring school teachers into the lab for a hands-on encounter with molecular biology techniques. As well as developing activities and educational games for teachers to take back to the classroom, ELLS also gives scientists a chance to work with teachers, and so helps to bridge the gap between research and schools.

The Kinderhaus grows up

At the beginning of May EMBL Heidelberg's Kinderhaus hit double digits by opening its tenth group. The Fröschegruppe (Frog Group) offers up to 20 places for children aged between three and six years and has new rooms on the first floor of the main building. This marks the culmination of two years of expansion, which started with the building of the new Waldhaus in 2008. Even though the Kinderhaus now has 124 children, the family atmosphere and flexibility that parents appreciate so much hasn't been lost. Francesca Peri, a group leader at EMBL whose daughter attends the Kinderhaus is convinced: "You'll never find this in any other kindergarten."

July

Something for everyone

Where else would you find a prize-winning British novelist and a famous Italian neuroscientist sharing the podium but at the Euroscience Open Forum (ESOF)? A.S. Byatt and Giacomo Rizzolatti were among the 780 speakers and exhibitors at ESOF 2010 in Turin in July. Held every two years, ESOF is renowned for its multidisciplinary, pan-European approach. It is a hub for everyone from school pupils to Nobel laureates, and aims to fuel curiosity about all disciplines of science. As one of the seven intergovernmental research organisations of EIROforum, EMBL participated in the ESOF buzz. EIROforum also hosted a stand and a reception for invited guests at Turin's Lingotto centre. The seven-day event attracted 4300 participants and more than 400 journalists, and the Science in the City satellite event in downtown Turin drew 75 000 visitors. The next ESOF will be held in Dublin in 2012.

June

Buckets of bioinformatics

Instead of sun, sea and sand, attendees of the joint EMBL-EBI-Wellcome Trust Bioinformatics summer school encountered sequence searching, structures and systems biology. The course, held at EMBL-EBI on 14-18 June, brought together 29 PhD students and postdocs from across Europe all eager to get to grips with using bioinformatics resources in their own research. Help was provided by an expert collection of speakers and trainers, including six EMBL-EBI group and team leaders and external experts. Feedback showed a high level of appreciation for the trainers, who were on hand throughout to answer questions.

A glimpse into the future

Following three-and-a-half-years of development, EMBL Hamburg has seen the first beams in its BioSAXS and MX beamlines that take X-rays from PETRA III, the high-brilliance synchrotron radiation source on the DESY site in Hamburg.

The first beam was successfully guided into the SAXS beamline on 15 July following a series of steps and tests in the weeks leading up to the milestone. The first users to benefit from the facility are expected at the BioSAXS beamline before the end of the year.

Spreading the word

The annual Federation of European Biochemical Societies (FEBS) congress has become a fixture on the EMBL conference agenda and the 35th meeting of its kind was held in Gothenburg from 23-26 June 2010. The majority of the visitors to the EMBL stand were PhD students or postdocs who had already heard about EMBL but wanted to find out more about career opportunities and working conditions here. Brochures describing the new EMBL Interdisciplinary Postdoctoral (EIPOD) Programme and the PhD Programme were two of the most sought-after brochures amongst interested young scientists.

2010

August

A reader's tour

For the third year running the local Heidelberg newspaper *Rhein-Neckar-Zeitung* organised an excursion to the EMBL main Laboratory, where their readers heard a talk by Beate Neumann called 'The cell – the basic unit of life'. The 30 participants of the RNZ Summer Tour were particularly impressed by the unique architecture of the ATC.

September

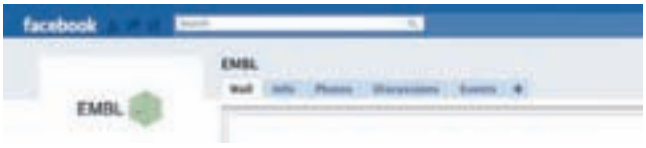
October

2010

Scientific speed dating

Imagine standing in a lecture theatre, face-to-face with someone you have never met before. A signal is given. You then have only six minutes to find out whether you have a future together – a scientific future, that is. The EMBL-EBI postdoc association, together with peers from other Cambridge-based research institutes, held a one-day symposium at the UK's Cancer Research Institute on 9 September and introduced a novel activity: a 'speed collaboration' game. The players were 35 postdocs with diverse backgrounds and areas of interest. In a style similar to speed dating, the participants rotated between small groups and took turns discussing their research with the aim of seeking common ground with other postdocs.

EMBL & friends



EMBL now has an official presence on Facebook to better connect with researchers, partners and collaborators, the public and employees. Alongside the new EMBL YouTube channel, the EMBL Facebook page provides a platform to communicate with an online audience in the many millions, enabling EMBL to join, share and inspire conversation and global collaboration. On the page is the latest EMBL news, striking science images, and links to articles, activities, events and videos that exemplify EMBL's unique research, culture and community. Join us at: www.facebook.com/embl.org

Stranger than fiction

PhD students and world-renowned experts convened at the EMBL Advanced Training Centre in Heidelberg for the 12th International EMBL PhD Symposium on 21-23 October to debate the synergy between science and fiction, the rapid progress in certain areas of science and our changing understanding of the natural world. Distinguished speakers included award-winning science fiction author Alistair Reynolds, who gave a presentation on the great effort some authors make to ensure science fiction is consistent with scientific reality.

New Titan at EMBL

Titans, once a thing of myth and legend, became a much-anticipated reality on 4 October, when EMBL Heidelberg took delivery of a new high-end microscope. The state-of-the-art Titan Krios is the latest addition to the experimental facilities of the Structural and Computational Biology Unit. The high-throughput transmission electron microscope is one of only a handful in use around the world. Housed in the former and now newly refurbished nuclear magnetic resonance (NMR) area, the new facility includes former laboratories that have been transformed into preparatory and control rooms.

November

SAXS award for Dmitri Svergun

On 3 November EMBL Hamburg group leader Dmitri Svergun collected a prestigious international prize for developments in nanodiagnostics at a plenary ceremony of the Rusnano Forum in Moscow opened by the Russian president Dmitry Medvedev. Dmitri, together with Lev Feigin of the Russian Academy of Sciences, was presented the 2010 Rusnano prize for work in the field of small angle X-ray scattering (SAXS). The approach was originally designed for studying biological complexes, but they have also successfully used it to analyse nanomaterials. The award recognises the rapidly growing scientific and commercial applications of SAXS in areas such as material science, biology and medicine.

Brains apart – the differences between the sexes

With more than 350 participants it was clear that the issue matters as much today as ever before. Held in the EMBL Advanced Training Centre for the first time on 5-6 November, the attendees of the Science and Society Conference 'Differences Between the Sexes: From Biology to Behaviour' heard speakers address a diverse interplay of psychological, social and physical factors during four distinct sessions. Presentations sparked lively and provocative discussion sessions, with members of the audience queuing up to offer their thoughts or challenge speakers. Topics moved from the nature of gender roles to personalised healthcare via scientific and social implications, with people from a broad range of backgrounds voicing their opinions. One highlight was when anthropologist Helen Fisher gave participants an insight into the science of romance before explaining how biology directly relates to different personality traits in men and women. The audience included people from over 35 different countries as well as around 20 journalists reporting on the event for international, national and local media, ensuring that the debate continued far beyond the plenary hall.

Tying the node

The third 'node' in the Nordic EMBL Partnership for Molecular Medicine officially opened on 11 November when Norway's Centre for Molecular Medicine (NCMM) was inaugurated at its launch event. Established in 2007, the partnership includes the universities of Oslo, Umeå and Helsinki, with established nodes at NCMM, the Laboratory for Molecular Infection Medicine Sweden (MIMS) and the Institute for Molecular Medicine Finland (FIMM). The partnership seeks to combine complementary expertise, working closely with EMBL in rising to challenges in biomedicine and fostering industry collaborations. Key research at NCMM will include neurobiology, medical genetics, infection medicine and cancer. NCMM is the second research centre in Norway to form a partnership with EMBL, the first being the Sars International Centre for Marine Molecular Biology in Bergen.

EMBL-EBI open day

On 2 November, EMBL-EBI welcomed 40 early-career scientists to a day of talks about bioinformatics research, training and career opportunities, as well as demonstrations of the EMBL-EBI's core data resources. Dean of Graduate Studies Helke Hillebrand provided visitors with insight into the work and social life of EMBL's predocs. This was complemented by the popular series of 'life as…' talks by an EMBL-EBI PhD student, a postdoc, a software developer and a database curator. The students also enjoyed an engaging talk by John Overington about his cheminformatics research group and the ChEMBL database.

December

A Memorandum of Understanding

Collaboration and cooperation were on everyone's mind when members of the Russian Federation for Basic Research (RFBR) visited EMBL Heidelberg on 3-4 December. A packed programme included an ideas exchange with EMBL senior scientists and a tour of the Core Facilities. In the spirit of reciprocity and accord, Academician Vladislav Panchenko also gave members of the EMBL Directorate a fascinating insight into the RFBR. EMBL already has close ties with Russia, not least through the EMBL International PhD Programme partnership with Moscow State University, and the scientific collaborations of the Lamzin, Svergun, Schultz and Arendt groups. Building on this burgeoning relationship, a Memorandum of Understanding was signed with a view to Russia becoming an EMBL member state.

Fresh insights

2010

On 10 December, EMBL Heidelberg group leader Jan Korbel delivered an EMBL Insight Lecture to 150 school children and teachers, while several hundred more watched live over the internet from classrooms across Europe. This event was the first in a series of lectures to be organised by the European Learning Laboratory for the Life Sciences (ELLS). Jan spoke of the advances that have recently been made in DNA sequencing technology and human genome analysis, and the possible implications that these advances could have for disease research – particularly, cancer research – in the future. Questions came from both the lecture hall and from classrooms via Skype. "As scientists we have an obligation to explain our research to the public, which obviously includes the young public in particular who are still undecided about their career path," says Jan. "School children often ask to the point and thus I was prepared for some tough questions, including the future potential as well as the ethical considerations of genomics research, which I feel are very important for the public to be aware of."

January

Men in black – the annual Corporate Partnership Programme gala dinner

Members of the EMBL Advanced Training Centre Corporate Partnership Programme convened in Heidelberg for their annual gala event on 20 January. Managing directors, vice presidents and other high-level guests from all 15 companies involved in the innovative programme gathered for a reception, followed by scientific talks from EMBL experts and a dinner held in the EMBL Advanced Training Centre foyer. Companies in the Corporate Partnership Programme, which launched in 2008, provide €100 000 per year in financial support for the EMBL Courses and Conferences Programme. A further €100 000 is provided for travel fellowships, which enables students and young scientists to participate in events that they would otherwise be unable to attend. Partners benefit from opportunities such as annual roundtable discussions, collaborations and links that could lead to further projects.

Out of Africa

It was the first in a series of many highlights in the 2011 EMBL Science and Society Programme when Christian Borgemeister, Director General of the International Centre of Insect Physiology and Ecology (icipe), whose headquarters are in Nairobi, Kenya, gave a talk on how science can contribute to poverty alleviation in Africa. In his talk he outlined the importance of a joined-up approach to insect control that recognises the complex challenges in controlling disease transmission from insects, and the dangers of over-reliance on insecticides to which insects could become resistant. The centre looks to develop methods and technologies to understand insects' behaviour and biology and then devise simple but effective control tools with an approach that focuses on human, animal, plant and environmental health.

2011

Firm foundations for future research centre

Construction of a new interdisciplinary research centre that bridges the gap between structural and systems biology moved a step closer in January. In the Centre for Structural Systems Biology (CSSB), to be built on the German Electron Synchrotron (DESY) campus shared with EMBL Hamburg, biologists, chemists, medical scientists, physicists and engineers will collaborate to investigate processes at the molecular level. In total, €50 million has been invested in the project. Construction of the new facilities is scheduled to begin in 2012.

February

Exploring science

Did you know that 15 February 2011 marked ten years since the first draft sequence of the human genome was published? Or have you ever been asked to explain a technique in layperson's terms? EMBL Explore, a new series on the EMBL website, employs a combination of podcasts, written articles and visuals to bring such information to life. Each edition explores a different topic related to EMBL science, complementing existing 'Research' and 'News' webpages. Aimed at the general public, EMBL Explore also appeals to scientists' natural curiosity, exploring the sounds and voices of the laboratory and uncovering little-known facts. In 2010 an average of 6000 people per day visited the EMBL websites and explored new features like the full text search engine, listened to podcasts reporting on a variety of scientific topics or watched one of the live streamed lectures. You can find EMBL Explore at www.embl.org/explore

March

The placebo effect: Making sense of a nuisance

The term placebo effect is widely used and discussed within science and medicine, and recent data indicate that there is a genuine neurobiological basis to this phenomenon. Different physiological and biochemical mechanisms take part in complex functions, like trust, hope, empathy and compassion. On 3 March Fabrizio Benedetti, Professor of Physiology and Neuroscience at the University of Turin Medical School and at the National Institute of Neuroscience in Italy, addressed these topics in his EMBL Forum lecture demonstrating once more the impact that work within the life sciences is having on society.

The Commissioner cometh

It was a bright spring day when Máire Geoghegan-Quinn, European Commissioner for Research, Innovation and Science, signed a Memorandum of Understanding between the European Commission (EC) and EMBL during a visit on 4 March. Following a welcome by Iain Mattaj and Director of EMBO, Maria Leptin, she was treated to a scientific presentation by Joint Head of the Genome Biology Unit, Eileen Furlong. In signing the statement, Geoghegan-Quinn and EMBL's Director General have formalised a commitment to cooperate to further the development of European research in the life sciences. "I am confident that it will set the stage for even better and more fruitful cooperation between us," said the Commissioner.

Index of group & team leaders

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Lena Raditsch, Sonia Furtado

DG Report
Iain Mattaj

Contributors
Claire Ainsworth, Chloe Balharry, Adam Gristwood, Dan Jones, Corinne Kox, Angela Michel, Sarah Stanley, Mary Todd, Anna-Lynn Wegener

Photography
EMBL Photolab (Hugo Neves, Udo Ringeisen, Marietta Schupp); p.16: K. Hodivala-Dilke & M. Stone, Wellcome Images; p.17: Annie Cavanagh, Wellcome Images; p.18: Anne Weston, LRI, CRUK, Wellcome Images; p.32/35: ESO/Mario Nonino, Piero Rosati and the ESO GOODS Team; p.98: Norman Seef

Artwork
Petra Riedinger

Layout
Nicola Graf

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EMBL Heidelberg
Meyerhofstraße 1
69117 Heidelberg
Germany

Tel. +49 (0)6221 387 0
Fax +49 (0)6221 387 8306

EMBL Grenoble
6, rue Jules Horowitz, BP 181
38042 Grenoble, Cedex 9
France

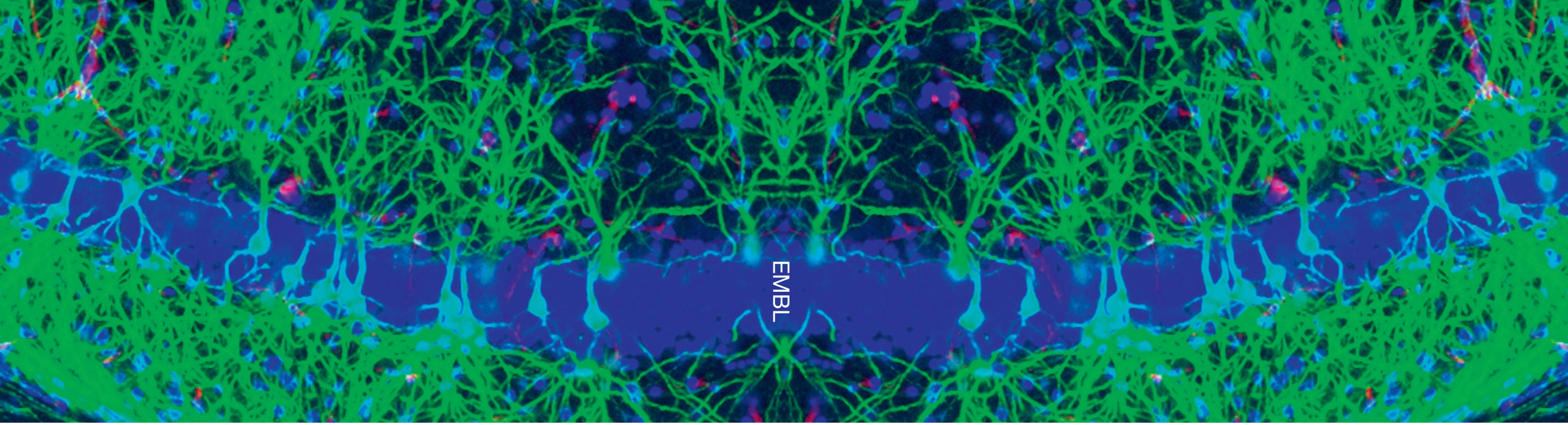
Tel. +33 (0)4 76 20 72 69
Fax +33 (0)4 76 20 71 99

EMBL Hamburg
c/o DESY
Notkestraße 85
22603 Hamburg
Germany
Tel. +49 (0)40 89 902 0
Fax +49 (0)40 89 902 104

EMBL-EBI
Wellcome Trust Genome
Campus, Hinxton
Cambridge CB10 1SD
United Kingdom
Tel. +44 (0)1223 494 444
Fax +44 (0)1223 494 468

EMBL Monterotondo
Adriano Buzzati-Traverso Campus
Via Ramarini, 32
00016 Monterotondo (Rome)
Italy
Tel. +39 06 900 912 85
Fax +39 06 900 912 72

www.embl.org



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