

A LIGHT FOR SCIENCE

# ESRF news

Number 55 September 2010

## Research on life

**Structural studies  
tackle tropical diseases**

**Fractal structures favour  
superconductivity in ceramics**



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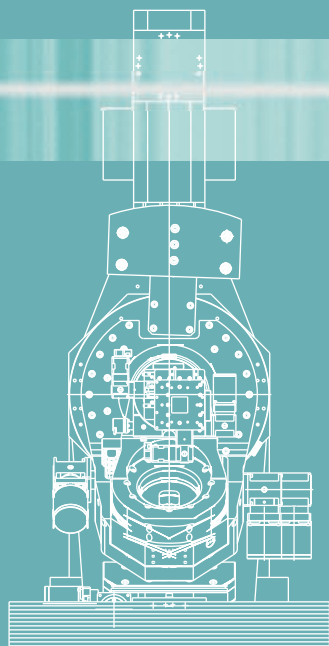
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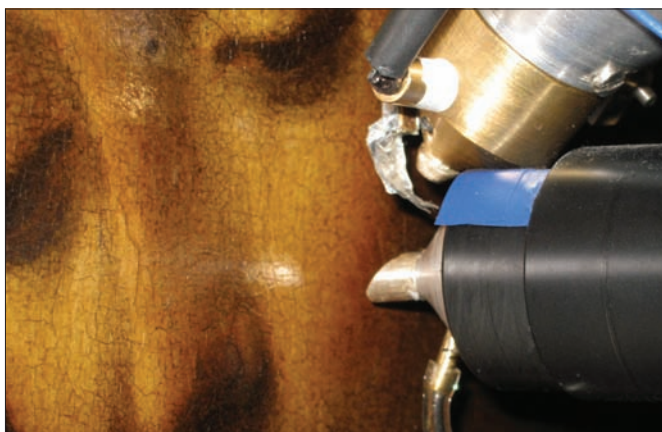
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## A light for science



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**On the cover:**  
A 3D structure of a molecule. Thanks to synchrotron sources, scientists can now more easily solve the structure of molecules.

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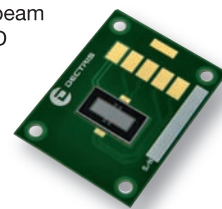
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# Structural biology: a success story with a promising future

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***“Opinionum commenta delet dies, naturae judicia confirmat,” Cicero vi Att 1***  
(Time obliterates the fictions of opinion and confirms the decisions of nature)

Life sciences are playing an increasingly important role within the ESRF science programme, where the depth and breadth of research in this field is displayed by the number of techniques and beamlines that are investing a significant portion of their time and energies on investigations in this domain. From the first days of ESRF's operation, macromolecular crystallography (MX) has been a key component of the life-sciences strategy. Having grown substantially during the last 15 years, structural biology now accounts for almost 50% of the visits made by the user community. The current issue of *ESRFnews* shares some of the exciting science and developments that are happening in this branch of research at the ESRF.

Knowledge of the 3D structure of proteins can play a key role in both understanding biochemical function of protein targets and developing small-molecule drugs that interact with these targets. Developments at the ESRF's MX beamlines have enabled the determination of protein structures to be faster and more reliable than ever before. By revealing the nature of the interaction between the drug and the receptor, a greater degree of control can be achieved over the next generation of drugs. Two articles in this edition of *ESRFnews* demonstrate different methods of employing structural information in order to start the development of new drugs. A group from the University of Dundee (UK) is working towards understanding the pathology of neglected tropical diseases and it is producing lead compounds for inhibitors of several key enzymes (p9). Meanwhile, researchers at the Medical Research Council in Cambridge (UK) are attempting to unravel the subtle details of key cellular-signalling pathways involved in a variety of diseases. The knowledge of the details of these signalling systems will allow for the design of inhibitors suitable for development as drugs (p10).

Fundamental biology also forms a part of the practice and the art of MX, in which the study of membrane proteins is not only of great interest but highly challenging. The scientist is confronted with a host of problems when studying this large class of proteins, but thanks to the steady application of new protocols, many new groups are making progress in elucidating the structures and mechanisms of membrane proteins (p14) – a group from the Max Planck Institute in Frankfurt (Germany) explains their work. Careful examination of the crystals of macromolecules reveals variations in the diffraction properties of these delicate samples (p21). Explaining these variations will enable better experiments to be devised and, when coupled with further developments of crystallographic methods, it will form the basis for the use of the new beamlines.

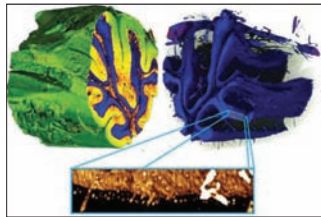
One of the older beamlines at the ESRF will ease into a well earned retirement in a few years' time. The beamline suite of ID14 is one of the most productive structural biology facilities in the world. However, time and excessive usage are starting to take their toll. To revitalise the facility and benefit from improvements in technology, a new set of beamlines are to be created as part of the ESRF Upgrade Programme. Construction of the new beamlines that will replace ID14 begins in September with an ambitious plan to boldly change methods of performing MX experiments.

**Sean McSweeney**, head of the structural biology group, and **Serge Pérez**, director of research

**“Structural biology accounts for almost 50% of the user visits to the ESRF”**



## Technique images cerebellum in 3D with cellular resolution



UNIVERSITY OF BASEL

White brain matter (orange) is distinguished by two types of gray matter (blue: stratum granulosum, yellow: stratum moleculare). Blood vessels (red) and single cells (below) are clearly visible.

The human brain is of outstanding functional complexity. It belongs to the most impressive and delicate three-dimensional (3D) structures in nature. Obtaining images of this structure is as much a necessity as it is a technological challenge. Until now, 3D visualisation of the human cerebellum with a spatial resolution down to the level of individual cells was a tedious task involving lengthy preparation and histological cuts, which inevitably destroyed the structure that was imaged. Scientists from the University of Basel (Switzerland), the ESRF, the Technische Universität München (Germany), the Karlsruhe Institute of Technology (Germany) and the Paul Scherrer Institut (Switzerland) have found a solution for this.

The team used X-ray grating interferometry – a new, highly sensitive imaging technique – to obtain phase-contrast as well as absorption-contrast synchrotron microtomography of a human cerebellum. The *in vitro* tomography data taken at the ESRF beamline ID19 showed that grating-based X-ray phase contrast discriminates blood vessels, the stratum moleculare, the stratum granulosum and the white matter. This includes the so-called Purkinje cells, which have a spherical shape and a diameter of 40–70 µm. The detection of individual Purkinje cells without the application of any stain or contrast agent is a novelty in the field of computerised tomography.

### Reference

G Schulz *et al.* 2010 *J. R. Soc. Interface* doi:10.1098/rsif.2010.0281.

# X-ray identifies Jabugo ham

Experiments at the ESRF are giving scientists from the Universitat Autònoma de Barcelona (Spain) and the University of La Sapienza in Rome (Italy) a possible identification of the different types of hams according to the breeding and feeding of pigs and the curing process. It is the first time that this product has been studied with synchrotron radiation.

Identifying a ham from a non-confined pig, fed on acorns, with the proper upbringing and a curing of two or more years is not easy. The methods to imitate this product are becoming more sophisticated, and there are few clues that can scientifically verify the authenticity. For this reason, the biomarkers that have been used, such as vitamin E (to tell if a pig was stabled), or the ratio of fatty acids (to decipher if a pig had eaten acorns), have become obsolete because they can be mimicked with feed. Manuel Valiente, a professor at the Universitat Autònoma de Barcelona and a native from the area of Jabugo, is leading a research project to identify new biomarkers.

During an experiment at the ESRF, Valiente suggested to Germán Castro, head of the Spanish experimental station SPLINE, to use X-ray spectroscopy to find information on changes in some compounds of the ham during the curing process, in relation to important parameters of product quality and traceability, such as breeding and feeding of the pig and the duration of the



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Jamón jabugo de bellota is a specific ham from the south of Spain where pigs are raised in special conditions to get a unique product.

curing process. These changes are responsible for the evolution of the colour of the ham and could be used as biomarkers of the final product. The first tests were conducted in March and found that the synchrotron measurements could reveal details that had never been seen before.

Metal compounds present in the proteins of the pig, especially those containing iron and zinc, are candidates to dictate the colour changes of the ham during the curing process. It is known that during the curing process, usually lasting two years or more, an exchange occurs between the iron and zinc, which are mainly found in proteins like myoglobin and porphyrin compounds.

The team studied 20 samples of cured ham from different years, from pigs in confinement and others free (fed with oak in Valdelarco meadow in the Sierra de Aracena, Spain) and samples of Italian ham from Parma and

San Daniele. The researchers used SPLINE during four days of experiments.

Preliminary results hint at the presence of 10 metals in the samples studied. “We were surprised at the variety of metals found and their quantitative relationship,” says Valiente. “This may indicate that perhaps not only zinc and iron are indicators of changes experienced by the ham,” he adds. Currently, the data acquired are under analysis, including the correlation with the hyperspectral imaging technique developed by the group of Giuseppe Bonifaci, at University La Sapienza, which was applied on the same samples that were later used in the synchrotron.

This first experiment will identify the most sensitive parameters and mark the development of a more comprehensive study in which the spectroscopic techniques applied now will be the protagonists.

## The ESRF helps to make plastic bags lighter and greener

Manufacturers of plastic bags and other types of plastic sheets have been trying to make thinner but stronger products. By requiring less material, they are more environmentally friendly.

The films used in the production of these bags are usually obtained by a film-blowing process, in which the molten polymer is extruded (through an annular die) as a hollow cylinder. This is then extended in the axial direction by rollers that are pulling on it, while, simultaneously, its radius expands under the effect of pressurised air.

Deformation of the macromolecular arrangement provoked by the biaxial flow field acting on the solidifying material has a dramatic impact on crystallisation kinetics, structure and morphology, and can lead to unexpected mechanical and optical properties in the final product.

Scientists from the University of Genoa (Italy) and the Eindhoven University of Technology (the Netherlands) have carried out experiments at the DUBBLE beamline at the ESRF on a film while it is made. They have used online wide- and small-angle X-ray scattering (WAXS, SAXS) on a pilot film-blowing unit to get information on the developing structures, morphologies and orientation of the film along the production line. The final aim is to gain a detailed picture of the crystallisation behaviour under the processing conditions.

Until now most experiments regarding production of films have been carried out offline. Scientists have used online optical techniques, such as Raman spectroscopy and low-angle light scattering (LALS), but the expected online results at the resolution achievable at the ESRF would be unprecedented.

## The Polygone Scientifique gets a tram makeover



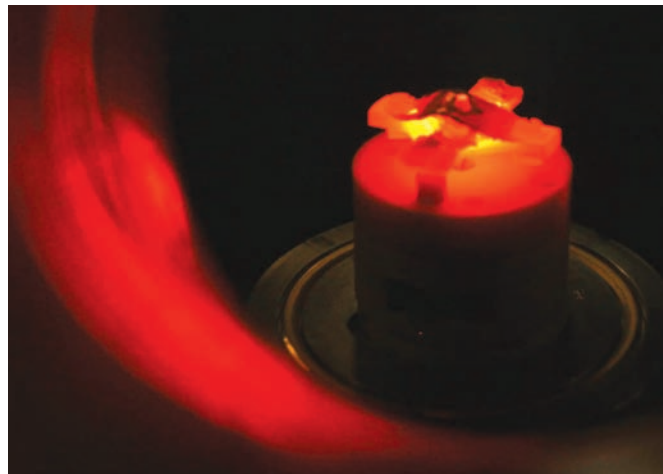
Proposed aerial view of the new tram line in December 2013.

For the next three years, when you come to the ESRF for an experiment you may find that construction works are omnipresent. This is for a good cause: tram line B will arrive to the Polygone Scientifique, connecting the ESRF site with the centre of town and the university campus. Works for the extension of the tram line are well underway and in the future the Avenue des Martyrs will be transformed into a wider road (45 m instead of the current 15–20 m). The opening of the new tramway line is planned for December 2013 at a total cost of €47.7 m.

# Research tracks surface catalysis

Catalytic converters in cars are responsible for, among other things, converting toxic carbon monoxide into harmless carbon dioxide. In heterogeneous catalysis, exposure to reactants can cause the formation of entirely new structures at the catalyst surface. These can influence the reaction by poisoning it or by acting as the catalytically active phase. Scientists from Leiden University (the Netherlands) and the ESRF have carried out *in operando* X-ray diffraction experiments on a palladium surface during the catalytic oxidation of carbon monoxide on the beamline ID3. This allowed them to reproduce realistic conditions because the surface of a catalyst has a different behaviour under real pressures than it does in vacuum.

The research showed that under the studied conditions the surface switches reversibly between two states. In one state the surface is covered by a thin layer of palladium oxide and one in which this oxide skin is absent.



A palladium catalyst being heated in the UHV chamber of ID03.

Even though this layer is thin, it changes the chemical reactions radically. In the presence of the oxide skin the CO oxidation reaction runs much faster. The researchers discovered that the driving force behind the periodic switching of the surface from one state to the other is the surface roughness. The oxide skin roughens due to the catalytic

reaction and thereby destabilises itself, whereas the metallic surface flattens due to the high temperature and eventually facilitates the formation of an oxide skin again.

### Reference

B L M Hendriksen *et al.* 2010 *Nature Chemistry* doi:10.1038/nchem.728.

## Users' corner

Following the 1 September 2010 deadline for proposal submission, the next Beam Time Allocation Panel meetings will take place on 21 and 22 October 2010.

Decisions will be communicated to proposers early in December.

Work on several Upgrade beamline projects has already started and users are advised to check the availability of beamlines for future proposal deadlines by consulting our beamline status table at [www.esrf.eu/UsersAndScience/UserGuide/Applying/beamline-status](http://www.esrf.eu/UsersAndScience/UserGuide/Applying/beamline-status). The following beamlines were closed to users for the September deadline: ID20, ID24, BM29, ID22N and ID18F. The new general-purpose XAS beamline BM23, replacing BM29, will open to users on 1 March 2011 and accepted its first proposals at the September deadline.

The plenary session of the 21st ESRF Users' Meeting will take place on 8–9 February 2011. The plenary session will last one and a half days as in 2010, a format that was warmly welcomed by

users and ESRF staff alike. The next ESRFnews will provide more information.

### News from the beamlines

● **BM23, the general-purpose X-ray absorption spectroscopy beamline at the ESRF (replacing BM29)** will be opened to users from 1 March 2011. It aims to meet the needs of the user community in the area of conventional X-ray absorption spectroscopy.

● **The Nuclear Resonance side-station ID22N** will definitely be closed from 1 March 2011. The capacities in nuclear resonant scattering will be retrieved by the construction of a fixed-energy (14.4 keV) side-station on the canted 6 m straight section ID18 in 2011. According to current planning, the side-station should be available after the first shutdown (tentatively scheduled from December 2011 to February 2012) of the accelerator complex for the construction of the experimental hall extension. Proposals in the field of nuclear

resonant scattering should be submitted to beamline ID18 in the future.

● **The Microanalysis End-Station ID18F** will definitely be closed from 1 March 2011. Proposals in the field of hard X-ray microanalysis (consisting of the combination of X-ray fluorescence, X-ray absorption spectroscopy, diffraction and 2D/3D X-ray imaging techniques) should be submitted to beamline ID22 in the future. Two stations are clearly identified on ID22 according to the spatial resolution required: the EH1 microprobe devoted to micro-spectroscopy and the ID22NI nanoprobe used for nano-analysis. Beamtime available on ID22 for allocation to new proposals will be increased following the closure of the ID22N Nuclear Resonance end-station and should help alleviate oversubscription on this beamline in the future.

● **An Attenuated Total Reflectance (ATR) objective** is now available on the FTIR

microscope at ID21. It enables users to analyse directly the surface of a sample, and is particularly helpful as an alternative to transmission measurements when thin sections cannot be obtained.

● **ID29 has been equipped with a 6M Pilatus detector.** This single-photon counting detector has detector quantum efficiencies of 100% at 8 keV and around 75% at 12 keV, which makes it a powerful device for experiments at longer wavelengths. The increased dynamic range of the detector, as well as its noiseless and extremely fast (4 ms) readout, will offer new possibilities for data collection and result in better quality diffraction data. Initial commissioning experiments have proved extremely promising.

● **The BM16 CRG operation contract between the Spanish Ministry and the ESRF** will expire on the 30 June 2011. The beamline decommissioning works are being planned to start in March 2011.

## High performance SDD Silicon x-ray detectors for beam-line applications

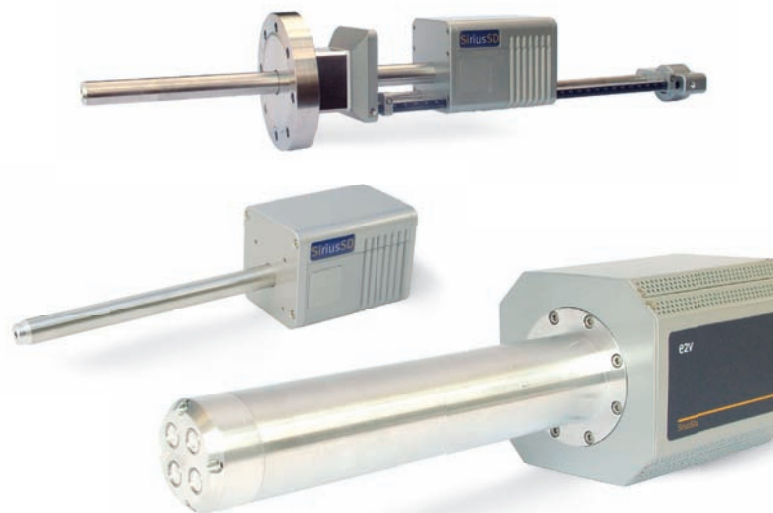
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# Structural studies tackle neglected tropical diseases

Tropical diseases such as African sleeping sickness do not receive too much attention from the pharmaceutical industry, which is more focused on treating first-world diseases. Yet these neglected diseases still cause untold suffering to many thousands of people worldwide. Scientists from the University of Dundee (UK) are using a structure-based approach to support early-stage drug discovery targeting these diseases.

Chagas' disease, leishmaniasis and African sleeping sickness are all diseases caused by protozoan (unicellular, non-fungal) parasites. Today, drugs targeting these diseases are toxic, expensive and often difficult to administer. William Hunter, a scientist at the University of Dundee (UK), his co-workers at this university and the University of Strathclyde (UK), together with colleagues from Italy, Brazil and Spain, are trying to find molecules with high affinity for one or more targets in the protozoan parasite that can disrupt an essential aspect of metabolism and quickly kill it.

The molecule that could inhibit the parasite's metabolism may potentially be folate-based. Such molecules are currently being used to treat bacterial infections, cancer, rheumatoid arthritis or psoriasis. These molecules should inhibit the enzymes pteridine reductase (PTR1), dihydrofolate reductase (DHFR) and possibly thymidylate synthase (TS), impairing DNA replication and resulting in cell death. The team studied 440 folate-related compounds designed originally as anti-cancer agents. Among these, they screened one-third of their candidates and the interactions between the target proteins and the compounds were studied at the ESRF's structural biology beamlines. They identified two selective inhibitors of PTR1, which worked in combination but not individually.



**A coloured SEM of a tsetse fly. This view from below shows the compound eyes (red) either side of the proboscis, extending upwards. The proboscis is used to pierce the skin of its host to feed on blood. The fly transmits *Trypanosoma protozoa*, which causes sleeping sickness in humans.**

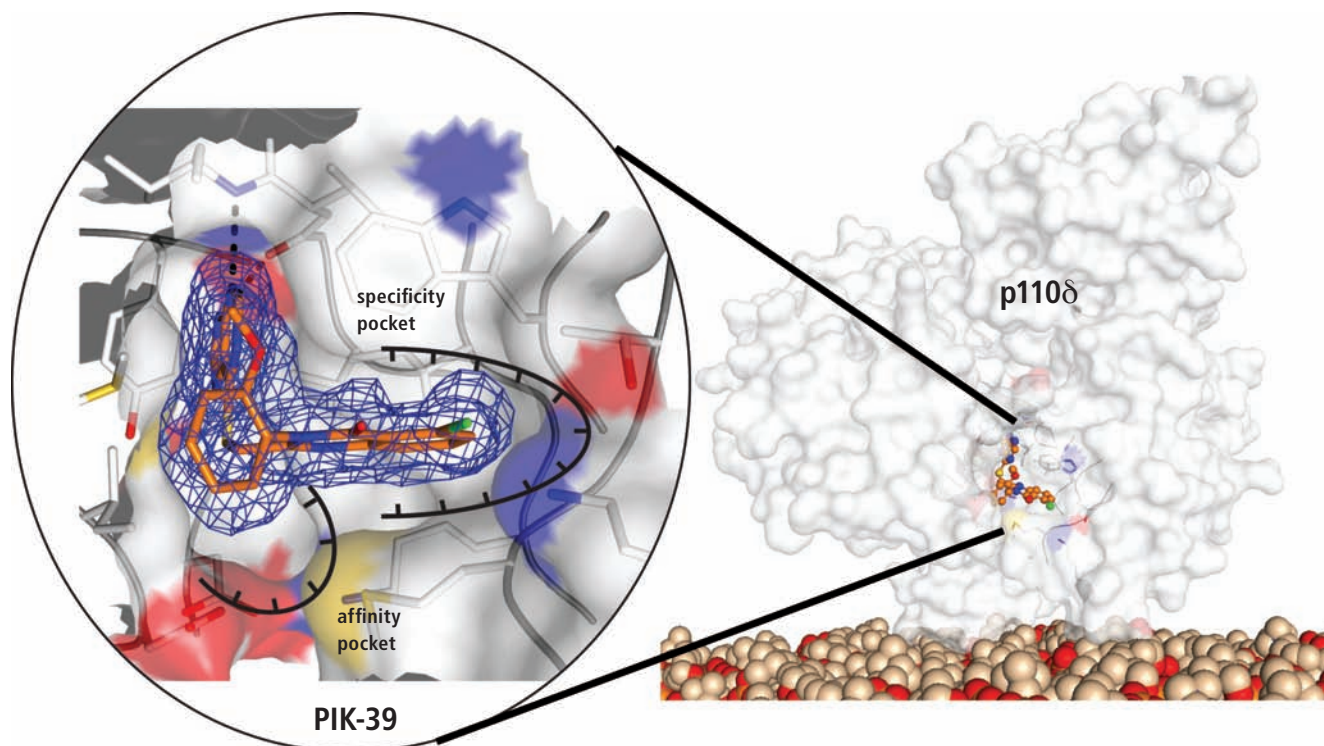
PTR1 contributes to antifolate drug resistance by providing a molecular bypass of DHFR inhibition. Therefore, combining PTR1 and DHFR inhibitors could be more efficient. The team tested two new compounds with known DHFR inhibitors, in particular the archetypal antifolate called methotrexate. Depending on how they combined these molecules, they became especially effective at killing trypanosomes.

These are only the first steps in the quest for drugs to cure these diseases, and there are currently tools, including synchrotron radiation, that can help to advance research in this field much faster. Automation has been a key in the evolution of structural biology

beamlines and thanks to these advancements they allow structure determination in high-throughput fashion. "This means that 3D structures of key therapeutic targets and ligand complexes can be obtained quickly, producing crucial data for early-stage drug discovery," says William Hunter.  
*M Capellas*

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- A Cavazzuti *et al.* 2008 *PNAS* **105**(5) 1449–1453.  
W N Hunter *et al.* 2009 *The Journal of Biological Chemistry* **284**(18) 11749–11753.  
L B Tulloch *et al.* 2010 *J. Med. Chem.* **53** 221–229.



The p110 $\delta$  PI3K with a specific inhibitor, PIK-39, on a lipid membrane. Inset: magnified features of the p110 $\delta$  inhibitor-binding pocket that the PIK-39 compound exploits to inhibit p110 $\delta$ . PIK-39 uses the flexibility of this PI3K to force open a specificity pocket into which part of the compound fits.

# Signalling pathways reveal the way to drug development

In the quest to fight diseases, phosphoinositide 3-kinases (PI3Ks) play an important role due to their involvement in so many conditions. Scientists know that an impaired PI3K signalling can lead to cancer, diabetes, thrombosis, rheumatoid arthritis and asthma.

PI3Ks are important components of an intracellular signalling network that regulates cellular functions such as cell growth, proliferation, differentiation, survival and intracellular trafficking. Their impaired signalling can lead to immunodeficiency, while its unrestrained signalling could be conducive to autoimmunity and leukaemia.

There are three classes of PI3Ks. Class I are heterodimeric complexes made up of a regulatory and a catalytic subunit (known as p110). Class II includes catalytic isoforms but no regulatory proteins. Class III is similar in structure to class I, but it associates with an unrelated p150 regulatory protein and it is mostly involved in the intracellular traffic of proteins and vesicles.

In mammals, most signal transduction pathways in cells involve enzymes such as PI3K, which modify phospholipids present in cell membranes. These enzymes are activated in response to a variety of primary signals such as hormones, cytokines and neurotransmitters. The modified phospholipids represent “second

messengers” that amplify the primary signal and eventually trigger a multitude of cell responses.

In human cancers, the class I PI3K p110 $\alpha$  undergoes frequent mutations that result in unregulated production of second messengers, which contributes to the development of tumours. Understanding PI3K structures can lead to the development of drugs that are tailored to inhibit a single type of PI3K, such as p110 $\alpha$ . These drugs could

**“Today there are pan-selective PI3K inhibitors in clinical trials for cancer.”**

have a central role in personalised medicine that is adapted to the generic make-up of a given individual or tumour. This offers the advantage of maximising drug effectiveness and minimising side effects.

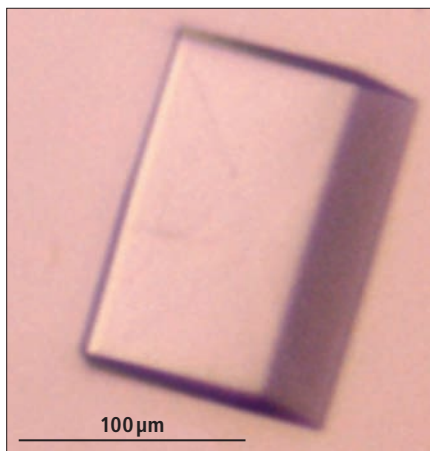
PI3Ks have been studied by a team of scientists led by Roger Williams. He is a group leader at the Medical Research Council Laboratory of Molecular Biology in Cambridge (UK) and a representative of the ESRF Block Allocation Group (BAG), which includes 28 groups of macromolecular crystallography users. By understanding the structures of the multi-protein complexes that form the components of the PI3K signalling pathway, researchers in Williams’ group aim to decipher how this pathway works and how it is regulated. They will use this information to help their collaborators, such as Kevan Shokat at University of California, San Francisco, Jeffrey Shaw at Merck-Serono and Christian Rommel at Intellikine, to design isoform-specific PI3K inhibitors that may be used in drugs.

The history of the development of PI3K



inhibitors goes back to the 1970s. In 1974 a molecule called wortmannin was used as an anti-inflammatory without the scientists knowing that PI3K was one of the molecular targets of this molecule. However, the first generation of inhibitors had flaws: low affinity, instability, non-selectivity and toxicity limited their clinical use. Today, there are still similar multi- and pan-selective PI3K inhibitors that are currently in clinical trials for the treatment of different types of cancer. The future, though, might be the PI3K isoform-selective inhibitors. Some of these have entered clinical trials for the treatment of leukaemia and thrombosis. Despite the newly developed isoform-selective compounds, it is still unclear what determines the selectivity at a structural level. But the answer might not be too far.

The MRC team recently reported 14 crystal structures of the catalytic core of the delta PI3K isoform (p110 $\delta$ ), on its own and in complexes with inhibitors of this enzyme (Berndt *et al.* 2010). This class I PI3K enzyme is important in leukocyte signalling and represents therefore a promising target for intervention in pathways in inflammatory and autoimmune diseases. X-rays of several structural biology beamlines at the ESRF, as well as the Swiss Light Source (Switzerland) and the Diamond synchrotron (UK) have been essential to collect diffraction data of these complexes. Their study provided the first detailed structural insight into the active site of this PI3K isoform and allowed to rationalise



A crystal of the p110 $\delta$  inhibitor complex.

and synthesise novel p110 $\delta$ -selective inhibitors with greatly enhanced potencies. "With our new set of p110 $\delta$  crystal structures and better models of flexibility resulting from molecular dynamics simulations, we are now starting to understand why p110 $\delta$  can be more easily deformed to open an allosteric pocket in which p110 $\delta$ -selective inhibitors can be accommodated," explain the authors.

#### Inhibiting the degradation of cells

Autophagy is the process of degradation of a cell. It is a regular process that takes place in the life cycle of a cell. However, better knowledge of this mechanism could allow

scientists to prevent or stop the progression of some diseases, such as cancer. The lipid kinase Vps34, a class III PI3K, has an essential role in autophagy. The team at the MRC have named it "the Cinderella of PI3Ks" because it is responsible for the cell's cleaning and self-feeding. Scientists still haven't found a specific inhibitor of class III PI3Ks. The team recently published the crystal structure of Vps34 alone and in complexes with multi-targeted inhibitors (Miller *et al.* 2010). The structures showed a completely ordered phosphoinositide-recognition loop, a feature that was not observed in any other PI3K structure so far. Furthermore, with the structures, the team was able to use molecular graphics and molecular dynamics calculations to model substrate binding and the catalytic mechanism. They also found a possible mechanism in which Vps34 is auto-inhibited in solution but adopts a catalytically active conformation on membranes. Regarding the structure of Vps34 in complexes with PI3K inhibitors, the structures illustrate that moieties can be added to the inhibitor to improve its drug-like properties without changing the affinity for Vps34, and at the same time increasing its specificity. *M Capellas*

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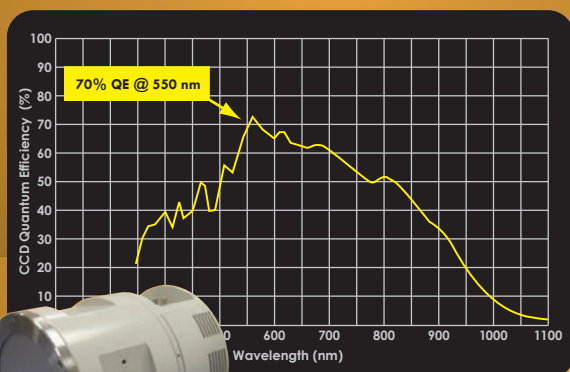
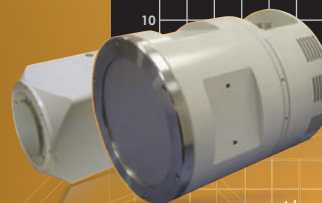
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# Moving to a new era

Created to provide much needed capacity for macromolecular crystallography (MX), the beamline suite on ID14 has proved to be an enduring and successful example of the ESRF's innovation. Now nearing the end of its productive life, it will soon be replaced by a new set of beamlines as part of the ESRF's Upgrade Programme.

In 1993 the number of beamlines available at the ESRF for MX was very limited – this comprised solely of a shared facility on ID02B and a planned multi-wavelength anomalous dispersion beamline, BM14. Due to the increasing demand from the user community it was decided to quickly expand the ESRF's capacity by designing a high-capacity suite of beamlines capable of providing sufficient experimental capacity for the following decade.

At the time, the beamlines were designated by the sequential number of their development. In this sequence the new beamline was designated BL20 and was to be built using the insertion device on ID14. It was proposed that two experimental stations should be built on ID14; however, the project was subsequently expanded to incorporate a total of four experimental facilities. Three of the beamlines took the unusual approach of employing single crystal diamond beam splitters to provide fixed-energy photons for experiments and one beamline would provide a tunable X-ray source for MAD experiments. Construction of the new complex started during 1995 with beamlines coming into operation for the community each year during the period 1997 to 2000. In common with the other MX beamlines of the era, it was foreseen that the beamline would be developed, and subsequently operated, in a collaboration between the ESRF and the EMBL Grenoble Outstation. This collaboration was eventually formalised by the creation of a joint structural biology group between the institutes.



The ID14 beamline as it looked in 2001. The beamline consists of four endstations that have been fully operating

The design of ID14 was particularly challenging; in order to fit four independent experimental endstations on one straight section of the storage ring, diamond monochromators were chosen. Despite some scepticism that the design could deliver the requisite independence of operation, the ID14 suite has delivered, and continues to deliver, first-class X-ray facilities for structural biology. The ID14 suite has delivered many significant ESRF "firsts" in its lifetime: the first independent multi-operational beamline; the first undulator source MAD beamline; the first beamlines to deliver 1000 structures to the public databases and the first dedicated protein solution scattering beamline.

Today, structural biologists are tackling increasingly ambitious projects and the demands posed by the samples associated

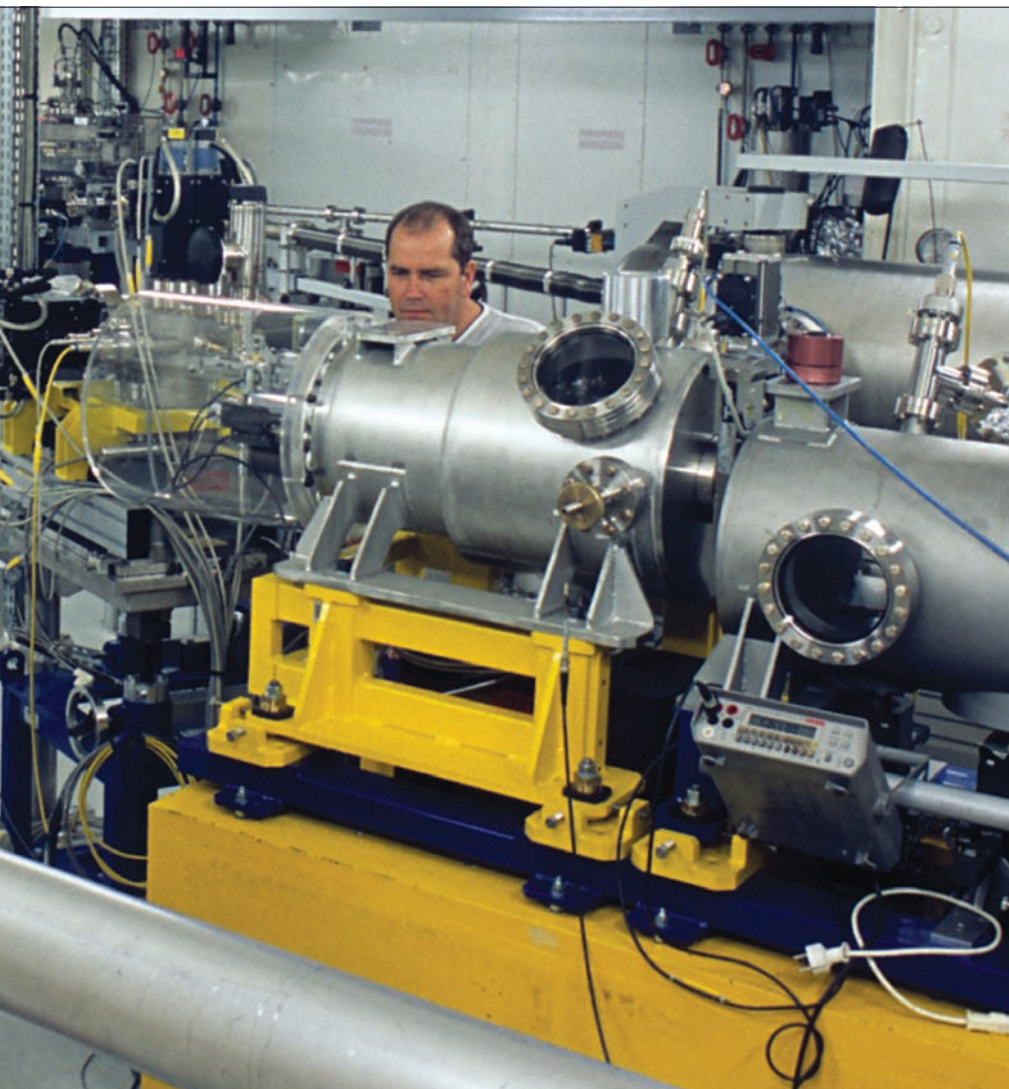
with these projects are highlighting the age of ID14. It has therefore been decided to retire the beamline and allow the creation of a new beamline suite with characteristics suited to today's samples and those of the future. Learning from the use that our user communities make of our beamlines and the experience of our colleagues at other synchrotron sites we have developed a radical vision for the new ESRF Upgrade beamline for structural biology.

## ID30 is the future

UPBL10 will be a unique resource, based on second-generation automation for MX experiments, designed to maximise the chances of a successful conclusion to these ambitious projects. The hub of the facility will be a sample evaluation and sorting facility



# in structural biology



DOVERNAX

for bound inhibitors and ligands, and screening in crystallisation plates, using both large and micro-focused beams. In addition, novel mechanisms for understanding the diffraction properties of the samples under investigation will be developed.

Identifying the “best” crystal is only the beginning of a successful MX experiment. UPBL10 will also provide a tunable canted end-station from an independent canted undulator. Exploiting the potential of a high- $\beta$  source, this end-station will have the possibility to adapt the X-ray beam size from a large beam ( $\sim 200\ \mu\text{m}$ ) to a few tens of microns. An innovative X-ray collimation system will be able to tailor the size and shape of the beam to that of the sample. This beamline will also be extremely useful in data collection from crystals with large unit cells ( $>1000\ \text{\AA}$ ) and in low-resolution studies ( $d_{\text{min}}$  to  $\sim 1000\ \text{\AA}$ ).

The bending magnet beamline BM29 will be modified for protein solution scattering (thereby replacing ID14-3). The new beamlines will amalgamate the synchrotron radiation facilities required by structural biologists for the next 10–15 years. The integrated resources centred around ID23, BM29, ID29 and ID30 will provide a set of beamlines for the collection of the highest-quality diffraction data and BIOSAXS data from the wide variety of samples that will arise from structural studies of challenging biological problems. It will also be able to cope with the projected three-to-five-fold increase in sample numbers arising from the search for appropriate crystals from which to collect data.

## Pushing automation further

In a field that is as competitive as structural biology, an upgraded MX resource that is readily accessible to all European researchers is of paramount importance. The ESRF has been a leader in the provision of the “first generation” of automation for MX beamlines, a development that has been ongoing for almost five years. This level of automation is only now being partially implemented at national synchrotron sources. The expertise acquired at the ESRF during the deployment of our automation developments makes it ideally, and uniquely, suited to embark on the provision of “second-generation” automated MX facilities. These will provide a paradigm shift for MX experiments that will benefit the entire European structural biology community. The upgrade of the ESRF’s MX resources will provide unparalleled facilities for structural biology, leaving the ESRF uniquely placed to support and lead the development of structural biology over the next 20 years.  
*S McSweeney*

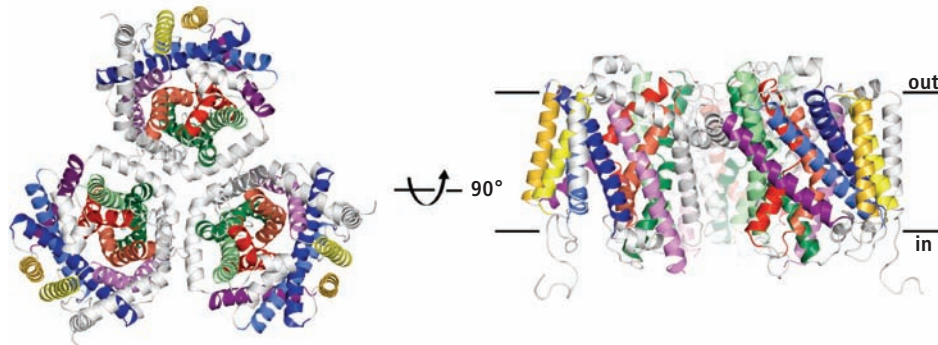
nal since 2000 and are now reaching the end of their lives. It will soon be replaced by a new set of beamlines.

**“UPBL10 will be a unique resource, based on second-generation automation for MX experiments.”**

(the Massively Automated Sample Selection Facility – MASSIF). The most suitable crystals from which to collect data will be redistributed to the most appropriate data-collection facilities in the structural biology group. In practice, the ability to identify those “one in a thousand” samples that are well ordered will enable new science to be performed with new, currently impossible, projects becoming viable. The crystal evaluation facility will be unique, providing an upgraded set of beamlines regenerating the existing ID14 beamlines on the new site of ID30. Three new end-stations will provide facilities for different types of sample evaluation, including the testing of the diffraction resolution limit, locating the best part of a crystal on which to perform data collection, detecting the presence of anomalous scatterers, screening

# X-rays help in the quest for membrane protein structures

Membrane proteins are fundamental in every living organism and yet scientists still don't know that much about them. Synchrotron X-rays are helping the community to increasingly solve more structures.



Membranes surrounding every living cell and the proteins located there carry out vital functions. They are a real challenge for researchers to study because one part is hydrophobic while another part is hydrophilic. The difficulty in studying them is evident in the Protein Data Bank, where scientists register protein structures. Membrane proteins account for less than 0.5% of entries, but 20–30% of the genes in organisms are thought to encode them.

Scientists at the Max-Planck Institute for Biophysics in Frankfurt (Germany) have been active users at the ESRF (mostly ID14) in recent years, in the membrane-protein domain. Their research extends to integral membrane proteins (like plant-harvesting complex LHC-II) (Barros, 2009), functional extra-membrane domains (like FeoB, which regulates the circulation and uptake of iron) (Köster, 2009) or proteins that form functional complexes with membrane proteins (such as GlnK1, which regulates nitrogen uptake in bacteria in three different functional states) (Yildiz, 2007).

Scientists use different techniques to unveil the structure of membrane proteins. Expression, purification and crystallisation of these proteins are challenging tasks and are a big part of the reason why they are not easily solved. Once the crystal is created, the screening and analysis are carried out on structural biology beamlines in synchrotron sources like the ESRF or the Swiss Light Source. An alternative method used to investigate these proteins is growing two-dimensional membrane crystals and determining their structure using electron microscopy.

Many of the proteins that they study come from the bacterium *Escherichia coli* because it is easy to grow, and is the preferred and most successful host for protein expression. Bacterial membrane proteins are often simpler versions of their eukaryotic equivalents, which may be more relevant to human health.

Today the Frankfurt team is focusing on the proteins that transport molecules in the

**Structure of the carnitine transporter CaiT, determined at 2.3 Å resolution by Schulze *et al.* (*Nature* 467, 233–236), using synchrotron radiation at the ESRF and SLS. CaiT is a membrane transport protein that forms trimers of three identical monomers in the cell membrane. Each protomer consists of 12 membrane-spanning alpha helices, including a core of 10 helices (coloured) that is conserved in other, structurally related secondary transporters. The CaiT structure was determined in two different states, with and without bound substrate molecules, indicating a new, allosteric mechanism of substrate transport across the membrane.**

cell, but in some diseases they fail to do so. Cystic fibrosis, for example, is caused by a faulty membrane protein that should transport chloride ions and that affects the cells of glands, including those that secrete mucus.

Another example is Crohn's disease. Carnitine is an important nutrient not only for bacteria, but also for humans, and a faulty carnitine transporter in humans causes this serious and – so far – incurable disease. In a publication in the journal *Nature* in September (Schulze, 2010), the researchers present the structure of the carnitine transporter CaiT in two states. CaiT takes a nutrient molecule from the environment (in the case of the bacterium) or the gut (in the case of the human homologue) and pushes it through the diffusion barrier of the cell membrane. In exchange, it expels the metabolic product of carnitine (gamma-butyrobetaine) from the cell as a waste product. *E. coli* (or human) cells

derive energy from metabolising carnitine.

"It is the first time that we could show that the activity of a transporter of this type is allosterically regulated by its own substrate. There are very few similar transporter structures in the Protein Data Bank and one big aim in the field is to understand the detailed transport mechanism. By comparing several structures in different states, the molecular mechanism becomes clear. We have determined not one, but two different new states of this type of transporter, so there is now, for the first time, a full picture of all stages of the transport mechanism," explains Werner Kühlbrandt, leader of the team and director at the Max-Planck Institute for Biophysics.

This research is still far from application. The team at Max-Planck is focused on getting the basic knowledge that is currently missing on membrane proteins. Synchrotron sources have helped them to carry out their research and the future looks promising: "With more brilliant synchrotron beams, smaller crystals can be examined, and the advent of robotic sample changers has made it much easier to screen large numbers of crystals. Both are essential for membrane proteins, where crystals tend to be very small and diffract weakly," explains Kühlbrandt.  
*M Capellas*

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Ö Yildiz *et al.* 2007 *The EMBO Journal* **26** 589–599.

**"Cystic fibrosis or Crohn's disease are caused by faulty membrane transport proteins."**



# Fractal structures favour superconductivity in ceramics

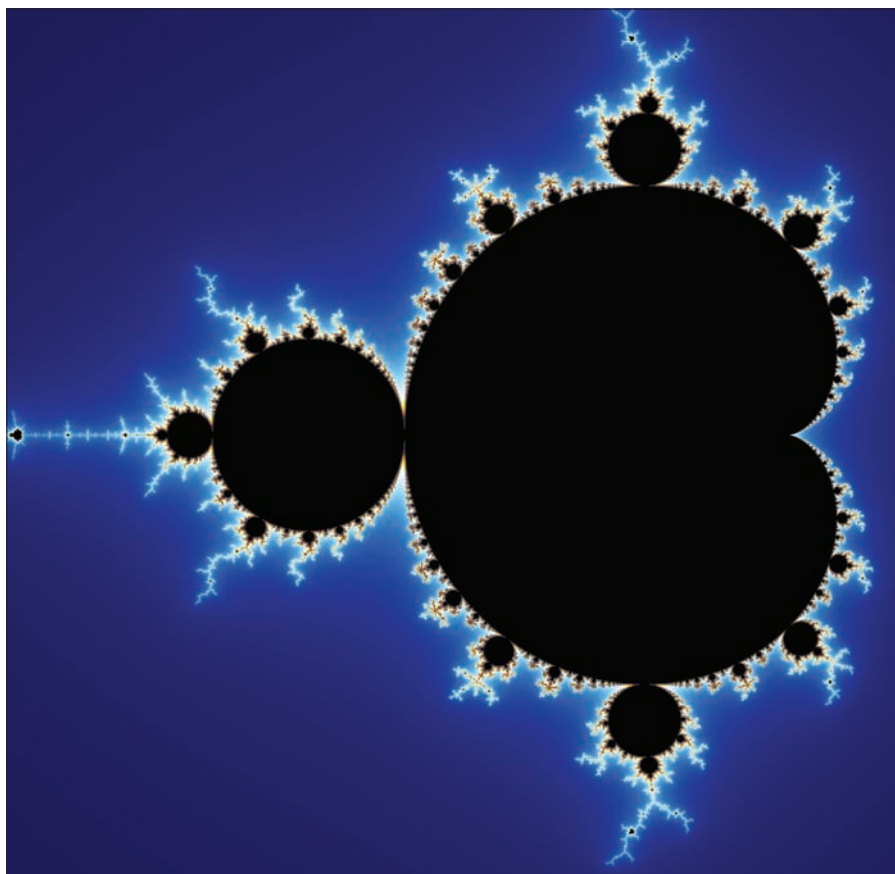
A recent breakthrough using the microfocus beamline ID13 at the ESRF has shown scientists that superconducting oxides of copper, the stock market and ferns have more in common than it first seems. Fractal structures are a key element in this unexpected association.

Fractal structures are “a rough or fragmented geometric shape that can be split into parts, each of which is (at least approximately) a reduced-size copy of the whole”, as defined by their “father”, Benoît Mandelbrot. Fractals are present in nature (for example, in ferns, broccoli and snow flakes) and in social sciences (such as the stock markets). Thanks to scientists from the University of La Sapienza in Rome (Italy), University College London (UK) and the ESRF, fractals are now an essential part in certain superconductivity systems.

The researchers used the beamline ID13 to study oxides of copper – the material that has held the record for operating at the highest temperature (well above the boiling temperature of liquid nitrogen) since 1986, when researchers discovered the superconductivity of this material. Oxide-based superconductors are very difficult to study due to the fact that extra (interstitial) or missing (vacancy) oxygen atoms, called dopants, are known to roam around in the skeleton of the material, formed by other elements, and they may freeze in ordered or random patterns when the samples are cooled.

The reason why this material has such high temperature conductivity was, until now, not known. For many years most scientists assumed that it was because of a homogeneous distribution of dopants, which made researchers concentrate on the nanometre arrangement of these dopants to find the answer to the superconductivity. The answer, however, was not at the nanometre scale but at all scales up to micrometres.

The experiments used X-ray diffraction microscopy to examine a copper-oxide superconductor that would modify its internal structure by changing the heat treatment of the sample. The discovery came when the researchers noticed that the best superconductivity effect was obtained when the microstructure contained paths



The Mandelbrot set is a well known example of a fractal structure in mathematics.

with the same nanostructure (exhibited by striped patterns of interstitial oxygen atoms) over a large distance. The high-temperature conductivity was promoted by oxygen-crystal defects that form geometrical patterns that look the same on different scales, ranging from a micrometre up to fractions of a millimetre. “We are very excited by our results because they show that fractals, which are ubiquitous in biological

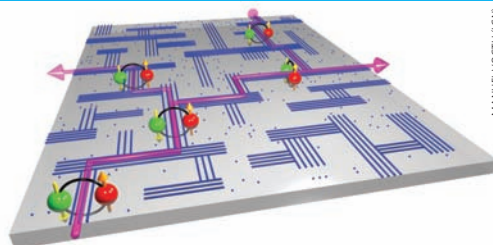
and social sciences, appear as a significant feature of seemingly simple ceramic matter,” explains Antonio Bianconi of the University of La Sapienza.

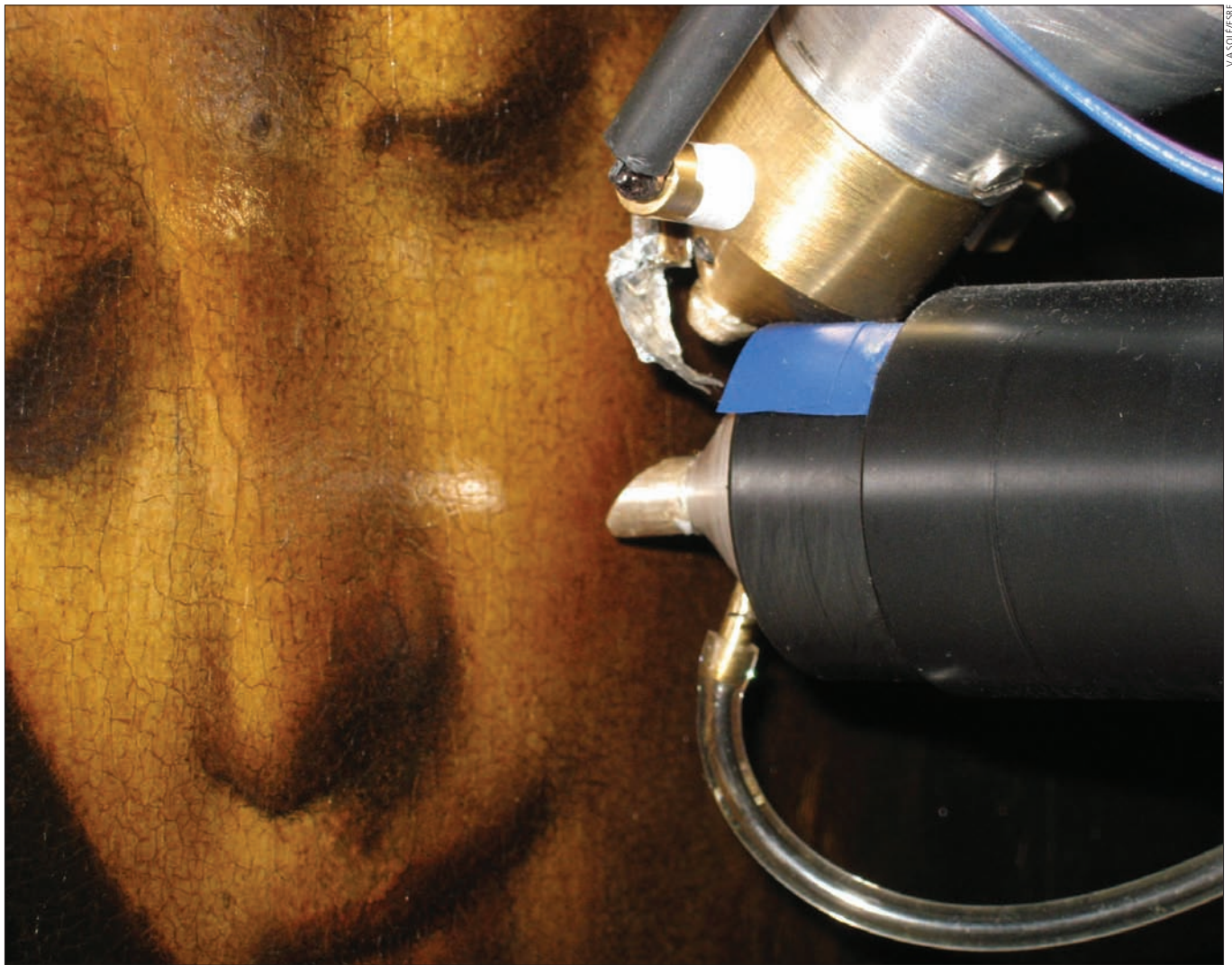
Synchrotron sources, and in this case the ESRF, have been a crucial tool in this research. As Jan Zaanen of Leiden University (the Netherlands) puts it in his “News and Views” article in *Nature*: “The experiment is conceptually straightforward but it needs the big machines installed at synchrotrons: it amounts to measuring X-ray diffraction on micrometre-sized patches of the sample and combining the results into real-space maps.” *M Capellas*

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J Zaanen 2010 News and Views *Nature* **466** 825–827.

**Heat treatment improves the superconductivity of a ceramic copper oxide by creating a fractal network of connected channels of ordered oxygen defects. The green and red spheres represent the paired electrons responsible for superconductivity.**





VASCOLEF

One of da Vinci's paintings: the face of the *Virgin of the Rocks* at the moment when it was being studied with X-rays in the Louvre Museum.

# Software at the ESRF analyses da Vinci's faces

Leonardo da Vinci's paintings are fascinating, partly due to a range of subtle optical effects that blur outlines, soften transitions and blend shadows like smoke. Known as *sfumato*, this technique is not only the result of the genius of the artist but also of technical innovations at the beginning of the 16th century. Minute observations, optical measurements and reconstitutions have already described *sfumato*, but new analysis can confirm the procedure of this technique, especially in

relation to how the gradation is done.

For the first time, Philippe Walter, from the Centre de Recherche et de Restauration des Musées de France (C2RMF-CNRS/Ministère de la culture et de la communication), and his team, in collaboration with the ESRF and the Louvre Museum, have brought new insight to *sfumato* thanks to a quantitative chemical study of the different painted layers.

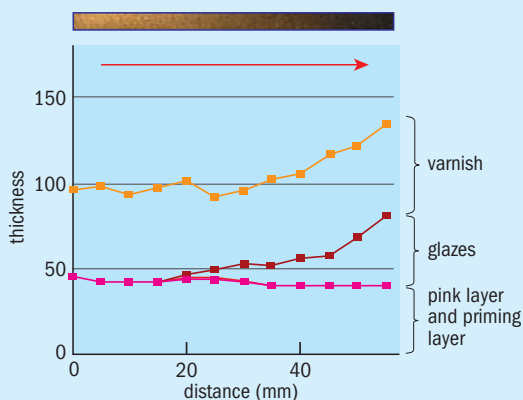
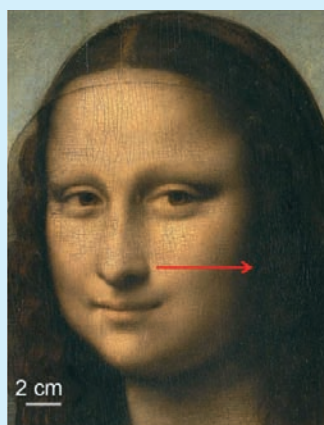
The software PyMca, developed at the ESRF by Armando Solé, provides unique

To many of the ESRF users, PyMca is a tool used just for visualisation purposes. Associating this software with Leonardo da Vinci would sound awkward, but this tool has been indispensable in the *in situ* study of this Renaissance artist's work.

X-ray fluorescence spectrometry analysis possibilities. "Its ability to model multilayered materials and its support of very low-energy X-rays can give quantitative access to the composition and thickness of the layers on multilayered material," explains Solé.

Seven paintings by da Vinci (*Virgin of the Rocks*, *Mona Lisa*, *St John the Baptist*, *The Annunciation*, *Bacchus*, *Belle Ferronnière* and *The Virgin and Child with St Anne*) were analysed without extraction in the





Representation of the superposition of layers in paintings in the face of *Mona Lisa*, on one light zone near the nose and the darker shadow of the hair. The graph shows the thickness and concentration of pigments in the different layers.



The team at work (from left to right): Philippe Walter, Laurence de Viguerie and Armando Solé during the experiment on the *Virgin of the Rocks* in one of the Louvre rooms.

rooms of the Louvre Museum. The scientists concentrated on the faces because they show the characteristics of *sfumato*.

The scientists found different recipes used by da Vinci to create the shadows on the faces. These recipes are characterised by a technique (the use of glaze layers or a very thin paint) and by the nature of the pigments or additives. A glaze is a fine, translucent layer, mainly organic, which contains a small amount of pigment. The superposition of glazes is used to create depth and volume. In the case of

the glazes, thin layers of 1–2 μm were applied to obtain a total thickness of no more than 30–40 μm. The results obtained in this study help to understand da Vinci's quest towards making his art look alive.

PyMca's analytical features were first used in cultural heritage experiments in 2005 to study a fragment of a painting by Matthias Grünewald, a German artist of the 16th century. This was the beginning of a long collaboration between Philippe Walter, Marine Cotte (at that time at C2RMF and the

ESRF) and Solé. Today, users from different light sources and X-ray tube-based laboratories around the world use it to analyse their data.

Walter is already thinking of the next painter to go under the scrutiny of PyMca and X-ray fluorescence. Raphael, a contemporary of da Vinci, is next on the list.

*M Capellas*

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# Work on the first Upgrade beamlines gets underway

Construction of the UPBL11 facility started this summer, marking the beginning of the realisation phase of ESRF's Upgrade beamlines.

UPBL11 features the combination of two new beamlines, BM23 and ID24, into a state-of-the-art X-ray absorption spectroscopy facility, offering the users community the possibility to perform standard high-quality EXAFS for material characterisation as well as new experiments that are currently impossible, combining sample environments for extreme conditions and time resolution.

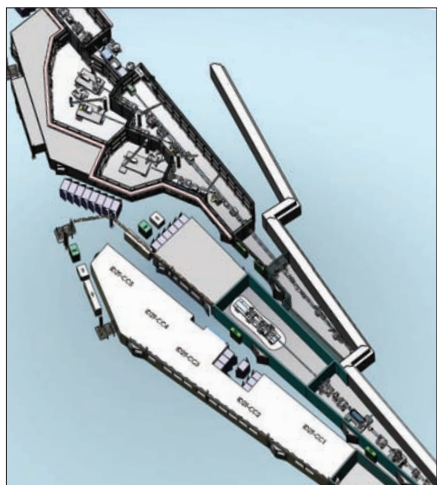
The general-purpose X-ray absorption spectroscopy beamline, BM23, will start its radiation tests in September and it is already open for proposals. First test experiments will start by the end of this year.

The strengths of BM23, equipped with a fixed exit double crystal monochromator, include a very large operational energy range, a high energy resolution, a high spectral signal-to-noise ratio, high beam stability and a high level of automation. Regarding scientific applications, it will be used to study structural properties in materials like liquids, molecular solutions, liquid crystals, single- and polycrystalline materials, amorphous and highly disordered solids and molecules, and macromolecules containing metals or partially substituted with heavy atoms.

Located next to BM23 there is now hardly anything left of what used to be ID24, the energy dispersive X-ray absorption spectroscopy beamline. The beamline



**Above:** the dismantling of ID30 left a gap in the experimental hall that will start to be covered again. **Left:** the "village" made up of ID30 and ID29. Ultimately ID30 will replace ID14.



shut down on 12 July and, after a period of dismantling, construction work for the new ID24 has started. The work will consist of building a new experimental hutch and an optics hutch, which will be added to the existing experimental and optics hutches of the old ID24. "We are working at full speed and although we are keeping 50% of the current infrastructure, we still have a lot to do in the next six months," explains Trevor Mairs, project manager for the new ID24. The commissioning for the new beamline will start in March or April 2011. The new beamline ID24 involves the upgrade of beamline ID24 in terms of spot size, stability, time resolution and energy range. With respect to the previous design, the X-ray beam, the optics, the detection systems, the

sample environments and the infrastructure have all been optimised to provide the ideal conditions to push the limits of time-resolved and extreme conditions XAS. For example, detection of short-lived chemical species down to the microsecond timescale will become possible in single shot experiments. Probing the structure or the electronic and magnetic properties of matter at extreme conditions of pressure, temperature or magnetic field that can be maintained only for a few microseconds will also become reality.

On the structural biology side, the construction of ID30A, also known as MASSIF, started during the summer shutdown and two optics and two experimental hutches will be built in the current experimental hall by the end of this year. First radiation tests will take



place in March 2011.

MASSIF will be a suite of beamlines operating at fixed energy and with a high photon flux. The beamlines will be highly automated so “they will be almost independent of human intervention”, explains Christoph Müller-Dieckmann, project manager of the structural biology’s Upgrade Programme. “We are aiming at evaluating 1000 samples a day on each of the three end-stations,” he explains. “The end-stations can also be used for full data collections and their characteristics will certainly make them interesting tools for our industrial users,” he concludes.

Another “new” beamline for the structural biology group is BM29. The former X-ray absorption spectroscopy beamline is being transformed to host the BioSAXS facility that is currently available on ID14-3. The BM29 optics hutch is being renovated and re-equipped. The new beamline should be operational at the end of 2011.

Eventually ID30 and BM29 will replace the existing ID14 end-stations and, together with ID23-1, ID23-2 and ID29, will be able to better cover the ever more challenging needs of the ESRF’s structural biology user community.  
*M Capellas*

#### Reference

Conceptual design reports for the upgrade beamlines of phase 1: [www.esrf.fr/AboutUs/Upgrade/future-beamline-portfolio](http://www.esrf.fr/AboutUs/Upgrade/future-beamline-portfolio).



BM23 was an empty beamline at the beginning of August, but it is slowly filling up.

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10-135

# J McCarthy: supporting the users

Joanne McCarthy is known for her welcoming manner and friendly nature while at the same time getting straight to the point. She has been heading the users' office for the past two years, but before that she had been living in the depths of the scientists' world.

"I was always interested in physics but never imagined I would end up in the field of research," explains Joanne McCarthy with a surprising honesty. "I studied physics because I liked to fix things and to do that you need to understand how they work – physics explains a lot about how things work and it's fascinating," she continues.

Her CV shows a physics background as well as many years spent in the macromolecular crystallography group. Currently, she works in administration as head of the users' office. McCarthy is probably one of the most versatile characters at the ESRF today.

Her first contact with the facility came through Malcolm Cooper, her professor at the University of Warwick and director of the XMAS beamline. He suggested to her to do a traineeship at the ESRF, back in 1992, and then a PhD on Compton scattering. Tempted by the project but also by the prospect of living abroad and learning a new language, McCarthy landed on the new ID15 high-energy beamline for three years. She continued there for another three years as post-doctoral researcher.

After these years of working as a scientist, she understood that it was the work on instrumentation that most appealed to her. The structural biology group was looking for a scientist with a physicist profile to work on the macromolecular crystallography (MX) beamline ID14-2 and push the effort to automate the MX beamlines, and she went for the job. This led, a short time later, to the position of BLOM for the MX beamlines. "I very much enjoyed the time that I spent on the MX beamlines," she confesses. She worked mainly on improving and automating the instrumentation on the MX beamlines and had a great deal of contact with the MX user



**Joanne McCarthy explaining to Daniele Antonangeli some procedures for the users. Behind her, two of her team members: Agnès Carlet (right) and Nadine Petricola. Missing in the photo is Sonya Girodon.**

## Outside working hours...

She was born in England but feels Irish as her family is Irish.

- Between the ages of five and 18 she won more than 700 medals in Irish dancing competitions. She was once fourth best dancer worldwide.
- She played with the local rugby team and won the French Cup in

1995, was French vice-champion in 2003 and 2008, and played at the highest national level for 10 years. She was named the best senior female player of the Alpine region in 2005.

- When she was eight, she was an extra in the Monthly Phyton film *The Meaning of Life*.

community, dealing with many aspects of user administration for the group. But her biggest motivation was that the research was much more applied and she could see the direct benefits of the work being done. "I got a real kick from seeing scientists being excited about solving a structure and feeling that I had contributed in some way by helping to provide them with world-class facilities," she says. And she has only good words for the MX group "It is a very dynamic and ambitious group where I was given significant responsibilities and the chance to prove myself. It certainly helped me to develop the skills required to do my current job."

## The turning point: from science to administration

After 14 years in France, McCarthy's life seemed

very established: she held a permanent position as a BLOM, she was winning trophies with her rugby club and enjoyed life in this new country, although she sometimes missed Ireland (and still does, judging by the traditional Irish music that her computer played during this interview). The BLOM position was ideal, but dealing with both instrumentation and user administration in a group with so many projects and such a high turnover of users was becoming difficult to balance, and she found herself shifting to the side of user administration.

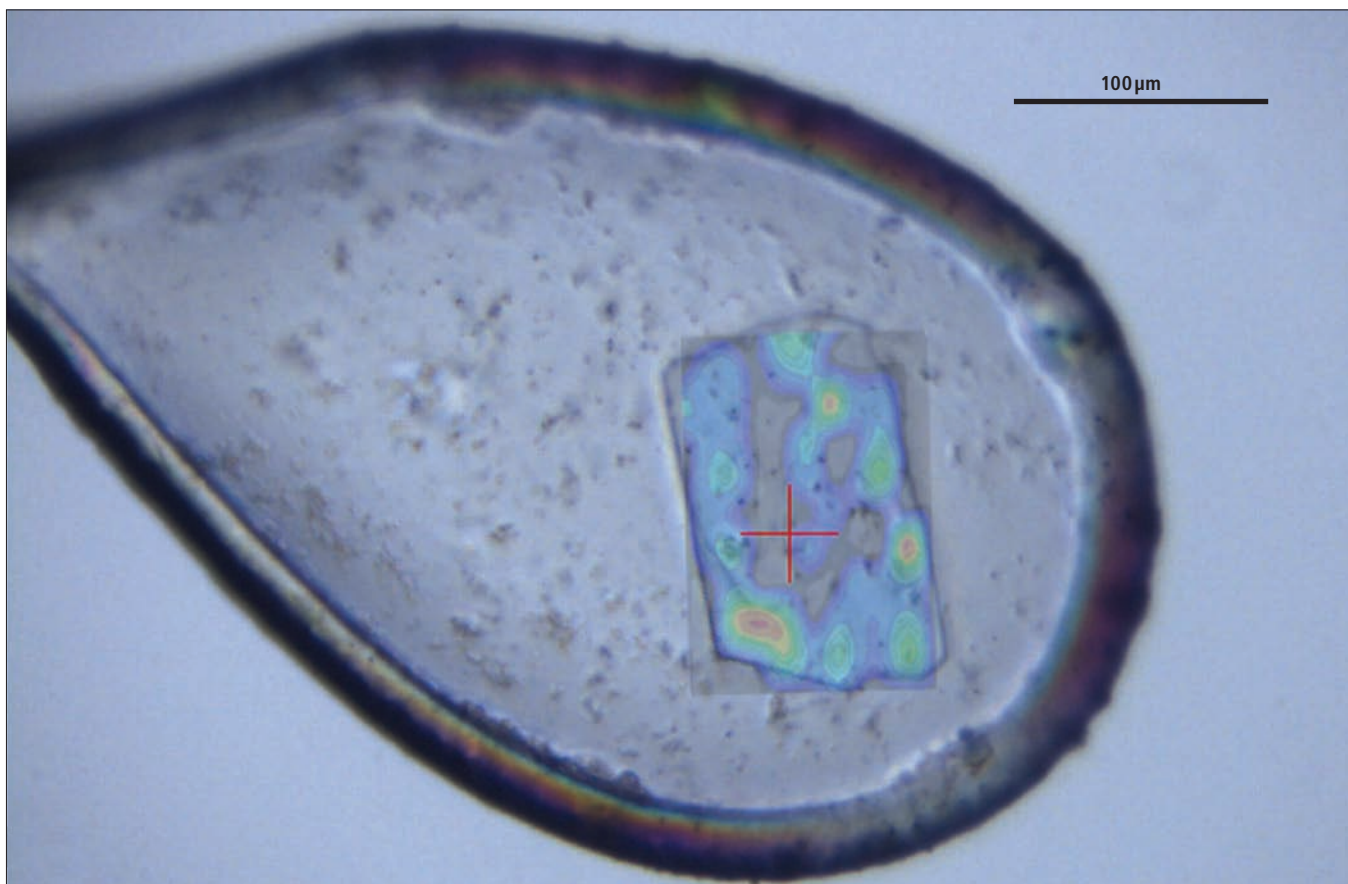
The opportunity to lead the users' office came following the retirement of Roselyn Mason, the former head of the team and gave McCarthy a chance to change her path. This new job would involve a lot of administrative work, but

the chance to work in a position with a much more general vision of the activities of the facility and the challenge of taking over at the start of the Upgrade Programme made the job very appealing. "I was already dealing with the MX users who make up 40% of all user visits to the ESRF each year, and so it was not such a big change for me to take on the rest of the community," she says, "But the big attraction for me was to be able to appreciate the activities of the other ESRF beamline groups and their users. It gives me a panoramic view of what we do here and makes me marvel even more at the success of the facility and what it can do for science."

Today, she is focused on renovating the proposal-review process. The aim is to speed up the processing of the review results and to automate procedures wherever possible. "The number of proposals received at the ESRF is still increasing and the current scheme is not viable in the long term. We are upgrading our facility and its beamlines and we cannot offer users world-class beamlines without first-class service and access procedures." In collaboration with colleagues from computing, she expects that the new system will be ready in 2011. She is also working closely with the directors of research to study the proposal review procedure to see if it can be improved for the future.

With all these goals for the future, McCarthy needs her group on her side, but that doesn't seem to be a problem. "The day-to-day tasks of the users' office are dealt with almost entirely by my colleagues. I am really lucky with my team: the three administrative assistants working with me are motivated, enthusiastic and efficient. They see that we are here to give a service to our users and they believe in what they do." *M Capellas*





**Diffraction cartography of a crystal of the  $\beta$ 1-androgenic G-protein-coupled receptor (GPCR).** GPCRs are membrane proteins that are the target of around 30% of pharmaceuticals. They are hard to crystallise and, when they do, finding an area upon which to collect data is problematic. Probing the diffraction properties with a micrometre-sized beam on ID23-2, in conjunction with the projection of these data as a contour map, defines the shape and internal order of the crystal, and hence removing the element of chance from finding the best ordered area. Diffraction cartography was featured on the front cover of the August issue of *Acta Crystallographica D*, see Bowler *et al.* 2010 *Acta Cryst.* **D66** 855–864.

## In the corridors

### ESRF on Facebook



Since June, the ESRF has been on Facebook. An official page has been set up by the communication group and regular posts are being put up. The reason for this initiative is to take advantage of the ever-growing phenomenon of social networks to provide a direct feed to scientists, professionals and the general public on the latest news and updates on what happens at the facility.

On the Facebook wall there will be a wide array of subjects: scientific achievements; news on the Upgrade Programme; recently published job offers; and any

other information that could be of interest to the audience. ESRF's aim is to have posts three times a month on average, so that "fans" of the page do not get overly bombarded with information.

At the moment, 176 people like the page and 54% are between the ages of 25 and 34. The men to women ratio is 61:37.

The communication group is currently studying the possibility of joining Twitter in the near future, so watch this space.

To find us on Facebook, go to [www.facebook.com/pages/European-Synchrotron-Radiation-Facility-ESRF/116961611670251](http://www.facebook.com/pages/European-Synchrotron-Radiation-Facility-ESRF/116961611670251).

### Recovering after experiments

US researchers have found that a 10-hour lie-in after several days of restricted sleep might not be enough time for most

people to recover. The scientists carried out a study where 159 adults were assigned to sleep a certain number of hours per night. After five nights of little sleep they were allowed to sleep for 10 hours. Despite recovering noticeably, they still had slow reaction times and fatigue lasted a few more days.

#### Reference

S Banks *et al.* 2010 *Sleep* **33(8)** 1013–1026.

### Stinky feet could become a thing of the past

Graphene, made of the thinnest possible sheets of carbon, is considered an excellent candidate to be used in computing, as it is strong, elastic and has an exceptionally high conductivity. Scientists from China have



**Smelly shoes: a thing of the past?**

discovered new applications such as anti-bacterial bandages, food packaging that keeps food fresher longer and shoes that eliminate foot odour, as the graphene can fight disease-causing bacteria.

The team made sheets of paper from graphene oxide and then tried to grow bacteria and human cells on it. Bacteria were unable to grow on the paper and it had little adverse effect on human cells.

#### Reference

W Hu *et al.* 2010 *ACS Nano* **4(7)** 4317–4323.



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The Neutron Optics Service plays a major role in the conception, construction and maintenance of most of the polarisation and optical devices used on the ILL's innovative instruments.

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You will head the Neutron Optics Service and supervise a staff of 4 engineers/scientists and 12 technicians, working in 3 different groups (monochromators/multilayers/polarised  $^3\text{He}$ ). You will be allocated the financial resources necessary to accomplish these duties.

You will work in close collaboration with ILL scientists to provide the technical solutions to their requests in neutron optics instrumentation. You will need to be creative and inventive in the production of new and well-targeted solutions in a rapidly evolving discipline.

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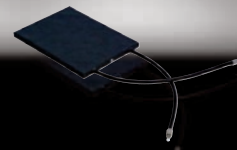
**2 Channels General Purpose Amplifier and Power Supply (SP5600)**

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- Output connectors: FC

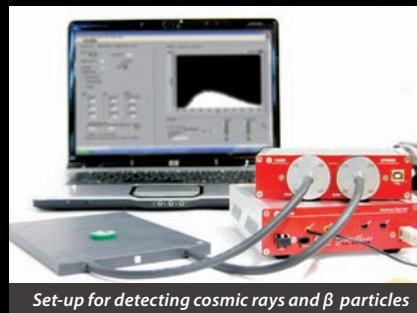


**Mini Spectrometer (SP5603)**

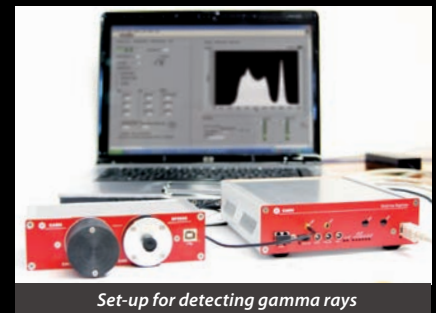
- Mechanical structure for optimal SiPM to crystal coupling
- Crystal dimensions:  $3 \times 3 \times 15$  mm<sup>3</sup>
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Set-up for SiPM testing & characterization



Set-up for detecting cosmic rays and  $\beta$  particles



Set-up for detecting gamma rays

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The kit was developed within the EC-FP6 project RAPSODI, licensed to CAEN by the Research & Technology Development parties.