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June 2020

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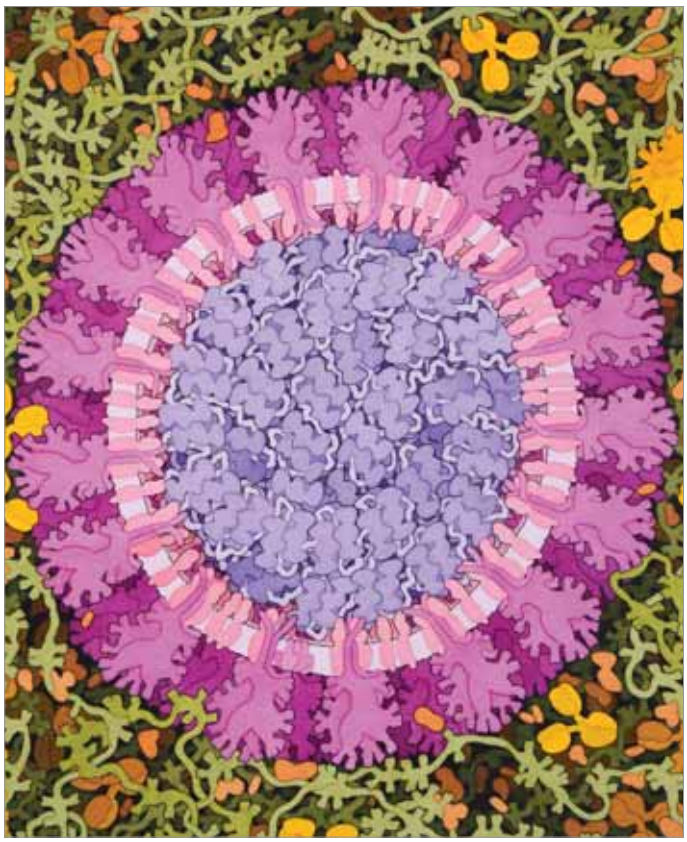

DAVID GOODSELL/RCSB PROTEIN DATA BANK

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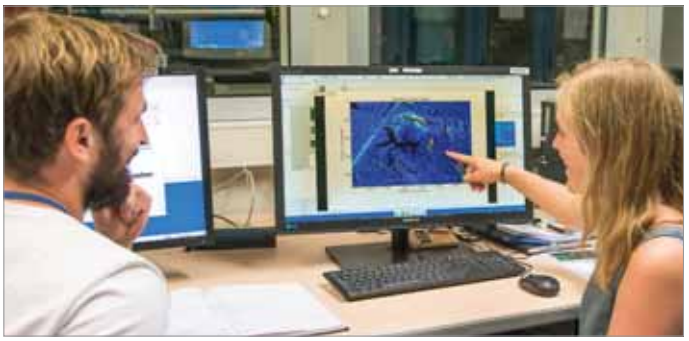

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The EBS: up and running

Francesco Sette
ESRF director-general

The new Extremely Brilliant Source (EBS) storage ring is ready for User Service Mode (USM) operation, five months ahead of schedule. Its commissioning, having started on 28 November 2019, was completed on 14 March this year. All design parameters to be reached by 25 August 2020, the planned restart of USM, have been delivered and often surpassed. The new HMBA lattice concept is now a reality, confirming the revolutionary ideas developed by Pantaleo Raimondi, the director of the accelerator and source division, and his team. As a result, the ESRF is once again the brightest synchrotron in the world, paving the way for many future generations of light sources.

The COVID-19 pandemic – declared a public-health emergency of international concern by the World Health Organisation at the end of January – has had a huge impact on everyday life, including the organisation of research facilities. In this context, the ESRF's priority is the health and safety of its staff and visitors, and a plan of still restarting USM on a maximum number of beamlines by 25 August. Following the measures imposed by the French authorities, the ESRF closed its site from 16 March to 11 May and implemented its pandemic continuity plan. Meanwhile, mostly working remotely, its staff ensured that ESRF activities continued to advance as much as possible, and kept in contact with the community and partners. As this issue of *ESRFnews* went to press, we were entering a new phase of progressively resuming activities at the ESRF site.

Inevitably, COVID-19 necessitates some revision of our restart plans, as well as our strategy to tackle future challenges. Nevertheless, the guiding objective of the ESRF is to provide, within the boundary conditions dictated by COVID-19, maximum service to users with the new EBS as soon as possible. With that in mind, the ESRF has implemented new guidelines for beam-time allocation for the 2020-II period, such that a majority of experiments are conducted or followed up remotely (see User Corner, p12). This is a great challenge for everyone, but it may also give insights into new operation models and how we can reduce the ESRF's carbon footprint.

The COVID-19 pandemic reminds us of the importance of excellence-based scientific research without frontiers. In this context, international research facilities such as the ESRF, with the support of its partners and in collaboration with the whole scientific community, have a key role to play.

ESRF news

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D CHENEVIER/ESRF

ESRF restart on target

The ESRF–EBS is gearing up for the restart of User Service Mode (USM) amid continuing restrictions on physical access due to the COVID-19 pandemic. Although travel and other restrictions mean that experiments will mainly be carried out remotely with the new high-energy synchrotron, the restart is set to take place on a maximum number of beamlines on 25 August this year, as originally planned.

"We want to provide maximum service to users as soon as possible, so that they can take advantage of the world's brightest synchrotron light source," says Jean Susini, the ESRF director of research for life sciences. "However, our utmost priority is their safety and well-being, as well as that of our staff." Anticipating the different constraints that are resulting from COVID-19, ESRF management have adjusted the guidelines for beam-time allocation over the next period, with "the constant aim to provide a productive environment for pioneering scientific research – including that which tackles COVID-19," Susini adds.

"We want to provide maximum service to users as soon as possible"

Francesco Sette, the ESRF director-general, believes that the current outbreak has shown the importance of "excellence-based scientific research without frontiers". "The ESRF has a key role to play with the new EBS," he says.

In itself, the launch this year of the upgraded ESRF – the first of a new generation of high-energy synchrotron sources – could not have gone better. The commissioning, having begun in November last year, reached USM performance parameters on 14 March 2020, five months ahead of schedule. By the middle of March, all the public insertion-device beamlines had seen light and had begun their beamline restart and commissioning procedures.

Like research institutions the world over, however, the ESRF has had to adjust its plans in the face of the COVID-19 pandemic. On 16 March, following a nationwide lockdown imposed by the French authorities, ESRF management implemented the ESRF continuity plan that was devised after the 2009 H1N1 "swine flu" outbreak to cope with such a pandemic situation. Most of the 600 ESRF staff immediately switched to teleworking, and in subsequent days only between two and 10 staff were allowed to come

on site in order to keep vital services running and to prepare an efficient restart of the facility. As this issue went to press, staff members were gradually returning to the site, in line with the recommendations of the French authorities and with new, strict health-and-safety measures to minimise the risk of viral transmissions.

According to Susini and Harald Reichert, the ESRF director of research for physical sciences, however, several factors mean that the ESRF has had to adjust its original restart schedule: travel restrictions home and abroad; reduced staff on site at any one time due to social-distancing requirements; and possible delays in the delivery of instrumentation and components. For these reasons, they say, some public beamlines and some bending-magnet beamlines operated by collaborating research groups may restart later than originally planned. Nevertheless, they add, the guiding objective of the ESRF "new master plan" remains the restart of USM, with a maximum number of beamlines, on 25 August 2020.

Record proposals

Meanwhile, there has been a great show of support for the new ESRF–EBS in the more than 1200 proposals submitted by the March deadline. At the end of April, 120 external experts gathered over three days across 12 parallel teleconference meetings to evaluate the proposals, the greatest number ever received relative to the number of available beamlines. According to ESRF management, preference has been given to experiments that can be carried out on samples that can be given to ESRF beamline staff and measured via remote-access and mail-in services (see User Corner, p12). "The quality was very high," says Reichert. "People have obviously been thinking carefully about what they can do with this new machine."

STEF CANDE/ESRF

X-ray facilities join forces

Francesco Sette, the ESRF director-general, is one of 22 representatives of X-ray facilities from all over the world to adopt a five-point action plan to jointly overcome the COVID-19 pandemic.

The plan was agreed via teleconference on 24 April at the SR20 Summit, in which the representatives said that the pandemic had united them and the scientists using their facilities "more than ever". The plan involves:

- sharing information and contributing to the co-ordination of scientific X-ray research addressing COVID-19;
- exploring the possibility of a worldwide network of X-ray science facilities, including university and industrial users;
- studying the development of a shared computer system to accelerate the distribution of information, improve global co-operation among facilities and enable the fastest access for scientific projects;
- sharing experiences with remote access and the mailing-in of samples, to improve those modes of experimental activity;
- co-ordinating the efforts of X-ray science with other analytical facilities, such as neutron sources, cryo-electron microscopes, lasers and nuclear magnetic resonance spectrometers.

The international network of X-ray science facilities "is deeply engaged with overcoming the pandemic," the representatives wrote in a statement. "[Our] role is to create and implement scientific and technological research activities to effectively study, understand and contribute solutions to the COVID-19 pandemic, including new drugs, therapeutic strategies and medical equipment developments."

COVID-19 projects get underway

Eaazhisai Kandiah, beamline scientist at the CM01 cryo-electron microscopy (cryo-EM) facility, is leading one of five projects at the ESRF to investigate COVID-19 and the novel coronavirus at the centre of the pandemic, SARS-CoV-2.

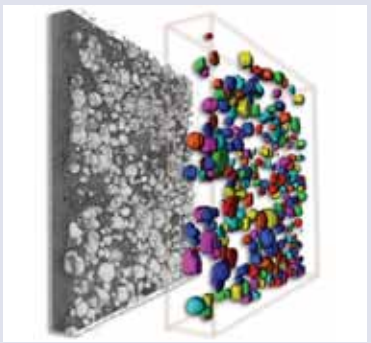
The other projects make use of the ESRF's structural biology beamlines, as well as BM05, a bio-imaging beamline that can be used to understand the impact of the virus on organs after infection.

Kandiah's project was made possible thanks to a grant from the French funding agency ANR, which issued a flash call for COVID-19 projects on 6 March to address research priorities identified by the World Health Organization. Carried out in collaboration with the Institut de Biologie Structurale on the EPN campus, it will focus on a polyprotein precursor to SARS-CoV-2 known as Nsp3, on which 15 individual proteins crucial to the function and life-cycle of the virus link before auto-cleaving to produce individual proteins. According to Kandiah, the project will have "an integrated, interdisciplinary and multi-level approach, wherein high-end molecular biology, biochemical and structural methods will be combined with sophisticated cryo-EM approaches, thereby integrating complementary trends in modern molecular biology."

A relatively new technique, cryo-EM can image single molecules or complexes directly. Because there is no need for crystallisation, and because data can be obtained quickly and at increasingly high resolution, cryo-EM facilities such as CM01 are expected to be very important in efforts to understand SARS-CoV-2.

STEF CANDE/ESRF

Cryo-EM facilities such as CM01 could be crucial in the battle against coronavirus.



YIJIN LIU/SSRL/SLA

Why the juice runs loose

An enduring problem with lithium-ion batteries is their tendency to lose capacity over time. Now scientists at the SLAC National Accelerator Laboratory in the US and the ESRF have understood part of the reason for this, in the battery cathodes.

The team used hard X-ray phase-contrast nano-tomography at the ESRF's ID16A nano-imaging beamline to observe how particles made of nickel-manganese-cobalt (NMC) in a charged cathode break away from their conductive carbon matrix. In addition to results from studies at SLAC's Stanford Synchrotron Radiation Lightsource, the researchers employed "computer vision" to better analyse the particles' behaviour. A subfield of machine learning, computer vision consists of algorithms that were originally designed to scan images and videos to identify and track objects.

The team discovered that the detachment of NMC particles contribute significantly to a battery's decline, in conditions typical in the running of consumer electronics, such as smartphones. Although larger NMC particles were more likely to incur damage and break away, smaller particles broke away too, often with more variety in their behaviour (*Nat. Commun.* **11** 2310). "That's important because researchers had generally assumed that by making battery particles smaller, they could make longer-lasting batteries," says Yijin Liu of SLAC, a senior author of the study. "Our study suggests that it might not be so straightforward."

According to ESRF scientist and co-author Yang Yang, the only way to observe electrode particles with their carbon binders in the past was to use electron microscopes. "They are destructive and very limited in statistics," she says. "The unique set-up of the high-energy X-ray nanoprobe at ID16A meant we could visualise hundreds of particles within their carbon matrix in the electrode, allowing a complete view."

ID21 users have a scream studying masterpiece

While COVID-19 keeps the world in anguish, ESRF users have been studying how to preserve the image that most vividly captures that mental state: Edvard Munch's *The Scream*.

The image – actually four similar images, which Munch created between 1893 and 1910 in both pastels and oil paints – is often regarded as the most famous example of artistic expressionism. To convey the intensity of feeling, Munch experimented with different combinations of binding media and synthetic pigments. Unfortunately, this unconventional approach has made it difficult for conservators to know how best to preserve the artworks.

To help them decide, an international collaboration of researchers led by the National Research Council (CNR) of Italy (including the University of Perugia in Italy, the University of Antwerp in Belgium, the Bard Graduate Center in New York City, US, the German Electron Synchrotron DESY in Hamburg, the Munch Museum in Oslo, Norway, and the ESRF) has studied the last of the four versions of *The Scream*. This version, an oil painting thought to have been completed in 1910, contains signs of degradation in areas where Munch used yellow pigments based on cadmium sulphide – parts of the sky and the neck of the central figure, both of which have turned off-white. The degradation is believed to have been exacerbated in an interlude between when the painting was stolen from the Munch Museum in 2004 to when it was recovered in 2006.

Together with some of her colleagues, Letizia Monico of the CNR took a microscopic sample of the painting to the ESRF ID21 beamline, where she could analyse it with techniques such as micro X-ray diffraction, X-ray micro fluorescence and micro X-ray absorption near-edge structure spectroscopy. Backed up by data from other sources, the results revealed that the degradation occurs in conditions of high moisture or humidity, when the original cadmium sulphide turns into cadmium sulphate in the presence of chloride-compounds – even when there is no light (*Sci. Adv.* **6** eaay3514).

Currently, the 1910 version of *The Scream* is stored at a relative humidity of about 50%, but the new analysis suggests an ideal relative humidity would be 45% or less.

Unconventional paint ingredients in Munch's most famous artwork have posed a problem for conservators.

STEFCANDÉ/ESRF

ID21 beamline scientist Marine Cotte helps the users perform the analysis

- Another recent cultural-heritage study on ID21 is one of the first to come under the umbrella of the ESRF-coordinated Photon and Neutron Open Science Cloud (PaNOSC) project, which makes publicly funded research data and methodologies accessible to all after three years. Sponsored by the coatings manufacturer Akzo Nobel, and involving Alessa Gambardella of the Rijksmuseum in Amsterdam, the Netherlands, and others, the study investigated how the properties of an historic blue pigment known as ultramarine affects the ageing of paint (*Sci. Adv.* **6** eaay8782).

SHUTTERSTOCK/MOHAMED ABDULRAHEEM

Plastic-munching enzyme comes to ESRF for analysis

Of the 350 million tonnes of plastic produced worldwide every year, according to estimates, somewhere between 40 and 55% ends up in landfills or the natural environment, including the ocean. Now, scientists at the Toulouse Biotechnology Institute (TBI) in France have teamed up with the French start-up Carbios to engineer an enzyme that can quickly reduce a major part of this waste back to its starting materials – and they have come to the ESRF to solve its structure.

The plastic that the enzyme tackles is poly(ethylene terephthalate), or PET, the most abundant polyester plastic of which almost 70 million tonnes are manufactured annually for bottles, food containers, textiles, and various types of packaging. PET can be recycled, but this usually worsens its mechanical properties. As a result, only about a third of PET bottles are actually made into new plastic – often products such as carpets, which make fewer demands on plastic quality and which ultimately end up in landfills.

In 2012, Japanese scientists discovered a microbial enzyme present in compost heaps that could break down PET plastics. Known as leaf-branch compost cutinase (LCC), the enzyme cuts the bonds between two of the building blocks of PET, terephthalate and ethylene glycol. Unfortunately, due to heat denaturing the enzyme, its reaction has a low yield.

"Users collected data from hundreds of crystals to determine the enzyme's structure"

The scientists from TBI – a joint laboratory of the University of Toulouse, the French National Centre for Scientific Research, the National Research Institute for Agriculture, Food and the Environment, and the National Institute of Applied Sciences in France – worked with Carbios, which specialises in the development of plastic enzymes, to engineer LCC by replacing certain amino acids with those that are faster acting and more thermostable. At the ESRF's ID30B structural-biology beamline, and the ALBA synchrotron near Barcelona, Spain, they collected data from hundreds of crystals to determine their new enzyme's structure. Subsequent tests showed that it could degrade 90% of PET waste in just 10 hours (*Nature* **580** 216).

"Carbios's recycling process, the first of its kind, initiates a real transition to a circular economy and can better prevent plastic pollution from harming our oceans and planet," says Alain Marty of the University of Toulouse and the company's chief scientific officer.

A new twist on tough algae

The helical structure of a type of algae makes it highly resistant to mechanical stress, and could lead to the development of lighter and more flexible concrete, according to users of three ESRF beamlines.

Jania, a red alga that exists in shallow parts of seas and oceans around the world, has to be stress-resistant to survive the pummelling of waves. Made of magnesium calcite, however, its skeleton is also very lightweight. Boaz Pokroy of the Technion–Israel Institute of Technology, together with colleagues from the Charité University in Berlin, Germany, came first to the ID16B beamline, where nanotomography allowed them to observe that the structure is helical – a shape that makes the alga 20% more compliant to bending forces than it would be otherwise. Next they went to the ID19 and ID22 beamlines, where the techniques of X-ray microtomography and X-ray powder diffraction revealed the alga's stem to contain micron-sized open cells, similar to wood but with mineral walls. The mineralisation was thicker on the walls closer to the exterior of the stem, which the researchers believe boosts the Jania's stress-resistance (*Adv. Sci.* DOI:10.1002/advs.202000108).

To make it less brittle and more stress-tolerant, builders usually add steel to concrete – a weighty combination. Pokroy believes that if the material could instead be designed with an open-celled, helical structure, it would be lighter, more flexible and more stress-resistant. "Our findings are of great importance in deepening our understanding of nature's designs, and they are potentially relevant for the development of new low-weight, high-compliance structures," he says.

SHUTTERSTOCK/ANTONIO MARTIN

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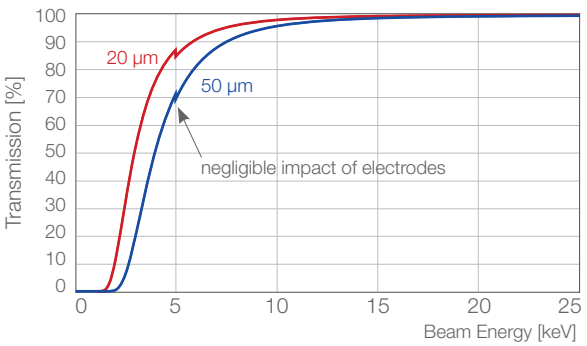

Figure 1: Transmission of the Diamond XBPM.

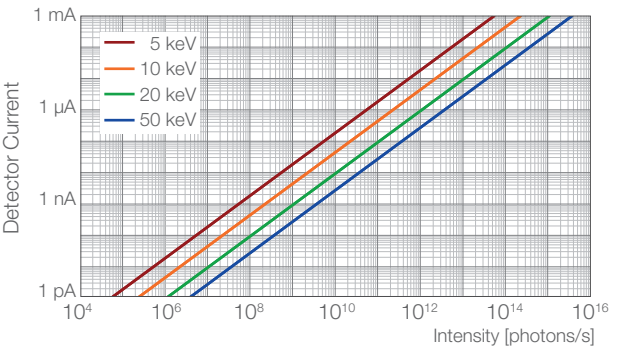

Figure 2: XBPM response as a function of the beam intensity.

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The Nobel that never was

The centenary of Rosalind Franklin's birth next month has reignited the debate about her involvement in the discovery of the structure of DNA.

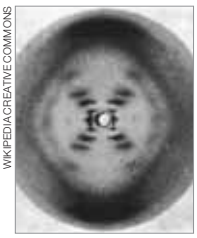
Who was Rosalind Franklin?
Born on 25 July 1920 into an affluent London family, Franklin was by most accounts a strong-willed and an exceptionally bright child, who knew from an early age that she wanted to be a scientist. Having attended St Paul's Girls' School – one of the few schools in London that taught girls physics and chemistry – she went to the University of Cambridge, where she achieved a second-class degree in natural sciences. That she did not attain a first was attributed by her supervisor to her spending too long on early exam questions at the expense of others – a fastidiousness that would return to haunt her.

How did she become involved in the study of DNA?
Franklin's early research had focused on the structure of coal – then a vital wartime commodity – first during a PhD at the British Coal Utilisation Research Association, and then during a postdoc in France at the Laboratoire Central des Services Chimiques de l'Etat (the central state laboratory for chemistry). At the age of 30, however, she returned to the UK, taking up a research position at King's College London. Together with his doctoral student, Raymond Gosling, a senior scientist at the institution called Maurice Wilkins had made much progress towards an atomic-level understanding of DNA – he had crystallised it, and obtained rudimentary X-ray diffraction images. Given that she had already mastered diffraction crystallography during her time in France, Franklin ought to have turbocharged these efforts.

What went wrong?
The head of the laboratory, John Randall, put Franklin in charge of the diffraction work on DNA – yet failed to tell Wilkins. As a result, the two scientists set off on the wrong foot, with Franklin believing Wilkins to be sticking his oar into the field in which she was an expert, and Wilkins wondering why Franklin was working on her own terms. Their personalities did not help: Franklin had grown to favour direct confrontation, whereas Wilkins was a retiring type who avoided eye contact. They ended up working independently, with Gosling stuck in the middle – although this didn't stop Franklin's discovery.

WIKIPEDIA CREATIVE COMMONS

Above: Franklin at work later in her career at Birkbeck, University of London. Below: Taken under Franklin's supervision by Raymond Gosling, "Photo 51" famously betrays the helical structure of DNA.



WIKIPEDIA CREATIVE COMMONS

What was that?
In September 1951, just eight months into her job, Franklin found via X-ray crystallography that there are two types of DNA, a drier form she called A-DNA, and a wetter form she called B-DNA. The discovery explained why previous diffraction imagery was blurry – because it had depicted mixes of both types. It caught the eye of a rival pair of DNA researchers at the University of Cambridge, Francis Crick and James Watson, who tried – and failed – to make a scale 3D model of DNA structure based on the new results.

Why didn't Franklin figure out the structure?
She nearly did. In May 1952, under Franklin's supervision, Gosling took a diffraction image of B-DNA – the now-famous "photo 51" (below left) – that clearly depicted a helical structure. Franklin herself had also determined that the structure of DNA was a type of "face-centered monoclinic", as she wrote in a report at the end of the year for the UK's Medical Research Council (MRC). Due to her fastidious nature, however, she was intent on finding out why the diffraction images of A-DNA were so different to those of B-DNA, and never fully turned her attention to the overall structural question. It was left primarily to Watson and Crick to find, in March 1953, that DNA is a double helix, a discovery for which they and Wilkins shared the 1962 Nobel Prize in Medicine, four years after Franklin's death.

Have her contributions been overlooked?
Nobels are not awarded posthumously. Nevertheless, there has been a growing feeling among subsequent generations of crystallographers that Franklin's data has not been given the acknowledgement that it deserves: controversially, both photo 51 and the MRC report containing her structural calculations were shown to Watson and Crick without her knowledge. In recent years, therefore, she has been honoured by more and more awards, memorials and scientific institutes; last year, the University of Portsmouth in the UK renamed one of its halls from James Watson to Rosalind Franklin. Meanwhile, young scientists are inspired by her resolve, according to Elspeth Garman, a crystallographer at the University of Oxford in the UK who gave a lecture about Franklin at the ESRF User Meeting this year. "When it came to the science," says Garman, "Franklin always followed her heart." ■

Jon Cartwright

DATES FOR THE DIARY

• 25 August 2020	Restart of user operation
• 25 August 2020 – 28 March 2021	2020-II scheduling period
• 10 September 2020	Next proposal deadline
• 29 March – 28 July 2021	2021-I scheduling period
• 15 January 2021	Next long-term proposal deadline
• 8–10 February 2021	User Meeting

At all times there will be access to all structural biology beamlines and the CM01 cryo-EM facility via the rolling proposal access mechanism.

KEY CONTACTS

Users with questions, comments and ideas are welcome to contact the User Organisation Committee (UOC) at any time. Representatives of each scientific community and their contact details can be found at www.esrf.eu/UOC. ESRF contacts: www.esrf.eu/contacts.

Right: Michela Brunelli, chair of the UOC.

NEWS FROM THE BEAMLINES

The ESRF will restart User Service Mode (USM) operation on 25 August this year with the new EBS storage ring and with a maximum number of beamlines. The EBS source, the brightest synchrotron source ever built, is fully commissioned and the USM design parameters have been obtained five months ahead of schedule. The restart will take place at the planned date despite unprecedented constraints imposed by the COVID-19 pandemic.

Beamline restart

In May 2020, activities on beamline restart and commissioning were resumed after a two-month closure (16 March – 11 May) of the ESRF site. The implementation of a gradual restart, limiting the number of people simultaneously present on site, will require adapting to a slower pace compared with the initial planning. In particular, the restart of some ESRF public beamlines and some of the bending magnet beamlines operated by the CRGs will not be possible for 25 August, due to delays in the delivery of critical components or delayed commissioning activities.

The guiding objective of the ESRF in establishing the new planning, while respecting the safety procedures required to cope with the COVID-19 pandemic, is to provide maximum service to the user community with the new EBS starting from 25 August 2020, as originally scheduled.

User experiments

Operational constraints linked to the COVID-19 pandemic are expected for ESRF staff and users alike. For example, impact on access to the ESRF site and on the operation of beamlines and facilities may be determined by:

- travel restrictions for users due to regulations adopted by authorities, the ESRF and/or the user's institution;
- reduced ESRF staff presence at ESRF facilities (including CRG beamlines) due to social-distancing requirements;
- delayed delivery of instrumentation and components required for beamline operation.

For these reasons, the ESRF management has decided to give preference to experiments that can be carried out on samples that can be made available to the relevant ESRF beamline staff and through remote communication between users and the local contact, i.e. to the highest-ranked proposals for sample mail-in and user remote-access experiments.

The implementation of such a plan entails a significant increase in responsibilities and workload for the ESRF beamline staff, which may be partly mitigated by the allocation of additional shifts beyond the request of the users in their proposals.

Proposal selection

Under normal operation conditions, the selection of proposals for beam-time allocation is the task of the Beam Time Allocation Panels (BTAPs), with allocation of beam time based on (i) the scientific ranking attributed to the proposals, (ii) the number of available shifts on each beamline, and (iii) the technical feasibility of the project. Further minor adjustments are introduced by ESRF management to optimise fair scientific return to our member and associate countries.

The BTAP meetings took place over three days at the end of April, when 120 members of 12 ESRF panels met via videoconference to discuss the proposals submitted for the March 2020 deadline. At that time, France was in lockdown and the ESRF site was closed, and therefore it was not possible to have clear and precise numbers and answers for points (ii) and (iii) above. The BTAPs were invited to provide their scientific ranking, as usual. In parallel, the ESRF has been collecting information from all beamlines on the expected capabilities for the 2020-II scheduling period, including the estimated number of shifts available, the suitability for mail-in/remote access to the proposed experiments, and the consent of the users to perform their proposed experiments remotely.

This information, combined with the BTAPs' evaluation of the proposals, will allow ESRF management to identify the proposals to which 2020-II beam time will be allocated.

To increase the amount of beam time available in 2020-II – considering the record-breaking number of proposals and the expected reduction in the number of operational beamlines – the ESRF has decided to extended the 2020-II scheduling period by one month, to 28 March 2021. Moreover, in view of privileging mail-in and remote-access experiments during this 2020-II period, the ESRF will reimburse users for the costs of shipping their samples to the ESRF.

Further information: tinyurl.com/BTAPs-2020-II.

Computing and infrastructure upgrades

A number of computing and infrastructure upgrades are being rolled out on all ESRF beamlines. In particular for the users, these include the move to a single sign-on (www.esrf.eu/SSO) for many aspects of ESRF activities (user portal, events registration, access to online catalogues such as ICAT and ISPyB), and the full implementation of the data policy (www.esrf.eu/datapolicy) on many beamlines, including assignment of DOIs (www.esrf.eu/DOI) to experiment data and the recording of experiment data and metadata to the ICAT catalogue (https://data.esrf.fr).

Beamlines are also making the transfer of their beamline control software from SPEC to the new BeamLine Instrumentation Support Software, BLISS (www.esrf.eu/BLISS), which provides a global approach to running synchrotron experiments that require the synchronous control of motors, detectors and various acquisition devices thanks to hardware integration, Python sequences and an advanced scanning engine. ■

The fight agains

Armed with a new, extremely brilliant source, the ESRF is joining the global effort to understand and overcome the COVID-19 outbreak.

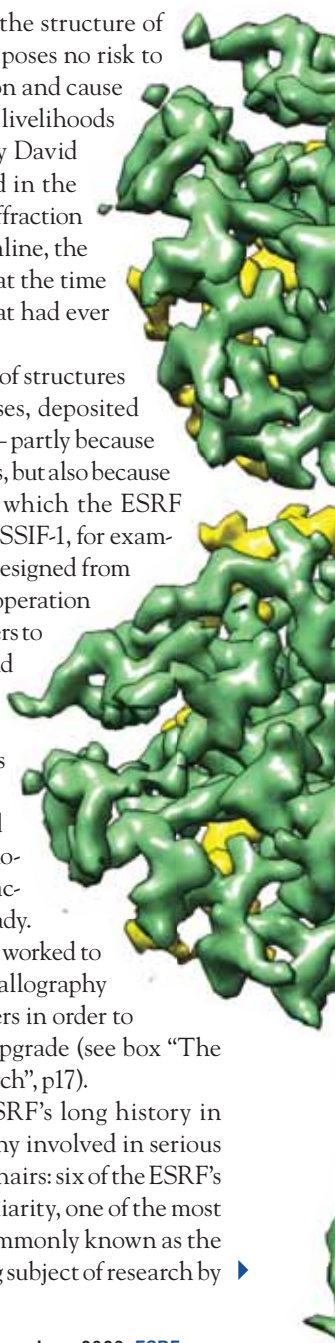
THESE days, as everyone is now unfortunately aware, viruses can spread fast. Just three months after Chinese authorities first alerted the World Health Organization (WHO) to the the presence of a new coronavirus in the city of Wuhan, Hubei province, at the end of last year, there was scarcely a country on Earth that did not have a reported case. Compare that progress with the Black Death, which over the same timescale in 14th-century Europe spread an average distance of just a few hundred kilometres. Little wonder: back then, the fastest mode of transport was by horse. Today, a person infected with SARS-CoV-2 – the virus causing the current COVID-19 pandemic – can travel from one side of the world to the other in a matter of hours.

Fortunately, modern science is also quick to act. By 5 February, when SARS-CoV-2 was still largely confined to China, researchers using the country's Shanghai Synchrotron Radiation Facility had already managed to obtain the atomic structure of the virus's main protease and upload it to the Protein Data Bank – the principal repository for structures of biological macromolecules. Other structural studies have swiftly followed. In April, representatives of X-ray science facilities, including the ESRF–EBS, assembled via video link for the SR20 Summit to share their responses to the COVID-19 pandemic so far. The result: a five-point action plan to co-ordinate strategy (see News, p7).

Major players

Like fellow light sources, the upgraded ESRF–EBS is providing exceptional access to its facilities to researchers who can pursue studies related to COVID-19. Such facilities include many world-class macromolecular-crystallography and bio-imaging beamlines, a cryo-electron microscopy (cryo-EM) facility, the collaborative environment of the Partnership for Structural Biology (PSB) – consisting of the European Molecular Biology Laboratory (EMBL) Grenoble Outstation, the Institut Laue-Langevin and the Institut de Biologie Structurale on the EPN campus – and, of course, a new, extremely brilliant X-ray source. All these mean that the ESRF will be a key player in the fight against the pandemic, according to the ESRF director of research for life sciences, Jean Susini. "I have no doubt that the ESRF is ideally placed to have a major contribution to COVID-19 research, in the near- and mid-future," he says.

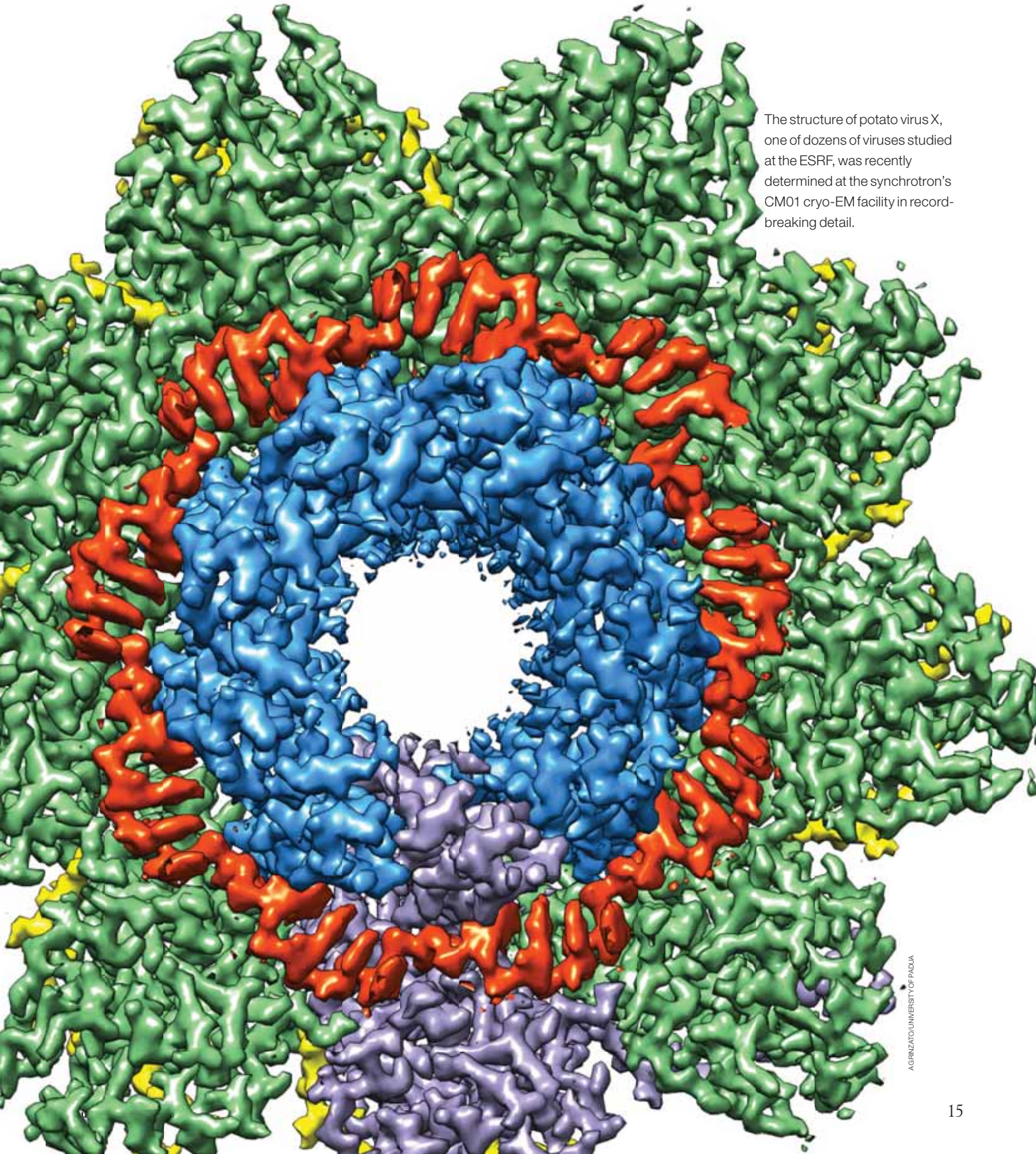
Back in the early 1990s, structure-based drug design was still in its infancy, with just a few dozen viral structures being deposited in the Protein Data Bank every year. The opening of the ESRF as the world's first third-generation synchrotron was a big step in the field's progression. Suddenly, macromolecular crystallography using very high brilliance X-rays made it possible to obtain viral structures that would otherwise have been too time-consuming to contemplate – for example the structure of bluetongue virus, which although poses no risk to humans can reduce milk production and cause infertility in cattle, decimating the livelihoods of farmers. Determined in 1998 by David Stuart of the University of Oxford in the UK and colleagues, and based on diffraction data taken at the ESRF's ID02 beamline, the bluetongue virus core particle was at the time the biggest molecular structure that had ever been recorded in such high detail.



Today, there are many hundreds of structures of viral proteins, and indeed viruses, deposited annually in the Protein Data Bank – partly because of the greater number of light sources, but also because of improved techniques, some of which the ESRF helped to pioneer. The ESRF's MASSIF-1, for example, was the world's first beamline designed from the ground up for fully automated operation when it opened in 2014, allowing users to sift through masses of samples to find successful instances of drugs binding to target proteins. The ESRF was also one of the first synchrotrons to offer a mail-in service where users need not even visit the facility, and can instead post samples to their chosen beamline and download diffraction and cryo-EM data when it is ready. Most recently, ESRF scientists have worked to develop variants of the serial crystallography practised at X-ray-free electron lasers in order to make best use of the ESRF–EBS upgrade (see box "The EBS: radiation-proofing virus research", p17).

All of this has added to the ESRF's long history in the study of viruses, including many involved in serious human epidemics (see "In the cross hairs: six of the ESRF's viral targets", p16). Despite its familiarity, one of the most dangerous of these is influenza (commonly known as the flu), which has been a long-running subject of research by

st coronavirus



The structure of potato virus X, one of dozens of viruses studied at the ESRF, was recently determined at the synchrotron's CM01 cryo-EM facility in record-breaking detail.

A GRINZATO/UNIVERSITY OF PADUA

IN THE CROSS HAIRS: SOME OF THE ESRF'S VIRAL TARGETS

SARS-CoV-2

SARS-CoV-2, the virus at the centre of the current COVID-19 pandemic, has already killed hundreds of thousands of people, and infected millions more. Building on its long-term contributions to studies of the coronavirus family, the ESRF is already involved with (at the time of publication) five studies investigating either SARS-CoV-2 or COVID-19. Although these studies are mostly making use of the ESRF's world-class structural biology beamlines and its CM01 cryo-electron microscopy facility, they are also employing the bio-imaging beamline, BM05 (News, p7).

Influenza

Every year, the flu kills in the region of 500,000 people, and novel forms, such as the 1918 Spanish flu, can be far deadlier. Stephen Cusack, the head of the European Molecular Biology Laboratory Grenoble Outstation, has been studying the virus for most of his career, and most recently employed cryo-EM in conjunction with X-ray crystallography at the ESRF to capture its polymerase in different stages to see how it transcribes, step by step. He believes that a detailed understanding of the mechanism such as this could be important in the search for new influenza drugs.

HIV

After Spanish flu, HIV was the most deadly pandemic of the last century, with a death toll currently standing at about 32 million. Last year, led by the Institut de Biologie Structurale on the EPN campus, users on the ESRF ID30A, ID30B and ID23-1 beamlines studied a novel "broadly neutralising antibody" (bnAb) in complex with the envelope glycoprotein epitope of the most common type of HIV, HIV-1. The structures showed that the bnAb, known as LN01, was highly effective against HIV-1, and could form the basis of a new vaccine (*Cell Host Microbe* **26** 623).

Dengue virus

Dengue fever leads to rashes, headaches, vomiting and, for some 40,000 people a year, death. Unfortunately, a recently commercialised vaccine has not been wholly effective. In 2015, however, using data from the ESRF's ID23-2 and ID29 beamlines, as well as from the SOLEIL synchrotron in France, Félix Ray at the Institut Pasteur in Paris and colleagues discovered a structural "Achilles' heel", present in all four known strains of the virus, to which human antibodies can bind (*Nature* **520** 109). Other scientists are hoping to develop an alternative vaccine for Dengue fever based on the results.

Norovirus

A highly contagious stomach bug, norovirus is especially dangerous for babies, who can quickly become dehydrated. However, there are few known ways to prevent infections. In 2016, based on data collected at the ESRF's ID23-1, ID30B and automated MASSIF-1 beamlines, Grant Hansman of the University of Heidelberg in Germany and colleagues found that "oligosaccharides" naturally present in breast milk appear to prevent infection, by blocking the virus from attaching to cellular ligands. Such oligosaccharides have the potential to serve as norovirus anti-virals (*J. Virol.* **90** 4843).

Hepatitis

Some 71 million people worldwide live with Hepatitis C, a serious liver disease, and every year some 350,000 die from it. While no vaccine exists, there is hope that drugs could target part of its structure known as the "internal ribosome entry site" (IRES). In 2013, solution scattering at the ESRF ID02 and former ID14-3 beamlines helped Julien Pérard, then at the University Grenoble Alpes, and colleagues to determine the structure of the entire IRES, giving them insights into how it changes shape during the virus's life cycle (*Nat. Commun.* **4** 1612).

STEF CANDÉ

Eaazhisai Kandiah, ESRF beamline scientist at the CM01 cryo-electron microscope, has a grant to study SARS-CoV-2, the virus behind the COVID-19 pandemic.

Stephen Cusack, head of the EMBL Grenoble Outstation. Seasonal flu alone kills up to half a million, and sometimes more, of the world's population every year, but the virus can be far worse when it emerges in a novel form, such as the Spanish Flu of 1918, which is believed to have killed up to 100 million people worldwide. There have been three further influenza pandemics since.

Cusack's work primarily focuses on influenza RNA polymerase, the molecular machine behind the virus's transcription and replication. Like other viruses, influenza has to produce a code for the production of its proteins known as messenger RNA (mRNA) and this should match the requirements for normal cellular mRNA. Some viruses have their own enzymes to synthesise this matching mRNA from scratch; influenza does not, and instead steals a "cap" of the host-cell RNA as a primer. Biochemists knew of this influenza "cap snatching" for many years, but in 2014 Cusack's group made use of the ESRF's high-intensity X-ray beamlines and state-of-the-art detectors to understand its basic mechanism at an atomic level (*Nature* **516** 361).

Cusack's latest research involves the use of another new tool in structural biology: cryo-EM. In close collaboration with the other three partners in the PSB, the ESRF cryo-EM "beamline" (CM01) was commissioned in 2017 and has proved highly successful, with one study this year setting a resolution record (2.2 Å) for the study of a flexible, filamentous virus – in this case potato virus X,

THE EBS: RADIATION-PROOFING VIRUS RESEARCH

STEF CANDÉ

The ESRF has pioneered multiple tools in structural biology (see main text), and now it is actively contributing to the development of another as part of the EBS upgrade: synchrotron serial crystallography (SSX). Already a technique used at X-ray free electron laser sources, serial crystallography involves taking diffraction data from hundreds, if not thousands of biological microcrystals in order to assemble a complete dataset. The process was designed to avoid the problem of obtaining datasets from single crystals, which can be damaged by X-ray radiation, but there are other benefits, too. For instance, data can be collected at room temperature rather than the usual cryogenic temperatures, which sometimes obscure important structural conformations. Even more excitingly, time-resolved experiments at sub-millisecond resolutions can be carried out.

Led by Daniel de Sanctis, an ESRF team is rebuilding the former ID29 beamline as an SSX beamline known as EBSL8. Maximising the brilliance available from the EBS upgrade, explains de Sanctis, it will allow the study of crystals just a few micrometers in size at room temperature, and perform dynamical studies to observe the movement of functional groups. That will make it possible to understand their molecular mechanisms and develop new drug compounds, he adds.

which affects various crops of the nightshade family (*Nat. Chem. Biol.* doi: s41589-020-0502-4). For Cusack and his colleagues, cryo-EM was the high-resolution, high-speed tool that, in combination with results obtained from X-ray crystallography also carried out at the ESRF, enabled them to snapshot different stages of the entire flu polymerase transcription process. The effect was to create a molecular movie that could potentially expose weaknesses targetable by drugs. "If you can stop this mechanism from working, you can stop the virus from replicating," Cusack says.

Main objective

Now, of course, everyone's focus is on the coronavirus SARS-CoV-2, and whether it too can be prevented from spreading and reinfecting. The ESRF has been involved in at least 19 published studies relating to coronaviruses: several of these have been co-authored by François Ferron at Aix-Marseille University in France, who has been coming to the ESRF for his coronavirus research for the past 12 years. He and his colleagues' most recent work concerned the coronavirus behind Middle East respiratory syndrome (MERS), which has so far killed some 800 people, mostly in the Arabian Peninsula. Drawing on crystallographic data taken on the ESRF's ID23 and BM29 beamlines, they determined the structure of part of the virus's nucleoprotein, which encapsulates and protects the viral genome. The results helped to reveal how the nucleoprotein assembles, and could contribute to the search for MERS drugs that interrupt that assembly. They could also help scientists better understand its relative, SARS-CoV-2 (*Acta Crystallogra.* **D75** 8)

"The facilities available at the ESRF have always been top of the line," says Ferron, who will be applying for exceptional access to the ERSF to continue his coronavirus research. "It's too early to say for sure how much the EBS upgrade will help us, but we are looking forward to trying these new developments in time-resolved X-ray scattering, which will certainly help us to understand catalytic reactions and their impact on structures."

Already five COVID-19 projects are underway at the ESRF, including one led by CM01 scientist Eaazhisai Kandiah, who has won backing from the French ANR funding agency for a SARS-CoV-2 research project involving potential therapeutic targets, crucial to the life-cycle of the virus. Gordon Leonard, the ESRF's structural biology group leader, is expecting the ESRF to be involved in many more studies in the future. "The recent COVID-19 outbreak has led to an acceleration in research into SARS-CoV2 and other coronaviruses," he says. "Structural biology at the ESRF and elsewhere can play a leading role in the search for vaccines and, in the longer term, the development of antiviral drugs – both against SARS-CoV-2 and novel viruses yet to be discovered." ■

"The ESRF can play a leading role in the search for vaccines"

Jon Cartwright

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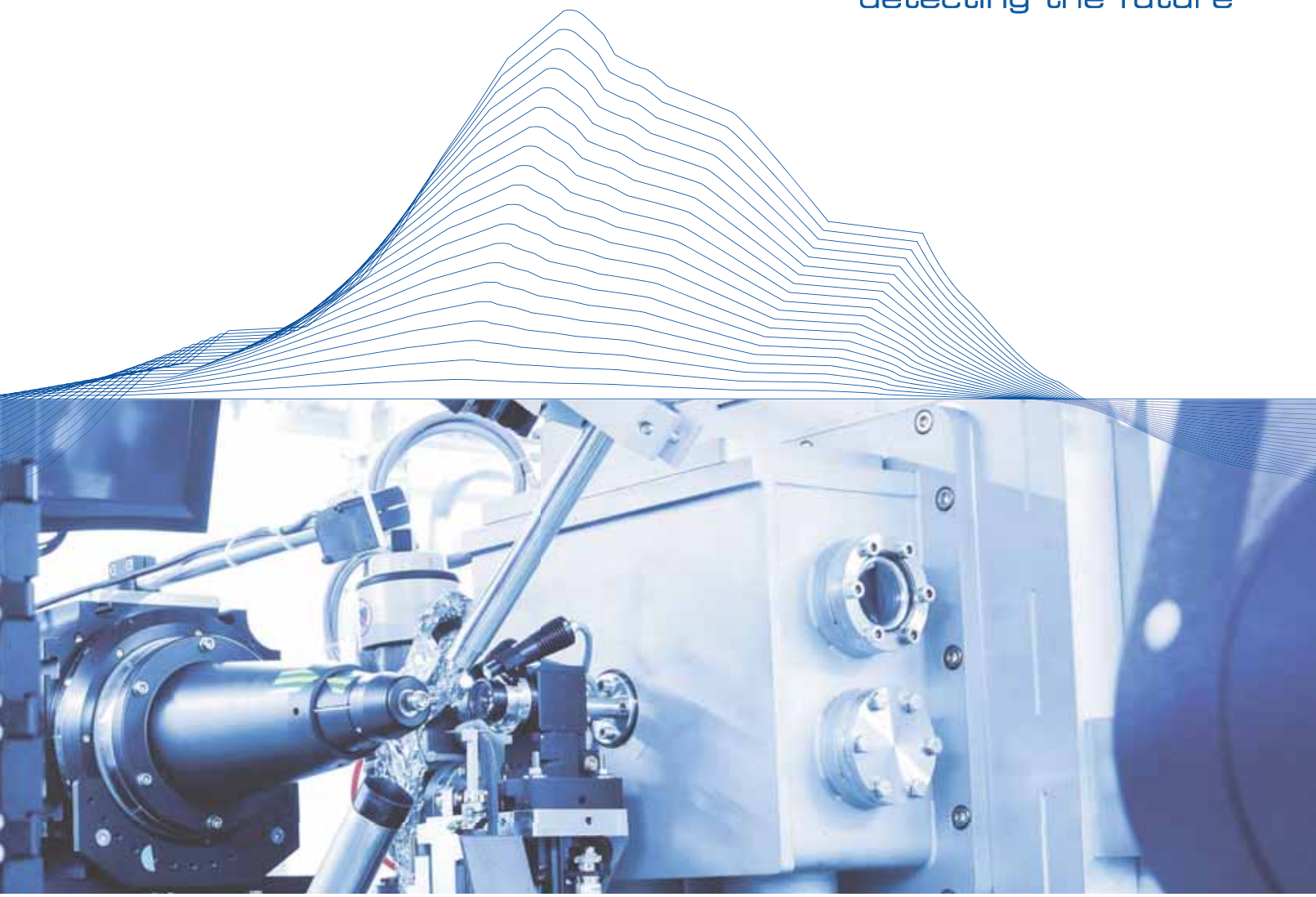

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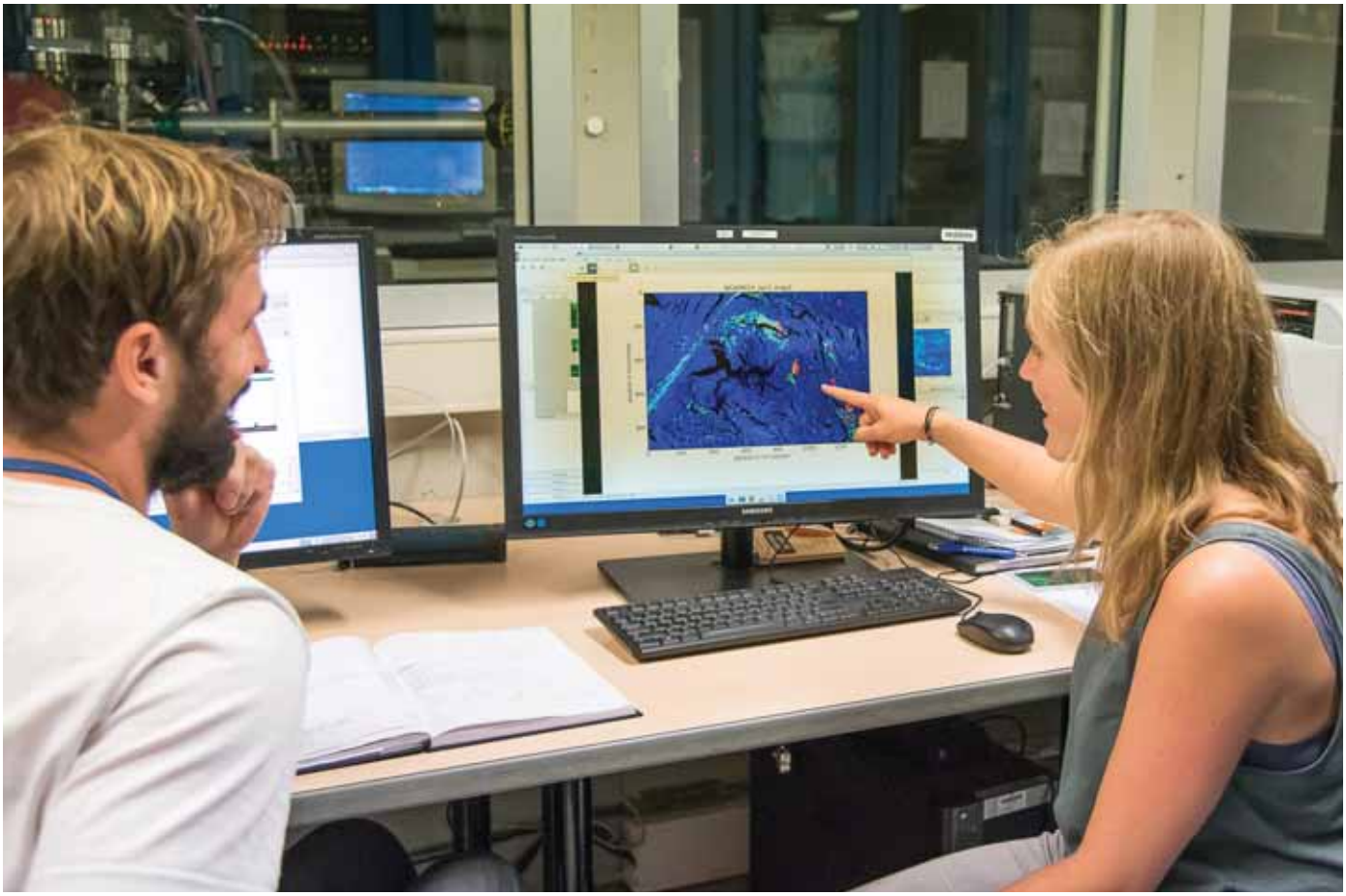

P JAYET/ESRF

The cultivation of InnovaXN

The first students are being recruited for a new doctoral training programme that pairs industry with X-ray and neutron science. *ESRFnews* explores some of the projects in store.

FEW people like to watch paint dry. Yet many students applying to study within the InnovaXN programme are hoping to do just that – because the research will be far from tedious. Working on ID21, an ESRF beamline that has already made pioneering contributions to the science of cultural heritage, the student will collaborate with leading industry and academic experts to better understand the chemicals that affect the drying of paint. In time, the results could improve the conservation of valuable works of art, as well as lead to the design of new, safer paints and coatings. "This will be a unique chance to look at paints with synchrotron techniques," says Jitte Flapper of AkzoNobel, a multinational coatings manufacturer and one of the project's partners.

Launched in October last year, InnovaXN (pronounced "innovation") is a doctoral training programme that matches synchrotron X-ray and neutron research to the

needs of pre-competitive European industry R&D. The idea was formed jointly between the ESRF and the Institut Laue-Langevin (ILL) on the EPN campus, and according to Ed Mitchell, the ESRF head of business development, it has benefits for everyone involved. It gives companies the opportunity to form deeper and longer-lasting relationships with facilities such as the ESRF and ILL, based on research needs and the joint supervision of the students. Meanwhile, he adds, the students themselves have the opportunity to be supervised not just by academic institutions, but by companies and research facilities too.

"They're going to get a very rounded experience" says Jean Susini, the ESRF director of research for life sciences and the co-director of InnovaXN. "By the end of their PhDs, they will have worked with world-class instrumentation on projects with real-world commercial significance. They will have experienced both industry and academic worlds, and be equipped with training to work at the hot spot where industry and academia come together to solve our future challenges."

BACK TO SCHOOL

P. JAYET/ESRF

PhD students are central to life at the ESRF – be they supervised internally (for example, under the InnovaXN programme), or by other users whose groups come to the beamlines. Now, through InnovaXN, the ESRF is reinforcing its "Graduate School" for all ESRF-supervised students with a stronger framework and higher visibility. Run by ESRF scientists Patrick Bruno and Montserrat Soler-López, the new Graduate School will help to provide the young researchers with a broad skill set and diverse scientific experience. Details will be confirmed in coming months.

Numerous applications

The programme is partially backed by the European Commission as part of its Marie Skłodowska-Curie Actions (MSCAs); as an MSCA "COFUND", the Commission supplies half the cost while the other half is supplied mostly by the ESRF and the ILL, with support from the industrial and academic partners. It also ties in with a revamp of the ESRF Graduate School (see "Back to school", above). At present, with help from an independent advisory board of 30 international experts, the supervisors are recruiting the students from some 1200 applications to work on the first 20 PhD thesis projects, which range from agriculture to nanotechnology, and from consumer products to sustainable engineering.

Flapper, the industrial supervisor for the ID21 project about paint drying, is looking forward to the start of the research in September. He explains how the drying of paint is assisted by metal-containing substances, such as metal "soaps", and that the actions of these do not stop after the initial drying. As a result, some paints will peel or crack over time, a process that AkzoNobel is obviously interested in tackling. But Flapper can see the potential benefits of the research outside of industry, too, in the preservation of oil paintings; indeed, one of the other supervisors for the project is based at the Rijksmuseum in Amsterdam, the Netherlands. "The InnovaXN programme gives us access to word-class facilities – and scientists – which would normally not be so easily accessible," says Flapper. "It also gives us a chance to build and expand on a partnership with the Rijksmuseum, so that we can create better products and they can preserve their paintings for future generations to enjoy. I enjoy working with top scientists from various areas of chemistry – discussions with them challenge me to think about our technologies from different perspectives and sharpen my views."

Bruno Huet of LafargeHolcim, a multinational manufacturer of building materials, also sees the benefit of bringing together different expertise, for companies and students. He is co-supervising a project on the ILL D50 and the ESRF ID19 beamlines to investigate the structure of new, ecologically friendly binders for concrete that actually absorb carbon dioxide during the hardening process. He says this is an important topic for LafargeHolcim – which is trying to help reduce the 5% of total man-made global carbon dioxide emissions due to cement production – as well as for the student, who will have the "unique opportunity to support excellence in research and promote a European culture". The InnovaXN programme, he concludes, "is an excellent example of a European success: bringing a variety of priority topics, nations and institutions from academia to industry together to develop the European economy".

> "They're going to get a very rounded experience"

The InnovaXN projects have been chosen carefully to span all research disciplines. In the sphere of health, for example, the ESRF's Montserrat Soler-López will be supervising a student alongside Immusol, a French pharmaceutical company, and as well as the University of Rennes and the University of Grenoble Alpes in France, to investigate how enzymes known as tyrosinases produce the skin pigment melanin, which is involved in melanogenic diseases and pigmentation disorders. "We believe that our project will have a great impact in the areas of skin biology research and drug discovery," she says.

Indeed, everyone working on the programme is excited to get the students in and see what the young minds come up with. Jonathan Sharman, a researcher at the multinational chemical science company Johnson Matthey who is supervising a project on the degradation of catalysts in fuel cells at the ESRF and the ILL, believes that much of the value for his company is in the training of junior scientists. "Our company is motivated by inspiring science!" he says. ■

Jon Cartwright

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Sanofi troubleshoots MS drug

Multinational pharma comes to MASSIF-1 to find reason for side effects.

Natalizumab is administered to many people suffering from multiple sclerosis (MS), and yet about 6% have to discontinue it due to side effects. Now, however, scientists from the research and development department of the French multinational pharmaceutical company Sanofi and elsewhere have come to the ESRF to understand why these side effects occur. The results could help in the design of new antibodies for MS, as well as other autoimmune diseases and cancer.

Millions of people in the world have MS, a disease involving a gradual deterioration of the nervous system. It is believed to be caused when the immune system's T cells, which usually kill viruses, bacteria and other foreign objects, mistakenly begin to attack nerve cells – specifically their covering, or "myelin" – in the brain and the spinal cord. One treatment, natalizumab, is a therapeutic antibody that attempts to bind to the T cells and stop them well before the brain or spinal cord, at the intestinal lining and the blood–brain barrier. It is often highly effective, but its effectiveness is sometimes reduced by side effects ranging from mild headaches and itchy skin to severe anaphylactic shocks. The cause of these side effects is that the body's own immune system begins to attack natalizumab, but exactly why it does this has been unclear.

Fully automated

In collaboration with scientists at the Institute for Research in Biomedecine in Bellinzona, Switzerland, researchers at Sanofi came to the ESRF's MASSIF-1 beamline with samples of stable complexes of natalizumab and anti-natalizumab antibodies that had been isolated and crystallised, having been derived from two patients. Using the fully automated beamline, the researchers obtained structures of the complexes at a resolution of 2.8 Å or better.

The structures exposed the interaction of natalizumab and the patient antibodies, and the features of the binding region (figure 1).

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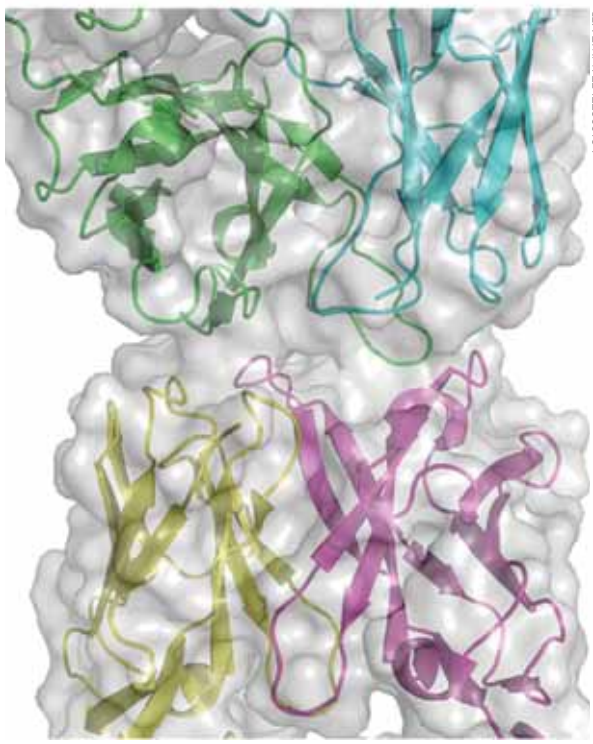


A CASSOTTA ET AL/*NAT. MED.*

A disease that affects millions the world over, multiple sclerosis is a gradual deterioration of the nervous system, believed to be due to the body's own immune system attacking nerve cells. In addition to exercising, sufferers can be prescribed the drug natalizumab, which interrupts this immune-system response.

Figure 1 The structure of the drug natalizumab (yellow and pink strands) bound to an antibody (green and blue strands) taken from a patient is helping Sanofi researchers to develop new drugs for multiple sclerosis.

The researchers found that each of the two antibodies tested bound to roughly the same part of the drug's surface, albeit with certain differences that helped to explain discrepancies in binding affinity and side effects experienced by the two patients. Taken together with data from computer simulations and peptidomics – the analysis of all peptides in the sample – the results identified the basis of a collaboration among T and B immune-system cells that leads to the natalizumab resistance (*Nat. Med.* **25** 1402).

Vincent Mikol of Sanofi says he and his colleagues have already "de-immunised" natalizumab, and confirmed in *ex vivo* tests that the variant antibody does not elicit an immune response. "Improved tolerability remains to be shown in clinical trials," he adds. ■

Speaking for many

Caterina Biscari, director of ALBA and head of the LEAPS partnership of light sources, believes that there are lessons to be learned from the coronavirus pandemic.

As an accelerator physicist, Caterina Biscari knows how hard it is to commission a new synchrotron. It is no surprise, therefore, that she was keeping an avid eye on the progress of the ESRF's EBS upgrade, from the installation of the new storage ring through to its ultra-fast commissioning between November 2019 and March this year. "For us on the outside, the EBS was considered very difficult," she says. "The deadline, the physical constraints – both of these were a challenge. So the fact that it has obtained the nominal beam parameters in such a short space of time – it's incredible. It sets an example to all the other facilities planning to upgrade to fourth-generation sources."

Biscari's experience in this area stems primarily from the electron-positron collider DAFNE at the INFN Frascati National Laboratory in Italy, which she saw from the concept stage in the 1990s through to operation and beyond, contributing to its design, optimisation and management. Given the collider's relatively small scale, Biscari had a complete overview of its workings and relevance to high-energy physics, which on reflection she calls a "privilege". Come 2009 however, she was collaborating on a project at the complete opposite end of science: the CNAO centre in Pavia, only the second facility in Europe to offer hadron therapy to cancer sufferers. Thus she has been involved with physics from the most fundamental to the most applied – a cross-spectrum influence that she has continued since 2012 as director of the ALBA third-generation synchrotron light source at the Cerdanyola del Vallès near Barcelona, Spain. "Our goal at ALBA has been to develop the facility and its user community, expanding the beamline portfolio while consolidating the operation," she says. "Thanks to the bright and committed staff, we've been doing very well."

This year, Biscari finds herself with even more responsibility, having taken over the baton from Helmut Dosch as the chair of the League of European Accelerator-based Photon Sources (LEAPS), a partnership of 16 light sources across Europe, including the ESRF. "There has always been collaboration, but LEAPS gives us the opportunity to know one another better, to share what we're doing." LEAPS intends to offer a "common vision" of using scientific excellence to solve global challenges – and now, of course, there is one global challenge everyone is talking about. "Everybody is looking at what we can do with COVID-19 research," she says. "Europe has the capacity to develop a vaccine, but whoever is first, we should be collaborating with them to test it." The LEAPS partners, she explains, are openly sharing the total capacity of experimental techniques for researchers studying the virus and publishing the first experimental results.

Taking advantage

What about the world after COVID-19 – can synchrotron research continue as before? "Travelling will certainly not be as easy, so we're obliged to consider alternative ways of working," she says. "More teleworking, facilities that are better connected. Personally, before all this started I was travelling eight, ten times a month for meetings. Now I'm doing everything from home." She believes that some of these changes undertaken to deal with the pandemic are worth taking on board to address climate change. While working from home full time is not realistic nor desirable, "something in the middle" could work, she says. "We need to take advantage of what we're learning now for our future development." ■

Jon Cartwright

ANA MARTÍNEZ/ALBA

BORN: 1957, Modica, Italy.
EDUCATION: Doctorate in physics, University of Naples (1982).
CAREER: Fellow, CERN (1982–1985); researcher, INFN–LNF (1985–2012); director, ALBA (2012–); chair, LEAPS (2020).

"Europe has the capacity to develop a vaccine, but whoever is first, we should be collaborating with them to test it"

Life without X-rays

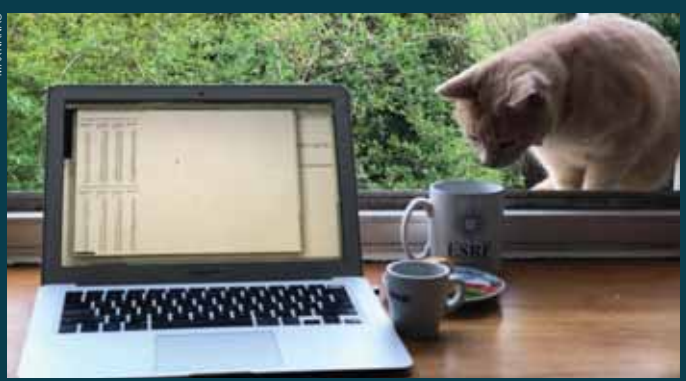
ESRF staff and users document their lives away from the synchrotron on social media, under the hashtag #ESRFhomeoffice.

CRISTINA GONZALEZ TORRES

DANIELE DE SANCTIS

MONTSERRAT SOLER-LÓPEZ

MAX NANAO



(Clockwise from top left) Cristina Gonzalez Torres of the survey group teaches her son to precisely align beamlines; Daniele de Sanctis of the ID29/EBSL8 beamline discovers that his children have kindly upgraded his laptop to the latest cardboard model; Montserrat Soler-López of the structural biology group catches up on some reading; and Max Nanao of the ID23-2 beamline leaves his home desk for one ill-judged second.

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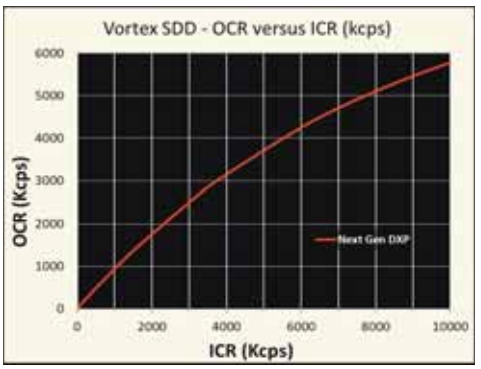

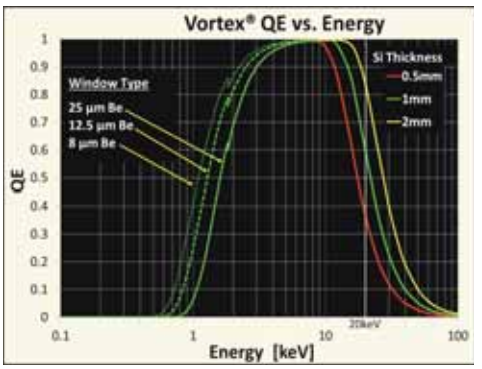

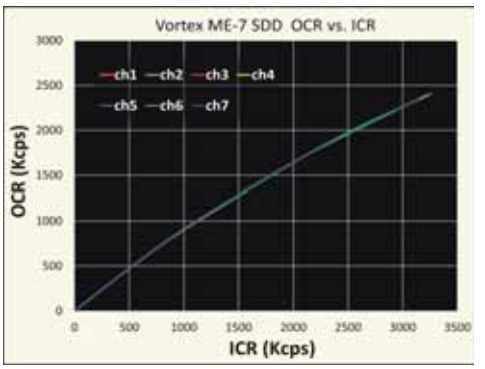

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