Review of the impacts of EMBL experimental services

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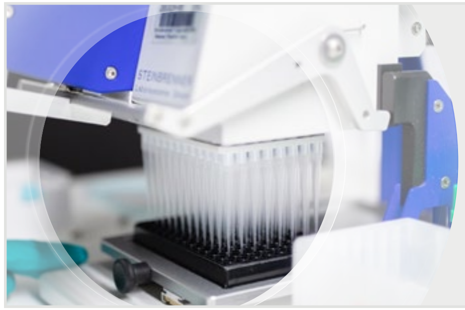
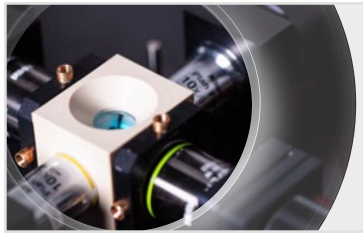




Executive Summary

Executive summary

The European Molecular Biology Laboratory (EMBL) offers a unique portfolio of integrated scientific services that enable external users from universities, institutes, companies, and third-sector organisations to access a broad range of world-class infrastructures through a single Europe-wide partner. EMBL experimental services encompass more than 20 infrastructures and facilities in the fields of structural biology, imaging, genomics, proteomics, metabolomics, in vivo gene editing, and chemical biology. Combined with EMBL facility scientists' expertise and support, these services enable fundamental discoveries in molecular biology to tackle global societal challenges.

This report presents the findings from a review of the impacts of EMBL experimental services, which was undertaken by Technopolis in 2021. This report set out to understand the scientific, technological, societal, and economic benefits that EMBL experimental services have created for the research community and EMBL member states, using an external user survey (targeting academic users and industry users) and case study methodology.

Summary of the main findings

EMBL experimental services are critical for research

Almost all academic users judged EMBL experimental services to be critical for their research and reported that they anticipate using EMBL experimental services in the future. This attests to the high relevance and unique capabilities that EMBL experimental services offer users and to the expectation that these services will remain at the cutting edge of research infrastructures in the foreseeable future.

EMBL pioneers integrative experimental services enabling scientists to remain at the cutting edge of research

EMBL facility scientists continuously innovate new technologies and methods and provide freely accessible tools that are driven by academic users' increasingly ambitious research projects. Among the most notable methodological achievements is EMBL's contribution to the development of cryo-electron microscopy, which has brought this technique into the mainstream for the benefit of scientists around the world. EMBL facility scientists also train and support external users to exploit the ever-expanding portfolio of experimental services. As a result, external users solve challenging research questions that could not be achieved using a single approach.

EMBL experimental services enable more research that is of higher quality

The scientific expertise and collaborative nature of the end-to-end support provided by EMBL facility scientists, combined with the state-of-the art experimental services available, are highly valued by academic users. This enables them to pose novel scientific questions and conduct more complex research that they could not easily do through local or national facilities.

EMBL experimental services create wider benefits for the research ecosystem

Through generating high-quality research results at EMBL, academic users are able to find opportunities to secure additional grant funding and build international networks to position themselves at the forefront of their field of research. This in turn helps academic users to attract high-quality research staff and students and also to establish new industry contacts, forming a thriving research ecosystem. This is exemplified by an interdisciplinary research collaboration between EMBL, academia, and industry, enabled by the Nordic EMBL Partnership, which led to a recent scientific breakthrough: solving a protein structure that has now opened up new ways to develop drugs to treat schizophrenia.

Research results generated at EMBL contribute to solving global societal challenges and generating economic impact

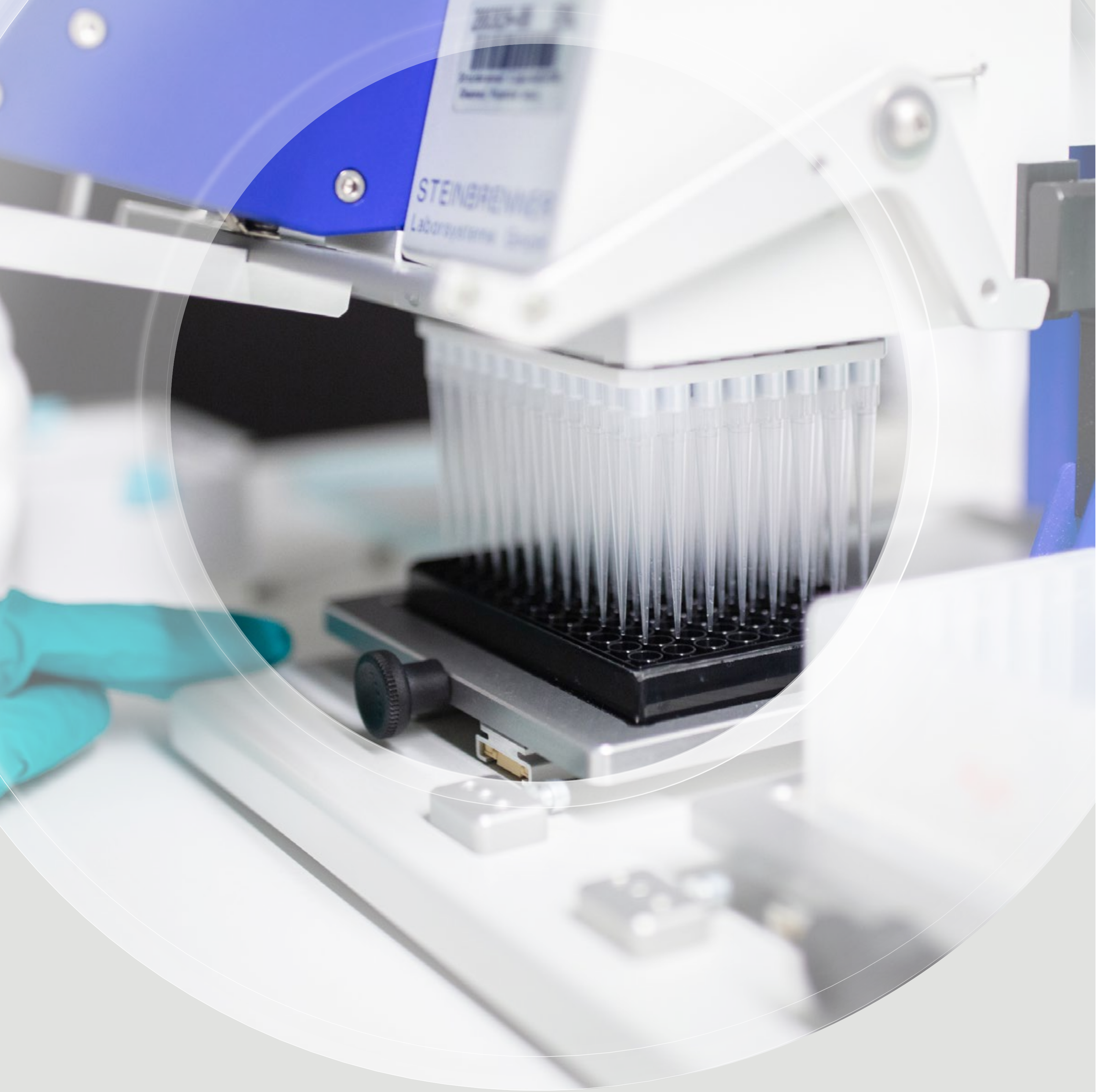
EMBL is helping academic users to deliver wider social impacts in a range of thematic areas beyond health, such as industrial biotechnology, environment and climate change, and food security and sustainable agriculture. Notably, EMBL-enabled research facilitated a new enzymatic recycling approach to lower the environmental impact of plastic waste. Academic users maximise the societal impact of their research through public engagement activities. A smaller proportion of academic users also generates economic impact through commercial activities, including research contracts and consultancy for industry and creating spin-off companies.

EMBL directly supports technology transfer and builds industry relations that maximise the impact of its experimental services

EMBL is transferring its technologies through licencing and establishing spin-offs for the benefit of the wider scientific community and society. EMBL also offers its services directly to industry users to apply technological solutions to industry-driven questions, helping them to develop new products and processes. For instance, as the COVID-19 pandemic unfolded, EMBL experimental services supported the biotech company BioNTech to develop a pioneering vaccine against COVID-19 that is now widely available around the world. The majority of industry users judged access to EMBL experimental services to be important to their companies' research and innovation activities, to advancing understanding of the properties and functions of their core technologies, to delivering insights necessary for new products or processes, and to improving their R&D productivity.

External academic users value EMBL experimental services at €17.5 million per annum

EMBL experimental services are valued at around €17.5 million per annum. This compares favourably with the €11.7 million annual operational costs associated with supporting those external users. Note that this figure likely underestimates the economic value of EMBL experimental services. Many experimental service outcomes are difficult to monetise, such as scientific publications, researcher training, or even cases where a scientist's career and core discoveries developed around research results enabled by EMBL experimental services. Experimental services contribute to the advancement of knowledge and flow of ideas, which may lead to future socioeconomic benefits only indirectly. The net present value (NPV) is defined as the current value of the future impact of EMBL experimental services. Based on the annual valuation, the NPV of EMBL experimental services over time can be calculated. Therefore, the NPV of EMBL experimental services over 30 years is around €187.5 million.



Main report

Main report

This report presents a summary of the findings from a review of the impacts of EMBL experimental services, which was undertaken in 2021. This report set out to understand the scientific, technological, societal, and economic benefits that EMBL experimental services have created for EMBL's external research community and EMBL member states.

EMBL was established as an intergovernmental organisation in 1974 by 10 founding countries. It is now funded by more than 27 member states, including much of Europe, as well as one associate member state and two prospect member states. The primary goal of EMBL is to serve its members states by enabling fundamental discoveries in molecular biology to tackle global societal challenges.

The provision of experimental services and the development of innovative technologies for molecular biology research are at the heart of EMBL's missions. EMBL's unique portfolio of integrated scientific services enables universities, institutes, companies, and third-sector organisations to access a broad range of world-class infrastructures through a single Europe-wide partner. EMBL experimental services encompass more than 20 infrastructures and facilities in the fields of structural biology, imaging, genomics, proteomics, metabolomics, in vivo gene editing, and chemical biology. Combined with EMBL facility scientists' expertise and support, these services enable fundamental discoveries in molecular biology to tackle global societal challenges.

To assess the impact of EMBL experimental services, the Technopolis study team surveyed external academic and industry users of experimental services at EMBL sites in Barcelona, Grenoble, Hamburg, Heidelberg, and Rome. A list of EMBL sites and experimental services surveyed is provided in **Appendix A**. The surveys, launched in June 2021, attracted responses from 560 academic users (from EMBL's 2,124 average annual external users between 2016 and 2020) and 20 industry users (from EMBL's 61 industry users in 2020). The summaries of the academic and industry survey analyses are presented in **Appendix B** and **Appendix C**, respectively.

In addition, using a combination of desk research and interviews, the study team developed five impact case studies, which are presented in **Appendix D** and cover academic and industry use of EMBL experimental services. The case studies serve to illustrate the types of socio-economic impacts that have been realised as a result of using one or more EMBL experimental services.

The following sections summarise the main findings from the survey analyses and case studies.

Key findings

1 EMBL experimental services are critical for research

Almost all academic users surveyed (91%) reported that being able to access EMBL experimental services was 'important', 'very important' or 'critical' for their research. Most were also clear that, although they could access similar services in another facility, non-access to EMBL experimental services would have a negative impact on their research (e.g. reductions in the quality, efficiency, or competitiveness of their research).

Almost all academic users surveyed (96%) anticipate using EMBL experimental services in the future. This attests to the high future relevance of EMBL experimental services for academic users across EMBL members states and to the expectation that the experimental services will remain at the cutting edge of research infrastructures and will not be replaced by other national or international facilities in the foreseeable future.

91 % of users

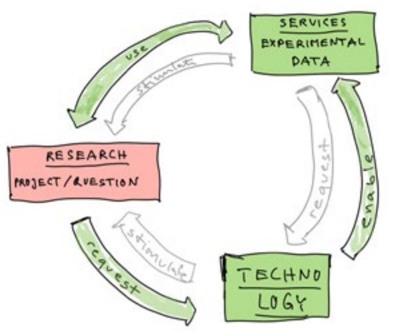
said access to EMBL experimental services was vital for their research

"EMBL provides streamlined access to state-of-the-art instruments indispensable for structural biology studies." EMBL academic user, Finland

2 EMBL pioneers integrative experimental services that enable scientists to remain at the cutting edge of research

The scope for methodological advances at EMBL is far greater than can be achieved in most national laboratories or universities. EMBL facility scientists continuously innovate new technological developments, methods, and tools, driven by external users' increasingly ambitious research projects. In addition, EMBL facility scientists train and support external users to exploit the ever-expanding portfolio of experimental services and to use them synergistically to solve research questions that could not be addressed using a single approach.

"Great facilities that provide us with cutting edge technologies to answer questions in life science." EMBL academic user, Germany



Research questions and service provision drive novel technology developments. Conversely, novel technologies or services frequently trigger new research questions and projects. Credits: Thomas Schneider/EMBL

Technological innovation and service provision are core activities for EMBL, helping to support the research community to be at the centre of scientific breakthroughs. Among the most notable methodological achievements is EMBL's contribution to the development of cryo-electron microscopy (cryo-EM), which has brought this technique into the mainstream for the benefit of scientists around the world (see Box 1 and Appendix D.1 for full case study).

Box 1: Development of cryo-electron microscopy at EMBL

Cryo-EM is a relative newcomer to structural biology. It enables researchers to study the structure and function of large molecular assemblies to understand how they form, work, and interact. Originally, electron microscopy of biological material was hampered by a range of challenges, including the lack of a suitable method for preparing biological material for measurements under the microscope while keeping them from being damaged.

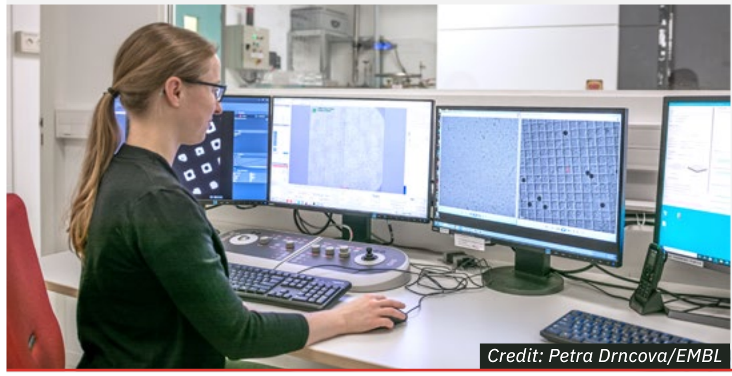
Working at EMBL in Heidelberg in the early 1980s, EMBL Group Leader Jacques Dubochet and technician Alasdair McDowall discovered that flash-freezing proteins in liquid ethane could hold them still and preserve their structure, a process called vitrification. This was a critical advance that laid the groundwork for the rise of cryo-EM and was a revolution in structural biology. In recognition of the importance of this work, Dubochet was one of three scientists awarded the 2017 Nobel Prize in Chemistry. Dubochet expressed his gratitude to EMBL by donating an official replica of his Nobel medal to the organisation, stating: "I am pleased to offer this copy of my Nobel medal to EMBL in testimony of my great thankfulness to an institution that, in my view, would deserve to be the laureate of the Prize."

Today, cryo-EM is a game-changing technique for structural biology, enabling large molecules to be imaged quickly and facilitating the development of new drugs and treatments for diseases. In recent years, the number of molecular structures determined by cryo-EM has exploded; in the past two decades, over 17,000 cryo-EM structures have been deposited (80% of which were deposited in the past five years).

Dubochet highlighted that EMBL not only enables researchers to access cryo-EM experimental services but also offers the necessary expertise to fully apply the technique to their research questions: "These methods are complicated and difficult and need to be used and exploited by many researchers. But the capability of exploiting them is by those who are at the cutting edge of cryo-EM." Cryo-EM clearly has come a long way since Dubochet and McDowall's crucial discovery at EMBL – but as McDowall noted: "Everybody has to vitrify [prepare] the sample. That's still step one."

One area in which cryo-EM has led to a step change in the level and speed of progress is in the design and development of vaccines. Scientists from around the world used cryo-EM to determine the structures of viruses such as the hepatitis B virus, hepatitis C virus, Zika virus, rhinovirus C, dengue virus, and tick-borne encephalitis virus. Most recently, cryo-EM yielded precise images of the virus that causes COVID-19, which informed the development of vaccines.

EMBL Heidelberg now hosts its state-of-the-art cryo-EM service in a new facility – the EMBL Imaging Centre – which offers a synergistic portfolio of imaging techniques to enable academic and industry users from the international research community to conduct new ground-breaking research.



Credit: Petra Drncova/EMBL

As Jacques Dubochet highlighted: "Trying to keep science open has been a major success of EMBL."

Electron Microscopy Facility manager, Sarah Schneider, at the console desk.

EMBL has also developed various freely available tools and software to enable researchers to exploit their experimental data. Among the most notable examples is ATSAS, a comprehensive suite of programs for the analysis of biological structural data (see Box 2 and Appendix D.2 for full case study).

“Without having access to EMBL experimental services, the portfolio of my research methods would be poorer.” EMBL academic user, Poland

**Box 2: Pioneering SAXS:
Using X-rays to make the invisible visible in biological solutions**

EMBL has developed data analysis tools and software for sharing and archiving structural biology data to enhance international collaborations.

One example is ATSAS, which is used to analyse and model large volumes of data generated by a technique called small-angle X-ray scattering (SAXS). Dmitri Svergun, Group Leader at EMBL Hamburg, has made significant contributions to SAXS instrumentation and related methods, analysis tools, and software over the past two decades. These contributions have unlocked the potential of using high-throughput SAXS data to derive models of 3D molecular structures to bring SAXS into the mainstream for the structural biology research community worldwide.

The comprehensive software package has been downloaded more than 100,000 times by over 18,000 unique users from over 50 countries. Svergun also coordinated an initiative to improve sharing of SAXS resources, as well as unifying data standards and guidelines across SAXS facilities and communities in Europe. SAXS data generated from different research groups around the world can now be easily shared and re-used in dedicated open-source databases such as the Small Angle Scattering Biological Data Bank (SASBDB), which is maintained by EMBL. SASBDB contains over 2,400 experimental datasets (30% produced by EMBL’s SAXS beamline), which have been used to generate over 3,500 models (80% of which used the ATSAS software).

EMBL Hamburg Beamline P12 at the Petra III storage ring

Credit: Udo Ringeisen/EMBL

3 EMBL experimental services enable more research that is of higher quality

>96 % of users

rated highly the expert support provided

“The collaborative spirit and openness of the people at EMBL have been a source of inspiration.” EMBL academic user, Greece

External users benefit from having access to high-quality, world-class instruments and analytical tools that enable them to pose novel scientific questions and conduct demanding experiments that could not easily be achieved at local or national facilities. In particular, academic users surveyed rated highly the level of sophistication of the experimental equipment (98%), the scientific data generated (97%), and the uniqueness of the services provided (59%).

External users also benefit from having access to top-quality EMBL facility scientists, who collaborate with them to solve experimental challenges, enabling more complex research questions to be addressed. This is achieved through provision of end-to-end support, from experimental design and support with operating the equipment, through to data analysis and access to data management resources. In particular, academic users surveyed rated highly the support provided on experimental design (96%), operation of experimental equipment (94%), data analysis (91%) and data storage and archiving (90%).

Most academic users (80%) surveyed indicated that using EMBL experimental services had positively impacted on the quality of their research. Furthermore, over half (53%) of academic users surveyed reported a positive impact on their research productivity, suggesting EMBL enables academic users to generate more output (publications) and higher-quality research than might have otherwise been possible.

“The support has always been excellent, from the initial application to the data acquisition and processing.” EMBL academic user, Spain

4 EMBL experimental services create wider benefits for the research ecosystem

“Using EMBL facilities not only opens up the way to large international networking [opportunities] but also helps to position scientists at the forefront of the field.” EMBL academic user, France

Over half of academic users surveyed reported that their use of EMBL experimental services to generate high-quality research results had been ‘very important’ or ‘critical’ for their subsequent ability to access grant funding (62%), establish international networks (53%) and build their personal reputation (55%), which serves to attract high-quality research staff and students.

EMBL facility scientists are deeply involved in training activities, either through direct training of external users or by organising and delivering practical courses and training activities in complex technologies and methods. The skills and expertise acquired from EMBL training opportunities can be further spread by external users indirectly to other research groups. Over half of academic users (55%) surveyed reported participating in EMBL training courses, most of whom rated the overall experience of the training as ‘good’ or ‘very good’ in terms of the relevance of the content and quality of the delivery (98%) and resulting impact on their skills (94%) and knowledge (91%). These training courses were considered particularly beneficial for students and early-career researchers.

“Hands on training on integrated approaches makes [students] more confident and has an impact on their way of thinking.” EMBL external user, Greece

Around one-third of academic users surveyed (32%) reported that their use of EMBL experimental services has had a positive impact on attracting industry contacts. This suggests EMBL experimental services is facilitating a higher level of interactions among public researchers and industry – scientific services companies and research-intensive businesses – than would be the case otherwise, potentially helping to shift the focus of basic research to applied science, as well as boosting socially beneficial knowledge spillovers. An example of how EMBL experimental services have facilitated collaboration between industry and academia to generate industry-relevant research for drug discovery is presented in Box 3 (see Appendix D.3 for full case study).

Box 3: EMBL enables academia and industry to find new avenues for developing drugs to treat psychiatric disorders

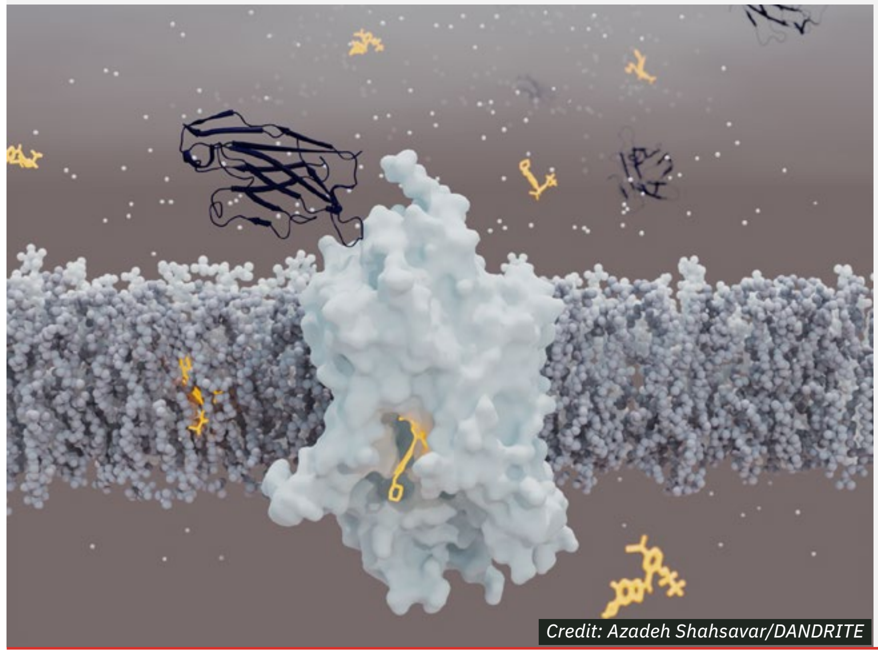
Schizophrenia is a chronic and debilitating mental health disorder affecting approximately 20 million people worldwide. Designing drugs to target glycine transporter 1 (GlyT1) could provide new treatments for schizophrenia and other psychiatric disorders. However, developing successful drug candidates has been hampered by the lack of knowledge of the GlyT1 structure.

Researchers from F. Hoffmann-La Roche (known as Roche), Linkster Therapeutics, and the Danish Research Institute of Translational Neuroscience (DANDRITE) at Aarhus University joined forces with EMBL Hamburg after attempts to use standard methods to reveal the structure of GlyT1 failed. The EMBL Interdisciplinary Postdoctoral (EIPOD) programme was an important enabler of this collaboration; EIPOD supports postdocs to work on research projects involving academic and industry partners in collaboration with EMBL scientists.

Scientists at EMBL Hamburg were able to develop a new methodological approach and software that allowed the structure of GlyT1 to be visualised at high resolution. The structure of GlyT1 was published in the leading scientific journal Nature. The study highlights the importance of both scientific excellence and the availability of cutting-edge infrastructure, advanced methodology, and software for progressing research – all of which are provided by EMBL Hamburg. Poul Nissen, Director of DANDRITE and senior researcher on the study, commented: “EMBL has proved time and time again they can really drive developments in imaging and bioinformatics.” DANDRITE continues to benefit from being part of the EMBL partnership. As Nissen explained: “We [DANDRITE] are more interesting to the outside world and to industry being so tightly connected to EMBL through a partnership.”

> ***“The game changer was when EMBL joined and brought the advanced methodology and software to enable this project to [reach] the end stage,” said Roger Dawson, founder and Chief Executive Officer of Linkster Therapeutics.***

The structure of GlyT1 now provides the blueprint for industry to develop new drugs to treat psychiatric disorders as well as improve the efficacy of new therapeutics.



3D molecular structure of glycine transporter 1 (GlyT1) within the cell membrane.

5 Research results generated at EMBL contribute to solving global societal challenges and generating economic impact

70% of users

indicated that EMBL experimental services delivered wider societal impacts

EMBL, through its experimental services, supports discoveries in molecular biology that eventually contribute to solving global societal challenges. Around 70% of academic users surveyed indicated that their use of EMBL experimental services has helped to deliver wider societal impacts.

> ***“Scientific advances will always help find solutions to societal challenges.” EMBL external user, France***

Of these respondents, 58% reported impacts in health and well-being. Other areas of social impact that were reported were industrial biotechnology (20%), environment and climate change (12%), and food security and sustainable agriculture (7%). Box 4 presents an example of a wider social impact where EMBL-enabled research facilitated a new enzymatic recycling approach to lower the environmental impact of plastic waste.

Box 4: EMBL enables a new recycling approach to lower the environmental impact of plastic waste

The widespread use and disposal of plastic is a significant and growing environmental issue. Polyethylene terephthalate (PET) is the most abundant polyester plastic, with almost 70 million tonnes manufactured annually worldwide for use in the manufacture of bottles and other forms of packaging.

A French team led by Professor Alain Marty from the Toulouse Biotechnology Institute and Chief Scientific Officer of the green-chemistry company Carbios used beamline ID30B, jointly operated by EMBL and the European Synchrotron Radiation Facility (ESRF) at the ESRF in Grenoble, among other synchrotron facilities, to obtain high-quality data to solve the structure of a new plastic-degrading enzyme. This novel enzyme can biologically degrade all PET plastic waste in an extremely efficient way. This innovation allows infinite recycling of all types of PET waste, as well as the production of 100% recycled and recyclable PET products with the same quality as if they were produced with new PET.

Carbios is now industrialising the development of this PET enzymatic recycling process to scale its application to global plastic recycling challenges, which has the potential to lower the environmental impact of plastic waste. Most recently, Michelin has successfully tested and applied Carbios’s enzymatic recycling process for car tyres. This is an important step towards 100% sustainable tyres – currently, 1.6 billion car tyres are sold worldwide annually, producing 800,000 tonnes of PET per year.

3D molecular structure of the novel plastic-degrading enzyme.

Around one-third of academic users (32%) surveyed are maximising the impact of their research through public engagement activities to communicate the benefits of EMBL-enabled research results to the public – helping to build understanding and appreciation of their work.

Evidence of economic impact being generated as a result of using EMBL experimental services was less widespread, but around 10% of academic users surveyed reported that their EMBL-related research is contributing to economic impact through commercial activities such as research contracts and consultancy for industry and creating spin-off companies. This is likely an underestimate, as some academic users may not recognise that their EMBL-enabled research has contributed to commercial activities or be able to disclose details due to confidentiality.

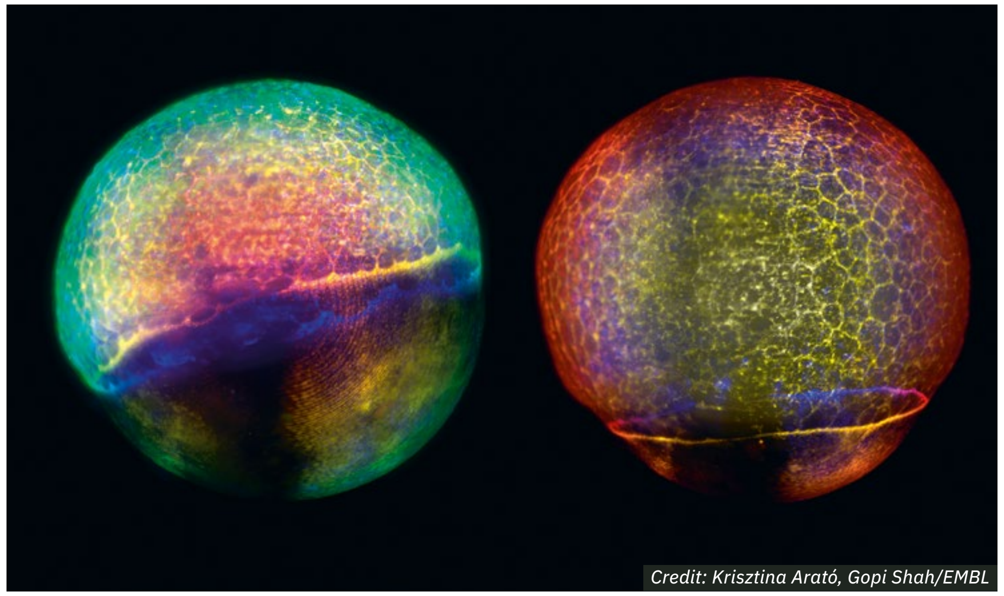
6 EMBL directly supports technology transfer and builds industry relations that maximise the impact of its experimental services

The interplay between EMBL's external users and EMBL facility scientists has inspired numerous developments in experimental techniques and instruments. EMBL is committed to maximising the social value derived from these developments through its technology transfer partner, EMBLEM (EMBL Enterprise Management Technology Transfer GmbH). From this perspective, EMBL is a member of a small group of world-class facilities that are continuously expanding the portfolio of experimental technologies and delivering advances that have the potential to benefit science and scientists across the globe.

EMBL's commitment to the advancement of technology, instruments, and software has also provided a platform for various spin-offs, with the resulting scientific services companies packaging EMBL technologies, products, and instruments and delivering them to industry and academia at scale. One example is EMBL spin-off Luxendo, which was founded to commercialise a novel microscopy technique that has the potential to be used in multiple health and disease applications (see Box 5 and **Appendix D.5** for full case study).

Box 5: Spotlight on Luxendo

Luxendo was founded in 2015 in Heidelberg to commercialise selective plane illumination microscopy (SPIM), a novel microscopy technique developed at EMBL. SPIM allows minimally invasive 3D imaging of multicellular specimens at high resolution and has many applications, such as modelling tissue development and disease progression. The start-up, which is based in Heidelberg, benefited from both external investment (€8 million in venture capital funding from EMBL Ventures and Life Science Partners) and internal scientific expertise and access to EMBL users, who provided feedback on prototypes and early versions of commercial products. The rapid success of the company increased the need to find an external partner to help with the distribution channel and increase Luxendo's international presence. In 2017, Bruker (a USA-headquartered public limited company manufacturing a wide range of scientific instruments for health and life sciences applications) acquired Luxendo with a valuation of €17 million. Through Bruker, SPIM microscopes are now available in more than 100 laboratories worldwide including across the USA, Europe, and Asia.



SPIM light-sheet microscopy image showing how zebrafish embryos start developing.

Another example of a successful EMBL spin-off is scientific services company ALPX, which has packaged screening technologies available at EMBL Grenoble to support structure-guided drug-design services primarily for industry users. The breadth and ease of remote access to EMBL's scientific infrastructure made these experimental services highly beneficial for the pharmaceutical and biotechnology sector (see Box 6 and **Appendix D.5** for full case study).

Box 6: Spotlight on ALPX

ALPX was founded in 2019 at EMBL Grenoble. It provides industry and academic users with access to its high-throughput crystallisation and fragment screening facility, the HTX Lab, based on the CrystalDirect technology developed at EMBL.

The Crystallographic Information Management System (CRIMS) software, which can be operated remotely from any desktop computer with an internet connection, provides users with access to fully automated crystallography pipelines. It is capable of screening small-molecule libraries of more than 1,000 fragments, over multiple projects, and is in high demand among academic and industry users, with particular interest from the pharmaceutical industry, which uses the screening facility to support structure-based drug development programmes.

These services are increasingly critical to industry's – and academia's – efforts to improve and accelerate the drug development pipeline, through faster screening of much larger numbers of candidate molecules and targets. This in turn could help to combat the spiralling cost of drug development and the resultant increase in the price of medicines.

EMBL is also building strategic partnerships with European industry, to secure additional investment in novel facilities and ensure the knowledge developed within these facilities and analytical services reaches a wider industry and academic audience. As an example, EMBL has a long-standing partnership with Arinax, an international instrumentation company, to provide technologies developed at EMBL to synchrotron facilities around the world (see Box 7 and **Appendix D.5** for full case study).

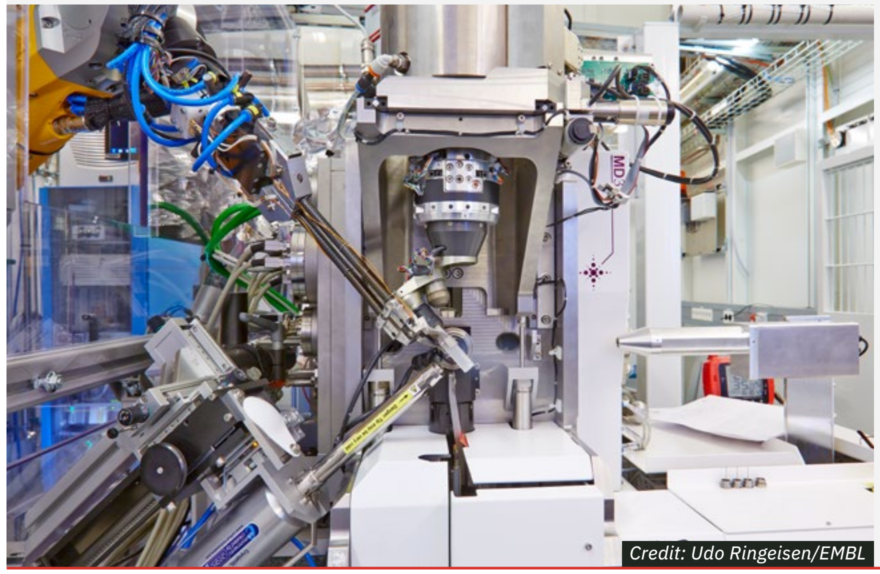
Box 7: Spotlight on Arinax

Scientific breakthroughs are often made possible only by innovative technological developments. When the high-brilliance, third-generation synchrotron source at the ESRF opened in 1994, the entire operation of sample handling on crystallography beamlines was done manually. Since then, the Instrumentation Team at EMBL Grenoble has worked closely with the ESRF Structural Biology Group to pioneer instruments and automate crystallography beamlines to increase the efficiency of structure determination processes, from sample preparation to data collection.

Two of the most notable inventions are micro-diffractometer devices (called MD2 and MD3), which are goniometer devices that enable the automated and high-precision positioning of protein crystals in an X-ray beam, significantly increasing the efficient use of beamtime at synchrotrons.

EMBL has partnered with Arinax, a scientific instrumentation manufacturer, to commercialise these devices for academia and industry. As of 2021, Arinax has installed micro-diffractometers in over 20 synchrotrons around the world. MD2 and MD3 micro-diffractometers cost around €450,000 and €600,000, respectively (depending on the options and services that customers choose), which is a sizable investment that synchrotron facilities are willing to pay to keep their services at the cutting edge.

Arinax has frequent discussions with EMBL about development projects based on feedback on device testing from other synchrotrons to fuel new innovations. The ability to adjust technologies to researchers' needs is one of the reasons why instruments developed at EMBL are – and will continue to be – widely used by the scientific community.



Credit: Udo Ringeisen/EMBL

EMBL Hamburg P14 beamline installed with ARINAX micro-diffractometer.

EMBL experimental services are increasingly used by industry, either directly, as is the case for many leading international pharmaceutical and biotechnology companies, like Biogen, GSK, Celgene, and Sanofi, or indirectly, by accessing technologies that were originally developed at EMBL, such as electron microscopy scientific services or through facilitator companies like Thermo Fisher Scientific. Most recently, EMBL experimental services supported biotech company BioNTech to develop a pioneering vaccine against COVID-19 that is now widely available around the world (see Box 8 and **Appendix D.5** for full case study).

Box 8: EMBL supports industry to develop a vaccine against COVID-19

In 2020, BioNTech, a biotech company working with Pfizer, used the structural biology services at EMBL Hamburg for Project Lightspeed, a ground-breaking programme to develop a vaccine against COVID-19. In the words of Ugur Sahin, Chief Executive Officer of BioNTech: "Our aim is clear: Making a potential vaccine available to the public as quickly as possible – worldwide." To realise this mission, BioNTech, together with researchers at Johannes Gutenberg University Mainz, Tel Aviv University, Leiden University, and Forschungszentrum Jülich, published the results of several studies showing how to improve the packaging and delivery of messenger RNA (mRNA) into human cells. These studies paved the way for the development of a new class of vaccines that use lipid nanoparticles to deliver mRNA into cells. In less than a year, this research resulted in a pioneering mRNA vaccine against COVID-19, which is now available in over 116 countries worldwide. The work showcases EMBL's important role in supporting industry collaborations to accelerate innovation in technology and medicine.

In line with furthering innovation and translation activities at EMBL, EMBL has begun asking facilities to distinguish between their academic and industry usage when submitting data in the annual metrics collection process. In the 2020 data collection exercise, EMBL experimental services recorded 61 direct industry users, which is notable given the lockdowns that took place in that year, with a potentially much larger number of users accessing the major experimental facilities indirectly through scientific services companies.

> ***"We have been able to attract more customers since we were able to provide top grade SAXS based analytics." Industry user***

> ***"EMBL's P12 beamline is the world's leading beamline for biological SAXS." Industry user***

> ***"At the start of my business, there was no knowledge and no machines/tools to perform the work: both of them have been provided by EMBL." Industry user***

> ***"EMBL facility suited my needs both in terms of quality of the result and of the overall experience." Industry user***

Our industry user survey indicated that the majority of industry users (61%) reported that access to EMBL experimental services was 'important', 'very important' or 'critical' to their company's research and innovation activities, advancing understanding of the properties and functions of their core technologies, delivering insights necessary for new products or processes, or improving their R&D productivity. While EMBL is not the only facility available, our user survey suggests it is a first choice for many in industry because of the quality of its technology and support provided by facility scientists.

7 External academic users value EMBL experimental services at €17.5 million per annum

Academic users were asked about their hypothetical willingness to pay (WTP) for access to EMBL services and their willingness to accept (WTA) a fee for giving up using EMBL services. Although it is challenging for users to place a monetary value on a service that has been provided for free or a nominal fee, the responses enabled the calculation of the likely range and midpoint of the monetary value of having access to EMBL experimental services for academic users.

> Users value access to EMBL experimental services at €17.5 million pa with future impacts of
> **€187.5**
> million over 30 years

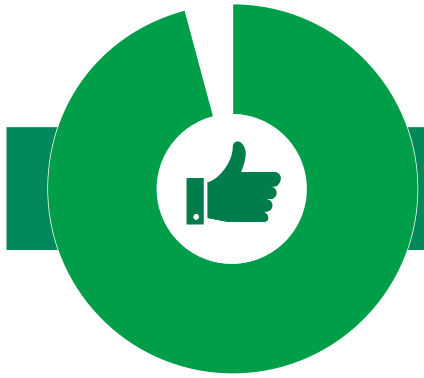
EMBL experimental services are valued at around €17.5 million per annum. This figure is the midpoint inferred from academic users' survey responses to specific WTP and WTA questions and extrapolated to EMBL's 2,124 average annual unique external users for 2016-2020. Bearing in mind that not all results stemming from the experimental services, such as scientific publications and researcher training, can be monetised at this stage, this figure already compares favourably with the €11.7 million annual operational costs associated with supporting those external users[1].

Experimental services contribute to the advancement of knowledge and flow of ideas, which may lead to future socioeconomic benefits indirectly. In addition, pushing the frontiers of human knowledge could create impacts in the much longer term (15 years or more), with incremental progress being made over time (in a non-linear fashion) and with the support of various other efforts, investments, and knowledge beyond those provided by EMBL.

The net present value (NPV) is defined as the current value of the future impact of EMBL experimental services given a specified discount rate. Based on the annual valuation, the NPV of EMBL experimental services over time can be calculated. In short, this discount rate is the rate at which society values the present compared to the future. Including a discount rate allows benefits with different lifespans to be compared on a common, present-value basis[2]. Therefore, the NPV of EMBL experimental services over 30 years is around €187.5 million[3].

1. The annual operational cost does not include any historic costs or capital investments.
2. For an in-depth discussion on this, see: HM Treasury (2020). The Green Book (2020). UK Government. https://www.gov.uk/government/publications/the-green-book-appraisal-and-evaluation-in-central-governent/the-green-book-2020
3. We applied a 3.5% discount rate, which is typically associated with research activities (see The Green Book (2020)).

Overall assessment



96 % of external users anticipate using EMBL experimental services in the future n=332

> *"Excellent facilities, excellent support."*
> EMBL academic user, United Kingdom

> *"Without having access to the EMBL experimental services, the portfolio of my research methods would be poorer."*
> EMBL academic user, Poland

> *"You are providing amazing facilities and services to the research community, essentially enabling scientific projects and building research careers."*
> EMBL academic user, Switzerland

> *"Running my experiments in the best beamline in the world is critical for the validity of these results."*
> EMBL academic user, Israel

> *"Great facilities that provide us with cutting edge technologies to answer questions in life science."*
> EMBL academic user, Germany

> *"It was a great experience in every possible aspect, one of the most productive and enjoyable time periods in my research career."*
> EMBL academic user, Greece

> *"Without EMBL facilities, the majority of the experimental work that supported our research for the last decade would have been unfeasible."*
> EMBL academic user, Portugal

Source: Technopolis analysis of EMBL external academic user survey

Appendix A

List of EMBL sites and experimental services surveyed

List of EMBL sites and experimental services surveyed

EMBL sites	List of services
EMBL Barcelona	Optical projection tomography facility Selective plane illumination microscopy (SPIM)/Light-sheet microscopy facility
EMBL Grenoble[4]	Cryo-electron microscope – beamline CMO1 facility High-throughput crystallisation, fragment screening and CrystalDirect services Macromolecular X-ray crystallography beamlines (ID23-1, ID23-2, ID29, ID30A-1, ID30A-3, ID30B) services Small-angle X-ray scattering beamline (BM29) service
EMBL Hamburg	Small-angle X-ray scattering – beamline P12 service Macromolecular X-ray crystallography – beamline P13/14 service Sample preparation and characterisation services Time-resolved crystallography – beamline P14 service
EMBL Heidelberg	Advanced light microscopy facility Chemical biology core facility Cryo-electron microscopy service platform (Imaging Centre)[5] Electron microscopy core facilityy Flow cytometry core facility Genomics core facility Proteomics core facility Metabolomics core facility Protein expression and purification core facility
EMBL Rome	Flow cytometry services Genetic and viral engineering services Gene editing and embryology services Microscopy services

EMBL experimental services had an average of 2,124 external unique users between 2016 and 2020. This amounted to an average of 3,410 on-site user visits, mail in samples and remote user access sessions in the same time period.

4. EMBL Grenoble facilities include the ESRF X-ray beamlines operated by the Joint Structural Biology Group (JSBG) and the ESRF cryo-electron microscope CM01 beamline operated with Partnership for Structural Biology (PSB) partners.
5. EMBL's Imaging Centre which opened in 2021 represents a new EMBL service for the highest resolution electron and light microscopy technologies and will incorporate and expand the current cryo-EM service platform.

Appendix B

Summary of the analysis of the academic user survey

Summary of the analysis of the academic user survey

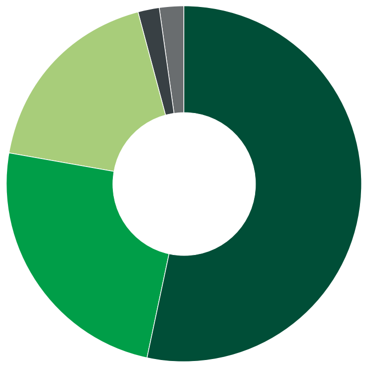
B.1 EMBL experimental services are working with scientists from all member states, at all career stages, and across most biological fields, facilitating the conduct of fundamental research in molecular biology

The online survey, launched in June 2021, was completed by 560 academic users located in 29 countries, predominately in Europe (96%). The largest number of survey respondents were based in Germany (33%), followed by France (14%), Italy (7%), Spain (5%), United Kingdom (5%), and Portugal (4%). Note that the distribution of responses largely reflects the distribution of actual academic users (2,124 annual average unique external users between 2016 and 2020) accessing the experimental services at EMBL.

The survey attracted responses from academic users at different career stages. Most academic users (93%) reported that they are conducting basic research, with only 7% working in applied research. The academic users are working in a wide range of biological disciplines, from neurobiology to biochemistry, with most (56%) reporting working in the area of structural biology.

Overview of academic users responding to the survey

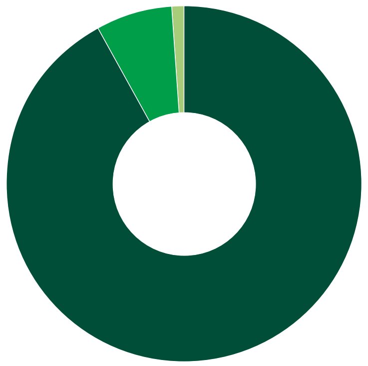
Career stage



- 53 % Established researcher
- 25 % Early-career researcher
- 18 % Post-graduate student
- 2 % Research technician
- 2 % Master's student

n=555

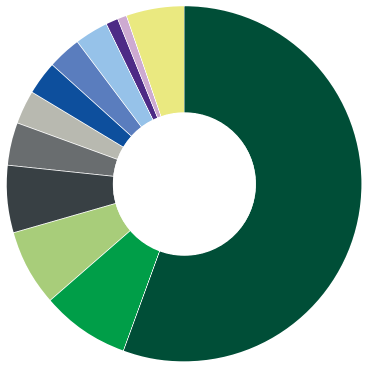
Research type



- 93 % Basic research
- 6 % Applied research
- 1 % Product development

n=553

Research area



- 56 % Structural biology
- 8 % Biochemistry
- 7 % Cell biology
- 6 % Genome biology
- 4 % Molecular biology
- 3 % Developmental biology
- 3 % Microbiology
- 3 % Neurobiology
- 3 % Tissue and organ biology
- 1 % Biophysics
- 1 % Immunobiology
- 5 % Other

n=553

Source: Technopolis analysis of EMBL external academic user survey

B.2 EMBL provides academics with access to high-quality experimental services and support

EMBL seeks to provide its academic users with access to state-of-the-art facilities and high-quality experimental services to enable them to answer complex biological questions. Academic users have access to around 20 experimental services in the fields of structural biology, imaging, genomics, proteomics, metabolomics, *in vivo* gene editing, and chemical biology (see **Appendix A** for a list of EMBL facilities and experimental services surveyed).

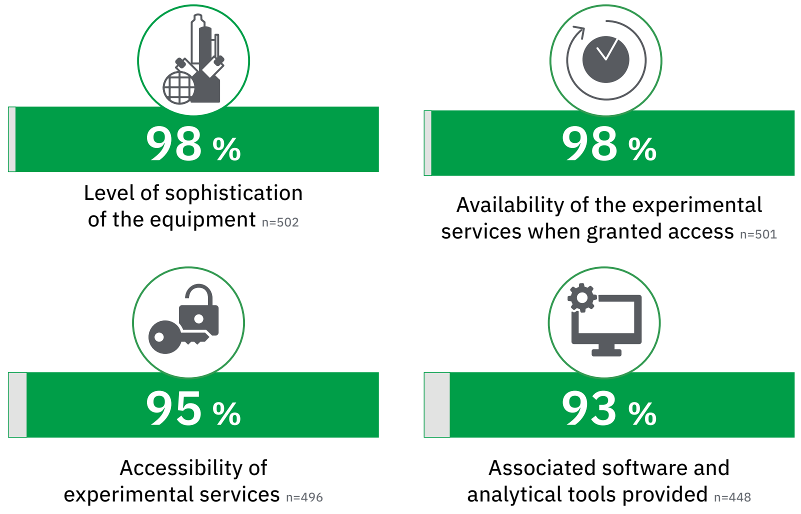
To that end, the user survey posed a series of questions with a view to gauging the extent to which EMBL experimental services are delivering on this goal, from the perspective of its academic users.

Most academic users rated the quality of EMBL experimental services as 'good' or 'very good', across a range of areas for all facilities. In particular, academic users rated very highly the level of sophistication of the equipment (98%), the availability of the services (98%), scientific data generated (97%), the accessibility of the services (95%) and the associated software and analytic tools (93%).

APPENDIX B: SUMMARY OF THE ANALYSIS OF THE ACADEMIC USER SURVEY

Quality of the experimental services

Experience of using experimental services: Poor/Fair Good/Very good



"Top notch facility that serves users in the best possible manner"
EMBL academic user, United Kingdom

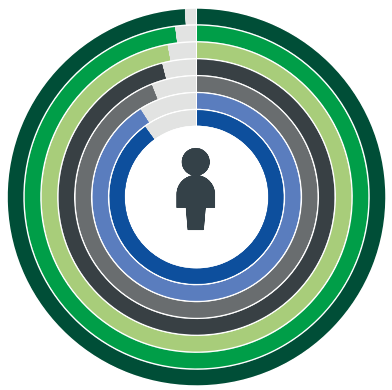
Source: Technopolis analysis of EMBL external academic user survey

In addition to providing access to experimental services, EMBL provides academic users with an opportunity to work alongside leading facility scientists who provide scientific and technical support, enabling them to solve experimental challenges, as well as get hands-on training in complex technologies and methods.

The facility scientists are delivering many benefits to academic research users: ≥90% of academic users rated their support as 'very good' or 'good' in areas ranging from experimental design through to operation of equipment, data analysis and data management.

Quality of the support provided by EMBL staff

Experience of support provided by staff reported as good or very good



- 99 % Timeliness of the support provided n=511
- 98 % Relevance of the support provided n=551
- 97 % Level of competence of the facility staff n=511
- 96 % Support provided on experimental design n=448
- 94 % Support provided on operation of experimental instrument n=438
- 91 % Support provided on data analysis n=398
- 90 % Support provided on data storage and archiving n=405

"The support has always been excellent, from the initial application to the data acquisition and processing."
EMBL academic user, Spain

Source: Technopolis analysis of EMBL external academic user survey

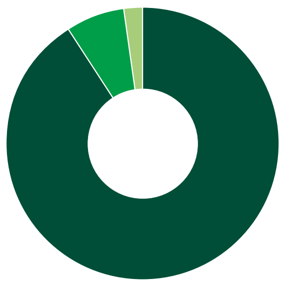
The survey found that the quality of the experimental services, expertise, and data generated are the top reasons why academic users choose to conduct their research at EMBL. Around 60% of academic users stated that they had chosen to use EMBL experimental services for their research because of the uniqueness of the services provided. 91% of academic users reported that the use of EMBL experimental services was 'critical', 'very important' or 'important' for the conduct of their research.

We also asked users what they would do if EMBL services did not exist, 87% of respondents stated that they would apply to access a similar service in another facility. However, over half of these academic users reported that this would have a negative impact on their research (e.g. by reducing the quality, efficiency, or competitiveness of their research). Furthermore, EMBL experimental services are not always or easily substitutable: 32% of academic users reported that they would use a different type of technique/measurement, while 17% would pursue a different research question instead.

Importance of EMBL experimental services to academic users

Reasons why academic users choose to use EMBL experimental services: n=411

- 93 % Quality of the services/technologies provided
- 77 % Expertise provided by staff
- 71 % Quality of the data generated
- 59 % Uniqueness of the services provided



Importance of EMBL experimental services for conducting research n=487

- 91 % Critical/Very important/Important
- 7 % Somewhat important
- 2 % Not important

Non-access to EMBL experimental services would have a negative impact on academic users in terms of quality and efficiency of their research

32 % would use a different technique/ measurement instead n=462

17 % would pursue a different research question n=458

"EMBL provides streamlined access to state-of-the-art instruments indispensable for structural biology studies."
EMBL academic user, Finland

Source: Technopolis analysis of EMBL external academic user survey

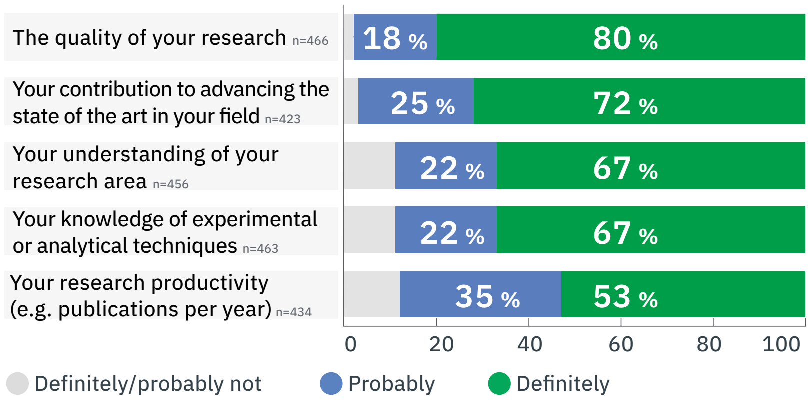
B.3 EMBL experimental services enable more research that is of higher quality

More than half of academic users reported that their use of EMBL experimental services had definitely had a positive impact on all aspects of their research, whether that was the quality of their research (80%) or their productivity (53%). This indicates that EMBL allows users to generate more output (publications) and impact (higher-quality research) than might have otherwise been possible.

The most widely cited examples of scientific outputs attributable to the use of EMBL experimental services were scientific publications and the development of new techniques, tools, or methods. This suggests that EMBL is enabling not only the creation of new knowledge that underpins scientific breakthroughs, but also the development of new approaches that can open up new avenues for research discovery. Note that the number of publications cited by survey respondents represents only a fraction of the total number of publications attributable to EMBL.

Scientific outputs and outcomes as a result of using EMBL experimental services

Extent to which use of experimental services has lead to improvements in the following areas:



"By using EMBL experimental services our lab started to add new techniques to our toolbelt. We widened our range of methodological expertise."
EMBL academic user, Portugal

143 publications were cited as being attributable to EMBL experimental services

38 new techniques/tools/methods were cited as being attributable to EMBL experimental services

Source: Technopolis analysis of EMBL external academic user survey

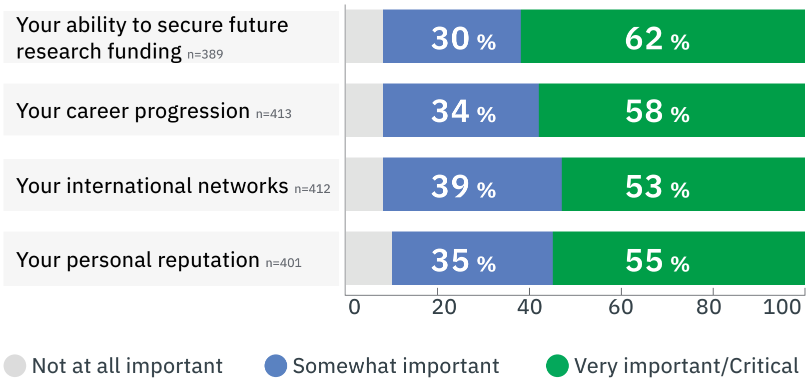
B.4 EMBL experimental services create wider benefits for the research ecosystem

Academic users are also directly benefiting from using EMBL experimental services. More than half of academic users reported that their use of EMBL experimental services was ‘critical’ or ‘very important’ for a range of academic benefits, with the ability to secure future research funding (62%) and career progression (58%) being the top-cited benefits.

Around half of academic users reported that EMBL experimental services are important for their personal reputation (55%) and international networks (53%). This suggests that EMBL is playing an important role in developing world-leading scientists in member states and facilitating international research networks.

Academic benefits resulting from use of EMBL experimental services

Extent to which use of experimental services has been important for:



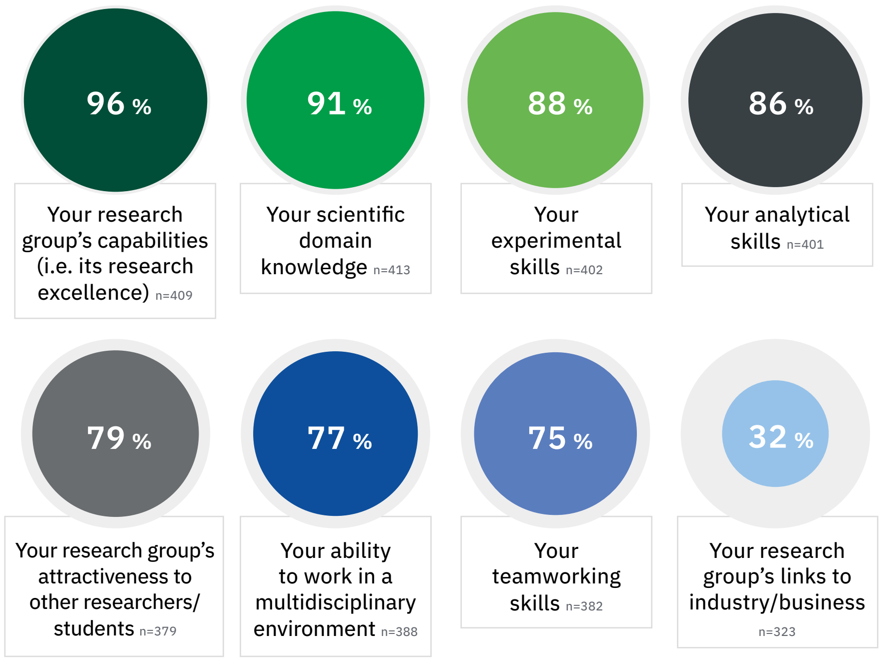
“Using EMBL facilities not only opens up the way to large international networking [opportunities] but also helps to position scientists at the forefront of the field”
EMBL academic user, France

Source: Technopolis analysis of EMBL external academic user survey

Most academic users reported that using EMBL experimental services and support has had a ‘large’ or ‘very large’ positive impact on their research skills and knowledge across a range of areas, with their research group’s capabilities (i.e. research excellence) and scientific domain knowledge being the top-cited areas of impact. While 93% of academic users are conducting basic research, the survey found 32% of academic users report that the use of EMBL experimental services has had a positive impact on their research group’s links to industry or business. This suggests that EMBL is facilitating a higher level of interactions among academic researchers and industry – including scientific services companies and more mainstream research-intensive businesses – than would be the case otherwise, potentially helping shift the focus from fundamental research to discovery science, as well as boosting socially beneficial knowledge spillovers.

Impact on skills and knowledge as a result of using EMBL experimental services

Extent to which use of experimental services has had a moderate, large, or very large positive impact on:



“An important bonus of using the service is the post-doc who will carry out the experiment is under the guidance of EMBL staff: top scientists in an outstanding multidisciplinary environment.”
EMBL academic user, Italy

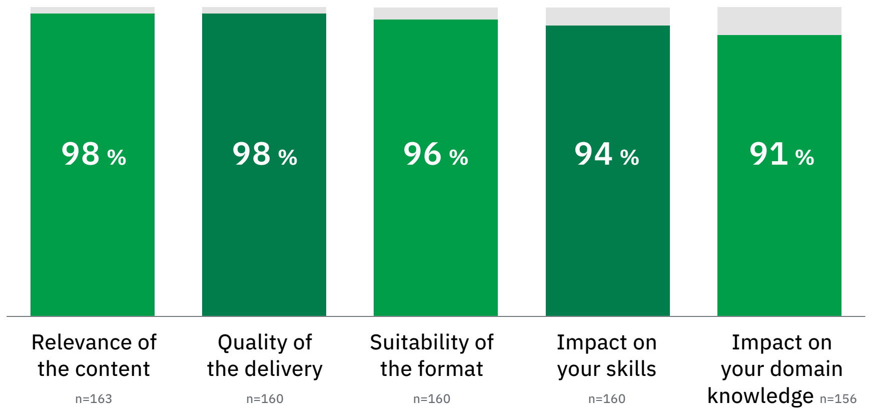
Source: Technopolis analysis of EMBL external academic user survey

The facilities hosting EMBL experimental services are deeply involved in training activities, either through direct training of academic users or by organising and delivering practical courses and training activities. EMBL training courses cover a diverse range of topics that bring experts and the scientific community together to share new ideas and techniques and foster collaborations. Over half (55%) of academic users have participated in EMBL training courses, and almost all of them rated the course content and resulting impact on their skills and knowledge as 'very good' or 'good'. Around 60% of participants were established researchers, and the remainder were early-career researchers, post-graduate students, or master's students.

Impact of EMBL training courses on knowledge and skills

55 % of academic users have participated in EMBL training courses n=427

Rating of EMBL training courses by academic users:



Poor/Fair Good/Very good

"Hands on training on integrated approaches makes [students] more confident and has an impact on their way of thinking."
EMBL academic user, Greece

Source: Technopolis analysis of EMBL external academic user survey

B.5 EMBL-enabled research is being translated into economic impacts

Academic users predominately conduct basic research at EMBL. Nevertheless, some academic users reported that the use of EMBL experimental services has or is expected to contribute to commercial outcomes:

- 52 academic users reported new intellectual property rights applications or registrations
- 33 reported generating new technology licencing agreements
- 31 reported new consultancy and industry contracts
- 23 reported new technology start-ups

In addition, 71 academic users reported that their use of EMBL experimental services had resulted in wider economic impacts in three main areas: increased industrial innovation (55 of 77), increased industrial competitiveness (22 of 71) and increased industrial productively (20 of 71). Around half of these respondents reported that use of EMBL experimental services had a positive impact on their links to industry.

This suggests that EMBL is enabling academic users to generate commercially relevant research. Some academic users may not know if their EMBL-enabled research has influenced commercial activities or could not disclose this due to confidentiality restrictions.

Innovation and commercial benefits resulting from use of EMBL experimental services

Number of academic users reporting their use of EMBL experimental services has or is expected to contribute to commercial outcomes which can be linked (in some part) to experimental data generated at EMBL:

52 users reported new intellectual property rights applications or registrations n=398

33 users reported new technology licensing agreements n=397

31 users reported new consultancy and industry contracts n=395

23 users reported new technology start-ups n=397

Number of academic users that indicated their use of EMBL experimental services has helped to deliver one or more wider economic impacts:

55 Increased industrial innovation

22 Increased industrial competitiveness

20 Increased industrial productivity

16 Increased industrial growth

Around half of these respondents reported that their use of EMBL experimental services had a positive impact on their links to industry n=71

Source: Technopolis analysis of EMBL external academic user survey

B.6 Research results generated at EMBL contribute to solving global societal challenges and generating economic impact

EMBL's goal is to support discoveries in molecular biology that can be used to tackle societal challenges. Around 70% of academic users indicated that their use of EMBL experimental services has helped to deliver wider societal impacts. Of these respondents, most (58%) reported impacts in health and well-being. Other areas of social impact that were reported were industrial biotechnology (20%), environment and climate change (12%), and food security and sustainable agriculture (7%).

Notably, these benefits were reported in a range of thematic areas, beyond the most obvious (health), which are helping to achieve global Sustainable Development Goals (SDGs)[6]:

- Food security and sustainable agriculture (SDG2)
- Health and well-being (SDG3)
- Industrial biotechnology (SDG9)
- Climate action (SDG13)
- Other societal areas

Societal benefits of using EMBL experimental services

Use of EMBL experimental services has helped to deliver wider societal impacts:

n=378 *Food security and sustainable agriculture ^Other societal areas

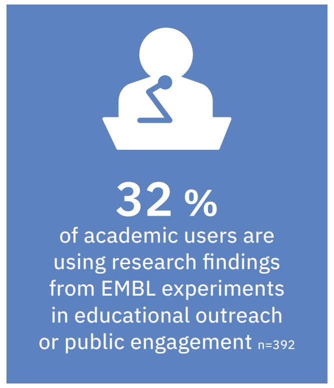
"Scientific advances will always help find solutions to societal challenges."
EMBL academic user, France

Source: Technopolis analysis of EMBL external academic user survey

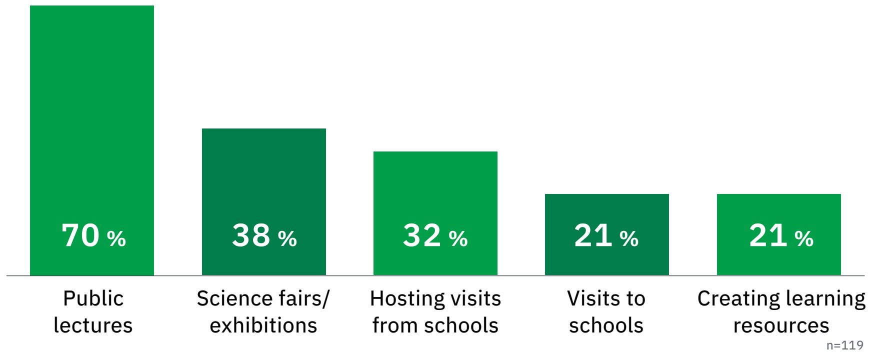
6. United Nations (2015). Transforming our world: the 2030 Agenda for Sustainable Development. UN Department of Economic and Social Affairs. https://sdgs.un.org/2030agenda

Public engagement plays an important role in communicating the benefits of scientific research. Around one-third (32%) of academic users reported using their research findings from EMBL experiments to support educational outreach or public engagement activities. The mode of engagement was typically through public lectures, but science fairs and hosting school visits were also common. Around 75% of academic users participating in public engagement were established researchers, and the remainder were early-career researchers, post-graduate students, or master's students.

Academic users are engaging the public with their EMBL research



Most common formats for delivering public engagement:



"The large public is given the opportunity to get informed about the latest advances of the work performed at EMBL experimental facilities, understand the importance of investing in research infrastructures, [and] realise the complexity of performing research in the field of structural biology and the challenges that scientists face."
EMBL academic user, Greece

Source: Technopolis analysis of EMBL external academic user survey

B.7 Academic users value EMBL experimental services at €17.5 million per annum

Academic users were asked specific questions about their hypothetical WTP for access to EMBL services and their WTA a fee for giving up EMBL services. The WTP corresponds to the amount a person is willing to pay for a product or service, whereas WTA corresponds to the amount a person is willing to accept to forego a product or service. Although it is challenging for users to place a monetary value on a service that has been provided for free or a nominal fee, the responses enabled the calculation of the likely range and midpoint of the monetary value of having access to EMBL experimental services for academic users.

EMBL experimental services are valued between €13 million and €22 million per annum. Taking the midpoint of the WTP and WTA values, EMBL experimental services are valued at around €17.5 million per annum. This midpoint is inferred from external academic users' survey responses to specific WTP and WTA questions and extrapolated to EMBL's 2,124 annual average (for 2016–2020) unique external users. Bearing in mind that not all results stemming from scientific publications and researcher trainings can be monetised at this stage, this figure already compares favourably with the €11.7 million annual operational costs associated with supporting those external users.[1]

Nevertheless, this figure likely underestimates the economic value of EMBL experimental services. Many experimental service outcomes are difficult to monetise, such as scientific publications, researcher training, or even cases where a scientist's career and core discoveries developed around findings enabled by EMBL experimental services. Experimental services contribute to the advancement of knowledge and flow of ideas, which may lead to future socioeconomic benefits only indirectly. In addition, pushing the frontiers of human knowledge could create impacts in the much longer term (15 years or more), with incremental progress being made over time (in a non-linear fashion) and with the support of various other efforts, investments, and knowledge beyond those provided by EMBL.

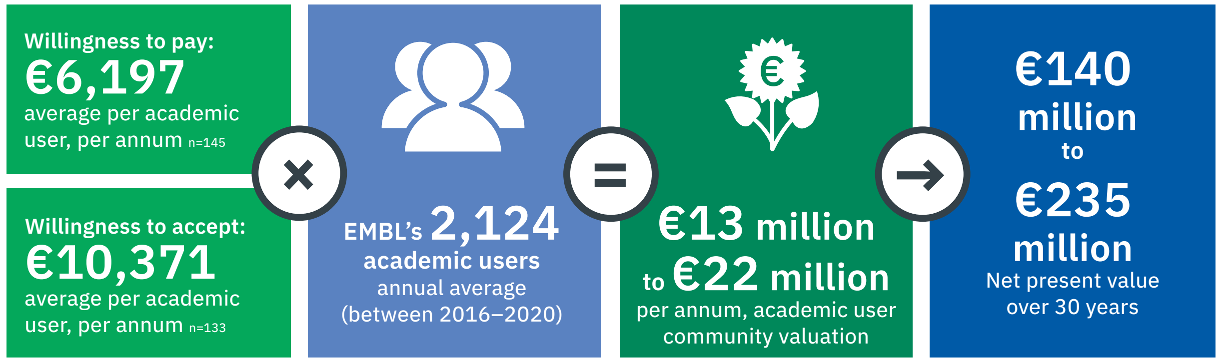
7. For an in-depth discussion on NPV calculations, see: HM Treasury (2020). The Green Book. UK Government. https://www.gov.uk/government/publications/the-green-book-appraisal-and-evaluation-in-central-governent/the-green-book-2020

APPENDIX B: SUMMARY OF THE ANALYSIS OF THE ACADEMIC USER SURVEY

The net present value (NPV) is defined defined as the current value of the future impact of EMBL experimental services given a specified discount rate. Based on the annual valuation, we can calculate the NPV of EMBL experimental services over time. In short, this discount rate is the rate at which society values the present compared to the future. Including a discount rate allows benefits with different lifespans to be compared on a common, present-value basis.[7] Therefore, the NPV of EMBL experimental services over 30 years is calculated to be in the range between €140–€235 million, with a mid-point of €187.5 million.

Academic users' valuation of EMBL experimental services

EMBL experimental services are valued between €13–€22 million per annum



*Net present value (NPV) is defined as the current value of the future impact of EMBL experimental services given a specified discount rate (3.5%). This discount rate is the rate at which society values the present compared to the future. NPV= number of years×((annual valuation))/(1+discount rate)^(number of years).

Source: Technopolis analysis of EMBL external academic user survey

B.8 EMBL is providing vital experimental services to academic users

When academic users were asked whether they anticipate using EMBL experimental services in the future, 96% of academic users chose 'yes definitely' or 'yes possibly'. This attests to the high future relevance of EMBL experimental services for academic users across EMBL members states and to the expectation that the experimental services will remain at the cutting edge of research infrastructures and will not be replaced by other national or international facilities in the foreseeable future.

Appendix C

Summary of the analysis of the industry user survey

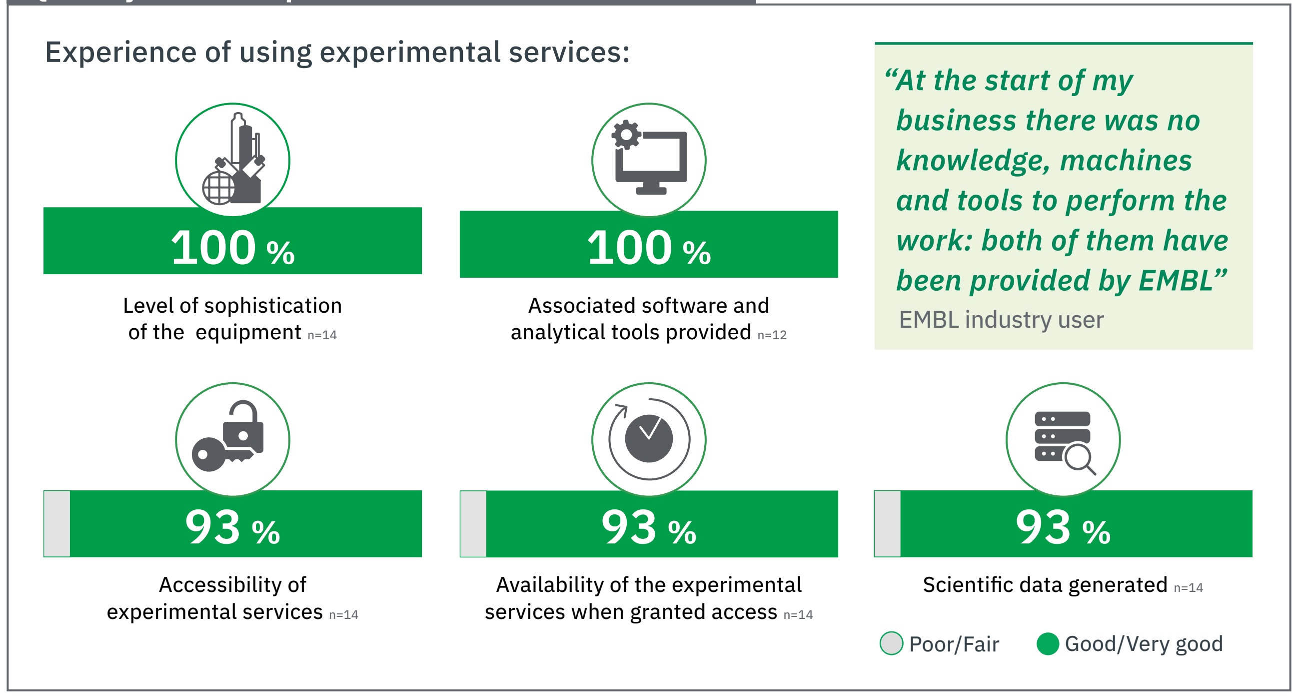
Summary of the analysis of the industry user survey

The online survey, launched in June 2021, was completed by 20 industry users. Half of the respondents (50%) reported working for a large company (>250 employees), with 33% working for a small company (≤50 employees); the remainder worked at micro (≤ 10 employees) or medium-sized (≤ 250 employees) companies. These companies were predominately based in Germany (56%,) or the United Kingdom (22%). The most common sectors in which respondents reported working were the pharmaceutical (46%,) and biotechnology (23%) sectors.

C.1 EMBL provides industry access to high quality experimental services and support

The survey revealed a high level of satisfaction with EMBL experimental services. Every industry user (100%) rated the level of sophistication of the equipment and the associated software and analytical tools provided as 'very good' or 'good'.

Quality of the experimental services at EMBL



Source: Technopolis analysis of EMBL external industry user survey

There was an equally positive response from industry users when asked how they would rate the support provided by EMBL facilities staff, with all industry users rating the level of competence of the facility staff and the support provided by staff as ‘very good’ or ‘good’.

Quality of the support provided by EMBL staff

Experience of support provided by staff reported as good or very good:

- 100 % Level of competence of the facility staff n=13
- 100 % Support provided on experimental design n=13
- 100 % Relevance of the support provided n=14
- 100 % Timeliness of the support provided n=13
- 100 % Support provided on data storage and archiving n=11
- 100 % Support provided on operation of experimental instrument n=13
- 91 % Support provided on data analysis n=11

“EMBL facility suited my needs both in terms of quality of the result and of the overall experience”
EMBL industry user

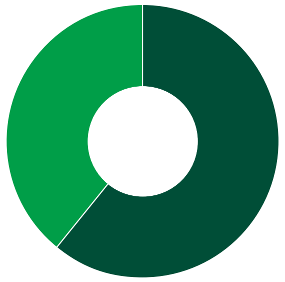
Source: Technopolis analysis of EMBL external industry user survey

Although EMBL is not the only facility available, our user survey suggests it is a first choice for many in industry because of the quality of its technology and facility scientists. Industry is choosing to use EMBL experimental services for several reasons, with the most widely reported motivations being the quality of the services or technologies provided, the quality of the data generated, and the efficiency of the services provided. Several respondents also noted the good value of EMBL-charged services. When asked to rate the importance of EMBL experimental services, 61% of industry users indicated that access to the services was ‘critical’, ‘very important’ or ‘important’ to their company’s research and innovation activities.

Importance of EMBL experimental services to industry users

Reasons why industry users choose to use EMBL experimental services: n=18

- 56 % Quality of the services or technologies provided
- 55 % Quality of the data generated
- 45 % Efficiency of the services provided
- 27 % Uniqueness of the services or technologies provided
- 27 % Expertise provided by staff



Importance of EMBL experimental services for company’s research and innovation activities: n=14

- 61 % Critical/Very important/Important
- 39 % Somewhat important
- 0 % Not important

Source: Technopolis analysis of EMBL external industry user survey

C.2 EMBL is helping industry to gain new knowledge and capabilities

When asked about the impact of EMBL experimental services on skills, most respondents reported a ‘moderate’ or ‘significant’ impact on all areas, with experimental skills (78%), analytical skills (67%), and knowledge in a particular subject area or discipline (67%) being the most commonly cited.

Extent to which use of EMBL experimental services has had a positive impact on the skills and capabilities of staff at organisations

Extent to which use of experimental services has had a moderate to significant positive impact on:

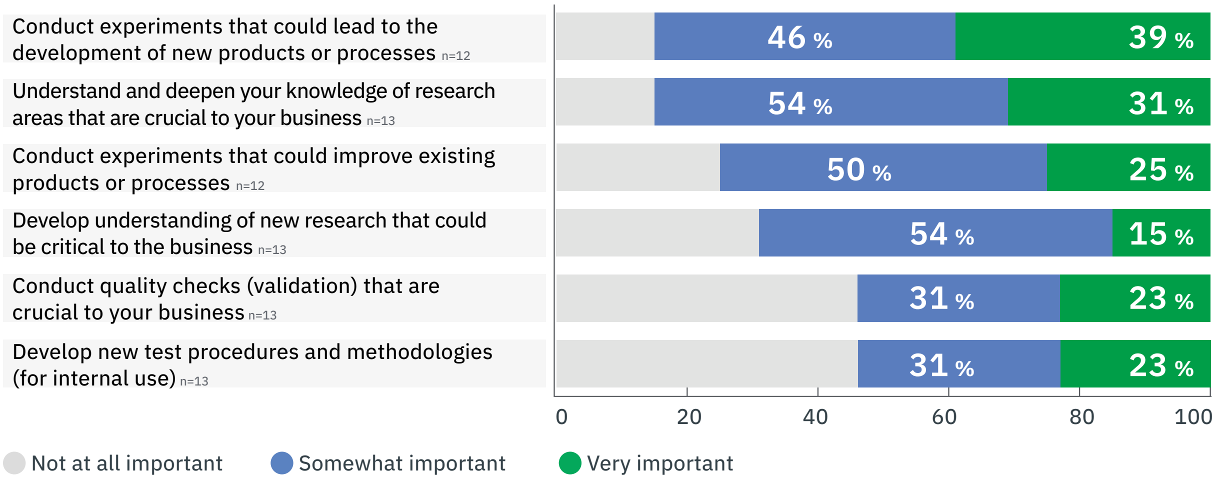
Source: Technopolis analysis of EMBL external industry user survey

C.3 EMBL is enabling industry to innovate

When asked about the importance of EMBL experimental services for their company's research and development, more than one-third (39%) of industry respondents indicated that use of EMBL experimental services had been 'very important' for enabling their company to conduct experiments that could lead to the development of new products or processes.

Importance of EMBL experimental services for company's research and development

How important EMBL experimental services has been in enabling companies to:

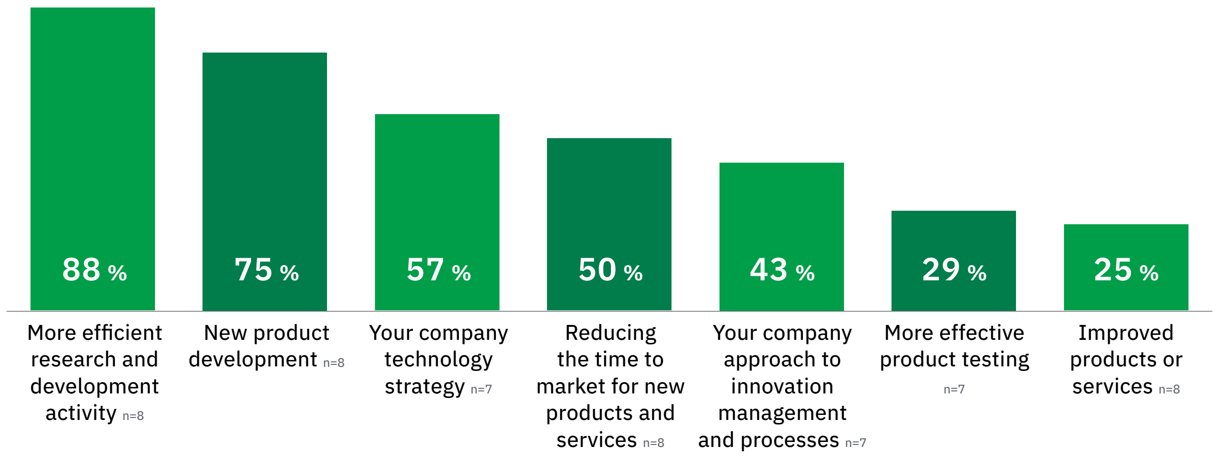


Source: Technopolis analysis of EMBL external industry user survey

Most industry users reported that use of EMBL experimental services had a 'moderate' or 'significant' impact on the efficiency of their in-house research and development activities (88%) and new product development (75%).

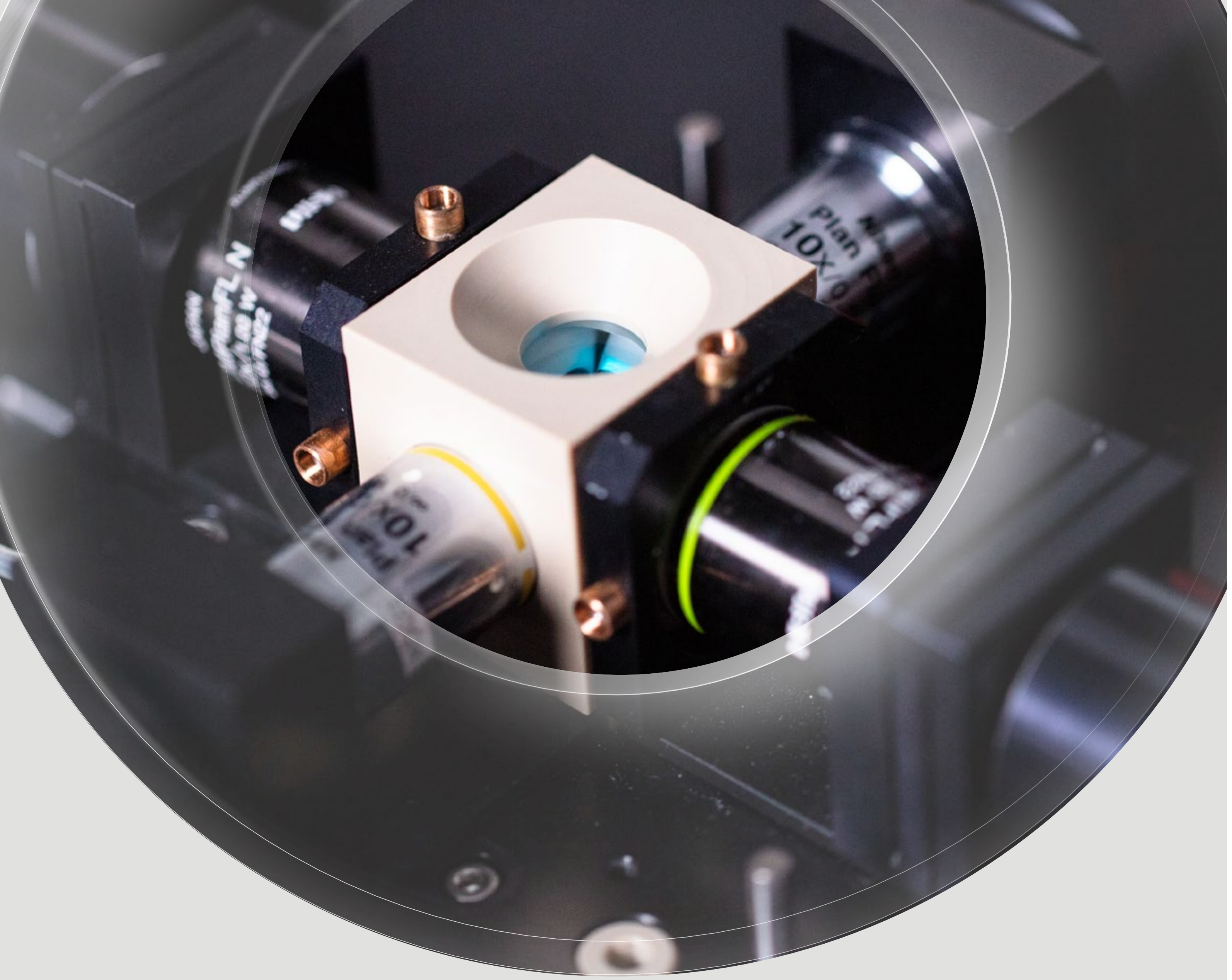
Importance of EMBL experimental services for company innovation

Extent to which use of EMBL experimental services had a moderate to significant impact on the following areas:



"We have been able to attract more customers since we were able to provide top grade SAXS based analytics"
EMBL industry user

Source: Technopolis analysis of EMBL external industry user survey



Appendix D

Case studies

D.1 Development of cryo-electron microscopy at EMBL

Introduction

Cryo-electron microscopy (cryo-EM) is a technique that determines the shape of frozen samples by firing electrons at them and recording the resulting images. Cryo-EM is a relative newcomer to structural biology – the study of the structure and function of proteins and other molecular assemblies to understand how they form, work, and interact; how they malfunction in disease; and how to target them with drugs. Originally, electron microscopy of biological material was hampered by a range of challenges, including a lack of a suitable preparation technique: a method that would allow researchers to prepare biological material for very precise measurements under the microscope whilst keeping it from being damaged.

Development of a revolutionary technique for structural biology

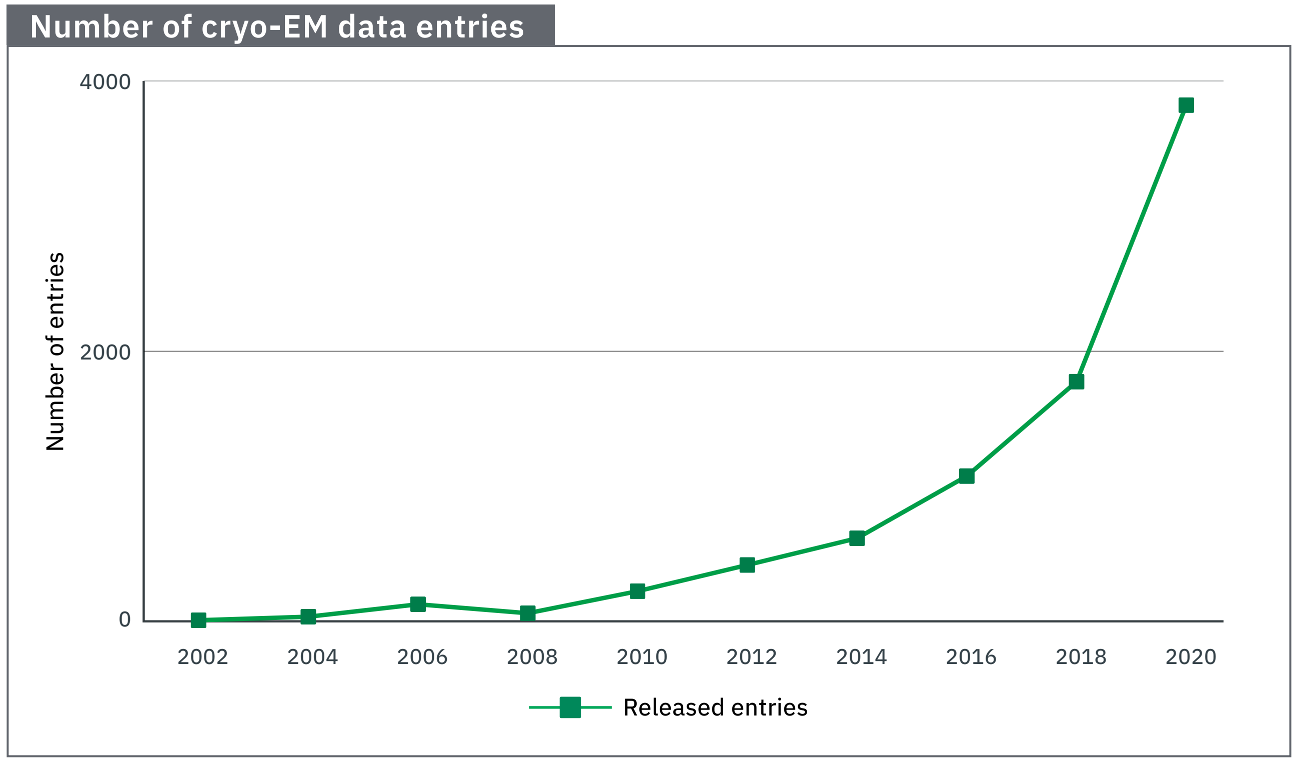
Working at EMBL in Heidelberg in the early 1980s, Group Leader Jacques Dubochet and technician Alasdair McDowall discovered that flash-freezing proteins in liquid ethane could hold them still and preserve their structure, a process called vitrification. This was a critical advance that laid the groundwork for the rise of cryo-EM and was a revolution in structural biology. In recognition of the importance of this work, Dubochet was one of three scientists awarded the 2017 Nobel Prize in Chemistry.[8] EMBL provided Dubochet with a working environment that he described as unique in allowing him to "explore avenues which had not been explored".[9] He expressed his gratitude to EMBL by donating an official replica of his Nobel medal to the organisation:

> ***"I am pleased to offer this copy of my Nobel medal to EMBL in testimony of my great thankfulness to an institution that, in my view, would deserve to be the laureate of the Prize."*** [10]

Jacques Dubochet holding his Nobel medal during Nobel week. Credit: Alexander Mahmoud/Nobel Media

Today, cryo-EM is a game-changing technique for structural biology, enabling molecules to be imaged quickly and in the variety of shapes that they naturally adopt in the cellular environment. In recent years, the number of protein structures determined by cryo-EM has exploded[11]; some experts believe that within the next five years, cryo-EM will become the dominant method for determining protein structures.[12]

8. The Royal Swedish Academy of Sciences (2017). Scientific background on the Nobel Prize in Chemistry 2017: The development of cryo-electron microscopy. https://www.nobelprize.org/uploads/2018/06/advanced-chemistryprize2017.pdf
9. Interview with Jacques Dubochet conducted by Technopolis in September 2021.
10. Furtado Neves S (2018). Jacques Dubochet donates Nobel medal to EMBL. EMBL News, 20 February 2018. https://www.embl.org/news/alumni/jacques-dubochet-donates-nobel-medal-embl/
11. Electron Microscopy Data Bank. https://wwwdev.ebi.ac.uk/emdb/
12. Callaway E (2010). Revolutionary cryo-EM is taking over structural biology. Nature 578:201. DOI: 10.1038/d41586-020-00341-9



Source: Electron Microscopy Data Bank (2021) [13]

EMBL continues to play an important role in this field. Dubochet highlighted that EMBL not only enables researchers to access cryo-EM experimental services but also offers the necessary expertise to fully apply the technique to their research questions: "These methods are complicated and difficult and need to be used and exploited by many researchers. But the capability of exploiting them is by those who are at the cutting edge of cryo-EM." [9]

Cryo-EM clearly has come a long way since Dubochet and McDowall's crucial discovery at EMBL – but as McDowall noted, "Everybody has to vitrify [prepare] the sample. That's still step one." [14]

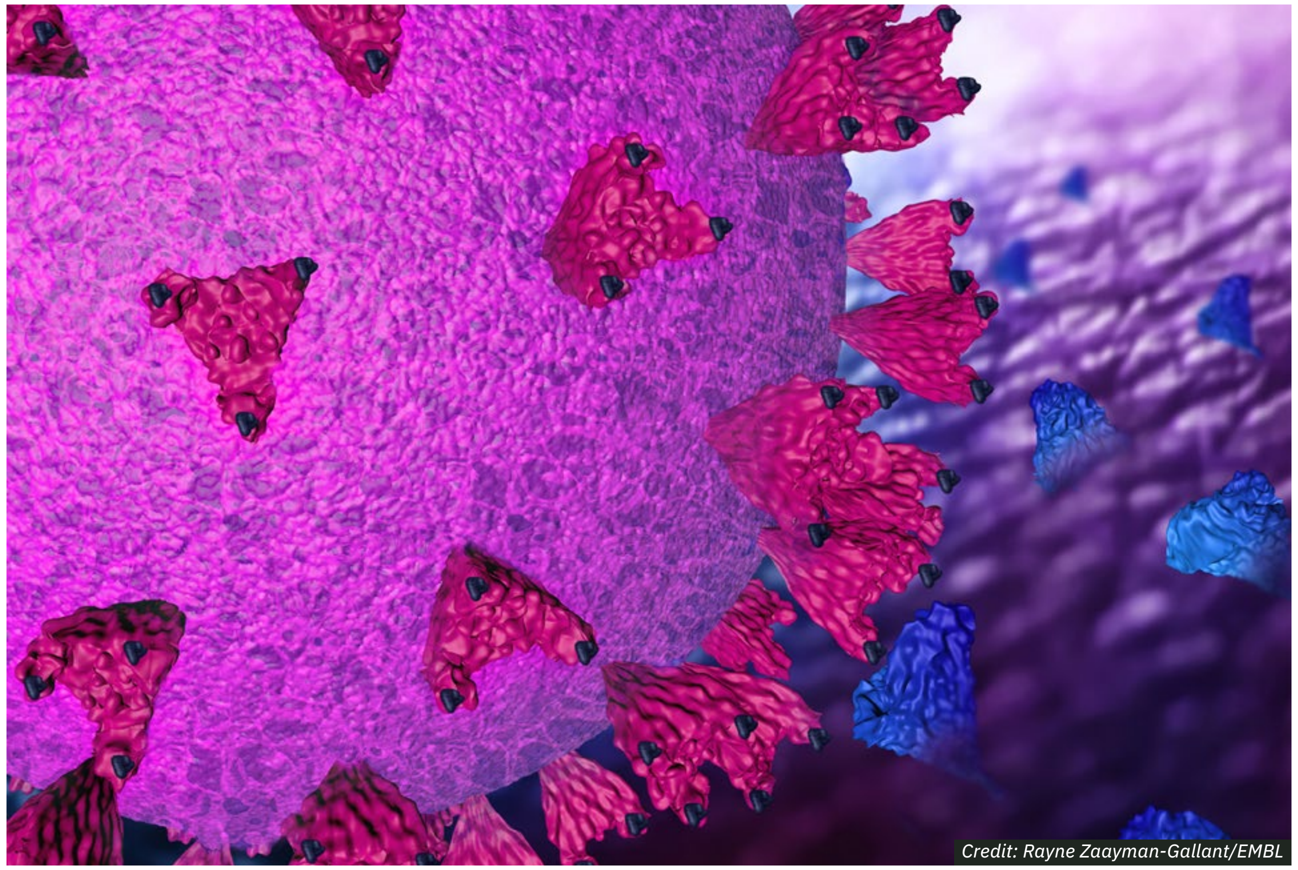
Advancing scientific discoveries towards application

One area in which cryo-EM has led to a step change in the level and speed of progress is in the design and development of vaccines. Starting in the late 1990s, scientists from around the world used cryo-EM to determine the structures of viruses such as the hepatitis B virus, hepatitis C virus, Zika virus, rhinovirus C, dengue virus, and tick-borne encephalitis virus.[15,16] EMBL researchers have played an important part, e.g. by providing insights into the structure of HIV.[17]

13. Electron Microscopy Data Bank. https://www.ebi.ac.uk/emdb/
14. Puschmann SB (2017). Alasdair McDowall's slow road to flash freezing. EMBL News, 8 December 2017. https://www.embl.org/news/alumni/alasdair-mcdowall-slow-flash-freezing/
15. Pool R (2020). Microscopy in the time of Covid-19. Wiley Analytical Science Magazine, 9 September 2020. https://analyticalscience.wiley.com/do/10.1002/was.00020151
16. Earl LA, Subramaniam S (2016). Cryo-EM of viruses and vaccine design. Proceedings of the National Academy of Sciences USA 113(32):8903–8905. DOI: 10.1073/pnas.1609721113
17. EMBL (2014) Same pieces, different picture. Press release, 2 November 2014. https://www.embl.de/aboutus/communication_outreach/media_relations/2014/141102_Heidelberg/

Research on viral structures also formed part of Ilaria Ferlenghi's work at EMBL in the late 1990s – experience she was subsequently able to bring to industry.[18,19] Some 15 years after leaving EMBL, Ferlenghi – now Head of Structural Vaccinology at GSK – has built the company's cryo-EM programme for imaging proteins on the surface of viruses to identify candidate targets for new vaccines.[20] This was possible because the technology has matured to the point where it can yield precise structural information suitable for drug development. Pharmaceutical companies around the world are exploiting cryo-EM for the development of new drugs and treatments for diseases.[21]

As the COVID-19 pandemic unfolded, cryo-EM yielded precise images at an unprecedented pace. Only three weeks after Chinese scientists reported the first genome sequence of the virus[22], researchers reported the structure of the SARS-CoV-2 spike protein[23]; a further five days later, they published images of the spike protein bound to its human target, angiotensin-converting enzyme 2 (ACE2).[24] These insights provided important information that was used in the development of COVID-19 vaccines.[25]



SARS-CoV-2's ability to infect cells relies on interactions between the viral spike protein (magenta) and the protein ACE2 (blue), which is present on the surface of human cells. These interactions can be disrupted by sybodies (black) – synthetic mini-antibodies similar to those produced by camels and llamas.

18. Ferlenghi I et al. (2001). Molecular organization of a recombinant subviral particle from tick-borne encephalitis virus. Molecular Cell 7:593–602. DOI: 10.1016/s1097-2765(01)00206-4
19. Steer E (2018). Translating blue-sky research into the clinic. EMBL News, 30 November 2018. https://www.embl.org/news/lab-matters/translating-blue-sky-research-into-the-clinic/
20. Coulthard-Graf R (2018). Career profile: Ilaria Ferlenghi, Head of Structural Microscopy at GSK Vaccines. EMBL Careers, 28 November 2018. https://blogs.embl.org/careers/career-profile-ilaria-ferlenghi-head-of-structural-microscopy-at-gsk-vaccines/
21. ABPI (2016). Cambridge Pharmaceutical Cryo-EM Consortium. https://linc.abpi.org.uk/case-studies/cambridge-pharmaceutical-cryo-em-consortium
22. Wu F et al. (2020). Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China. BioRxiv 2020.01.24.919183. DOI: 10.1101/2020.01.24.919183
23. Wrapp D et al. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367:1260–1263. DOI: 10.1126/science.abb2507
24. Yan R et al. (2020). Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 27:1444–1448. DOI: 10.1126/science.abb2762
25. Jackson LA et al. (2020). An mRNA vaccine against SARS-CoV2 – preliminary report. New England Journal of Medicine 383:1920–1931. DOI: 10.1056/NEJMoa2022483

Next revolution of cryo-EM

EMBL continues to push methodology development further. The group of John Briggs at EMBL pioneered cryo-electron tomography (cryo-ET)[26], a technique with origins in cryo-EM.[27] While cryo-EM examines highly purified molecules to determine their shapes, cryo-ET allows scientists to take 3D snapshots of molecular interactions inside the cell. This is important, because many complexes cannot be purified; information on both the structure and the location of large molecular complexes in the cell is crucial for understanding their function. Now at the Max Planck Institute of Biochemistry in Munich, Germany, Briggs was the first to achieve extremely precise visualisations of a biological structure using cryo-ET – areas of the protein shell of HIV.[28]

Recently, a group at EMBL led by Julia Mahamid used the same techniques to observe a key molecular machine in action: bacterial RNA polymerase, which turns the organism's genetic code into RNA and protein.[29] Her work has been described by other researchers as "a technical breakthrough".[30] Mahamid highlighted the importance of EMBL in achieving these advances:

> ***"We couldn't have produced this quality of research within just three years of starting a lab without the data and support we have at EMBL. This isn't an incremental advance, but rather a jump. Cryo-EM revolutionised structural biology a few years ago. Our new approach [cryo-ET] is likely to contribute to a second revolution where you can study structures directly while [they are] still inside cells."*** [27]

EMBL continues to develop imaging methods in collaboration with external research groups. "We [EMBL] help to develop methods that are relevant to questions of researchers in external universities by collaborating with them to develop cutting-edge technologies before they become accessible as a service," said Mahamid.[31] Recognising the facility's exceptional instrumentation, its willingness to fine-tune hardware and software as needed, and the lack of bureaucracy in accessing the service, Albert Weixlbaumer from the Institute of Genetics and Molecular and Cellular Biology (IGBMC) in Strasbourg, France, commented:

> ***"The experience at EMBL was as good as it can get. [...] The quality and amount of data we obtained is difficult to match at any of the sites I know."*** [32]

In 2020, Weixlbaumer's collaboration with EMBL resulted in a study revealing insights into bacterial gene expression that was published in the top-tier journal Science.[33]

26. Mattei S et al. (2016). The structure and flexibility of conical HIV-1 capsids determined within intact virions. Science 354(6318):1434–1437. DOI: 10.1126/science.aah4972
27. Kupec I (2020). Seeing deeper into cells. EMBL News, 7 December 2020. https://www.embl.org/news/science/seeing-deeper-inside-cells/
28. Blavatnik Awards Young Scientists (2018). John Briggs – 2018 United Kingdom Award Finalist - Faculty. http://blavatnikawards.org/honorees/profile/john-briggs/
29. O'Reilly FJ et al. (2020). In-cell architecture of an actively transcribing-translating expressome. Science 369(6503):554–557. DOI: 10.1126/science.abb3758
30. Oldach L (2020). New studies define transcription–translation coupling. ASBMB Today, 20 August 2020. https://www.asbmb.org/asbmb-today/science/082020/new-studies-define-transcription-translation-coupl
31. Interview with Julia Mahamid conducted by Technopolis in September 2021.
32. EMBL. Albert Weixlbaumer's story. https://www.embl.org/about/info/imaging-centre/user-stories/albert-weixlbaumer/
33. Webster MW et al. (2020). Structural basis of transcription-translation coupling and collision in bacteria. Science 369(6509):1355–1359. DOI: 10.1126/science.abb5036

What the future holds

EMBL Heidelberg now hosts its state-of-the-art cryo-EM service in a new facility – the EMBL Imaging Centre – which offers a synergistic portfolio of imaging techniques to enable academic and industry users from the international research community to conduct new ground-breaking research.[34] As Ferlenghi described:

> ***"When you have many different techniques in the same place that can be combined, and you can discuss them with the different experts in each field, this is the advantage of having a place like EMBL. On top of that, the passion and curiosity that EMBL [scientists] have is different from what you can get from any other institution."*** [35]

Credit: Foto Tobias Schwerdt/Heidelberg Marketing

EMBL Imaging Centre

34. EMBL. Cryo-electron microscopy. https://www.embl.org/about/info/imaging-centre/cryo-electron-microscopy/
35. Interview with Ilaria Ferlenghi conducted by Technopolis in September 2021.

D.2 Pioneering SAXS: Using X-rays to make the invisible visible in biological solutions

Introduction

Small-angle X-ray scattering (SAXS) is a powerful technique for studying the size, shape, and dynamics of large biological molecules to help unveil their function. SAXS is one of few structural biology technologies that can provide essential information about molecules directly in solution without the need to crystallise or flash-freeze samples. This opens up the possibility of probing proteins and nucleic acids in a variety of experimental conditions and of addressing biological questions relevant to applications ranging from drug discovery to synthetic biology.

The beamline P12 at EMBL Hamburg
Credit: Svergun group/EMBL

Dmitri Svergun, Group Leader at EMBL Hamburg, has made exceptional contributions to SAXS instrumentation and has developed new methods, analysis tools, and software over the past two decades to bring SAXS into the mainstream for the structural biology research community worldwide.[36,37]

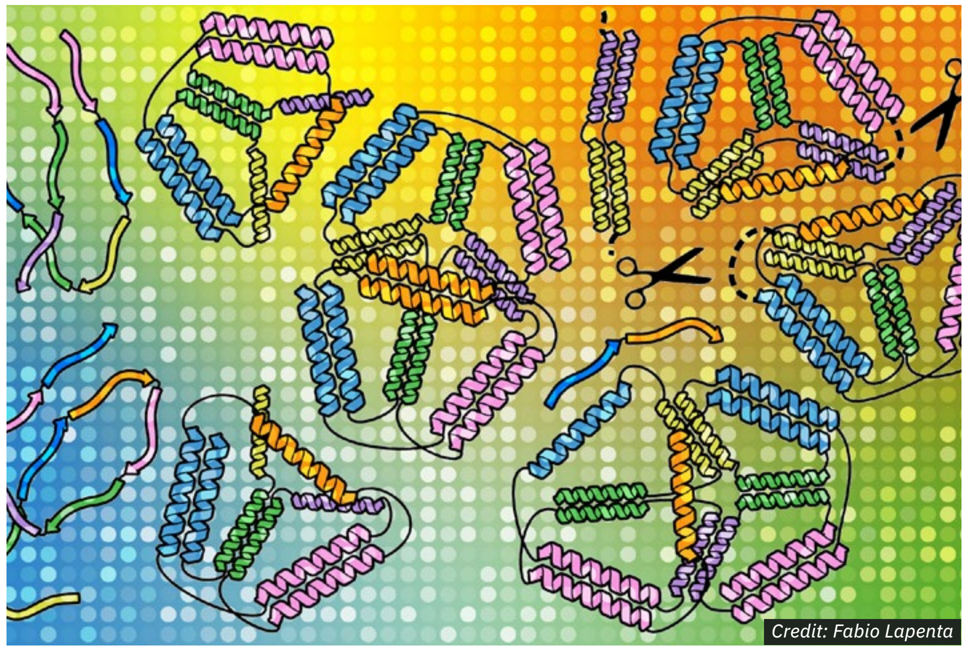
The Svergun Group developed (and now operates) EMBL's SAXS beamline, which is powered by one of the world's brightest X-ray radiation sources, PETRA III at the German Electron Synchrotron Radiation Facility (DESY) in Hamburg. In conjunction, improvements in associated software tools have unlocked the potential of using high-throughput SAXS data to derive models of 3D molecular structures. ATSAS, developed at EMBL, is one of the most popular and comprehensive software packages for analysing and modelling SAXS data.[38] The software has been downloaded more than 100,000 times by over 18,000 unique users from over 50 countries.[39] Svergun also coordinated an initiative to improve sharing of SAXS resources and the unification of data standards and guidelines across SAXS facilities and communities in Europe.[40] SAXS data from various research groups using beamlines around the world can now be easily shared and re-used in dedicated open-source databases such as SASBDB, which is maintained by EMBL.[41] SASBDB contains over 2,400 experimental data sets (30% produced by EMBL's SAXS beamline), which have been used to generate over 3,500 models (80% of which used the ATSAS software).

36. Gräwert M, Svergun D (2020). A beginner's guide to solution small-angle X-ray scattering (SAXS). Biochemistry (London) 42(1):36–42. DOI: 10.1042/BIO04201036
37. The Svergun Group at EMBL Hamburg. https://www.embl.org/groups/svergun/
38. EMBL. Data analysis software ATSAS 3.0.4. https://www.embl-hamburg.de/biosaxs/software.html
39. Manalastas-Cantos K et al. (2021). ATSAS 3.0: expanded functionality and new tools for small-angle scattering data analysis. Journal of Applied Crystallography 54(Pt 1):343–355. DOI: 10.1107/S1600576720013412
40. SAXIER: Small-Angle X-Ray Scattering Initiative for Europe is coordinated by EMBL Hamburg. See: https://www.saxier.org/aboutus/mission.shtml
41. For an overview of the Small Angle Scattering Biological Data Bank, see: https://www.sasbdb.org/aboutSASBDB/

Advancing scientific discoveries

Today, SAXS is accessible to even novice users and has become an invaluable tool for structural biologists to determine nanoscale structures and their dynamic changes over time. Since EMBL's newest SAXS beamline became available to the scientific community in 2012, an average of 250 users from around the world have taken advantage of this service every year. [42]

One area where SAXS has been transformative is in synthetic biology. Recently, a team of Slovenian researchers led by Roman Jerala from the National Institute of Chemistry, Ljubljana, determined the molecular structure of artificial proteins using SAXS, in collaboration with EMBL scientists.[43,44] This work builds on previous research where Jerala's group invented a method to design new protein structures named 'coiled-coil protein origami' after the Japanese art of paper folding.[45] By using EMBL experimental services, the researchers were able to determine the molecular structures of synthetic proteins, show that they folded into the desired shape, and study the self-assembly process. This collaboration demonstrates EMBL's strength in taking an integrative structural biology approach: the molecular structures were verified and probed by combining SAXS data with data obtained from multiple other techniques at EMBL, such as electron microscopy, calorimetry, and computational modelling. Such an approach can have wide-reaching potential, according to Jerala: "We can tailor designed proteins to make new materials, deliver drugs and vaccines, and much more."[8] Scientists at EMBL provided not only their expertise in SAXS but also the "tools to help make sense of the SAXS experimental data and create 3D models". Fabio Lapenta, a postdoctoral researcher working on the project, highlighted the importance of working with EMBL: "SAXS analysis was crucial in identifying which design leads to the desired shapes, and the superb tools developed at EMBL allowed us to detect unique features of our designed cages [proteins]."[8] The results of the study were published in the leading scientific journal Nature.[44]



Credit: Fabio Lapenta

Using EMBL Hamburg's world-class beamline P12 at DESY's PETRA III synchrotron, researchers directed powerful X-ray beams at artificial proteins called coiled-coil origami proteins.

42. Data provided by the Small Angle Scattering Biological Data Bank on 31 August 2021.
43. Kupec I (2021). EMBL Hamburg lights the way to folding next-level origami. EMBL News, 9 April 2021. https://www.embl.org/news/science/embl-hamburg-lights-the-way-to-folding-next-level-origami/
44. Lapenta F et al. (2021). Self-assembly and regulation of protein cages from pre-organised coiled-coil modules. Nature Communications 12:939. DOI: 10.1038/s41467-021-21184-6

EMBL Hamburg's reputation for the application of SAXS in complex research projects has led to growing interest from and collaborations with industry. In late 2015, EMBL launched BIOSAXS, a spin-off company offering SAXS services to industry for medical and material sciences research.[46] Projects are planned in close consultation with industry users and carried out by the expert team at EMBL, ensuring high-quality results.

In 2020, BioNTech, a biotech company working with Pfizer, used BIOSAXS for Project Lightspeed, a groundbreaking programme to develop a vaccine against COVID-19.[47] In the words of Ugur Sahin, Chief Executive Officer of BioNTech:

> ***"Our aim is clear: Making a potential vaccine available to the public as quickly as possible – worldwide."*** [48]

To realise this mission, BioNTech, together with researchers at Johannes Gutenberg University Mainz, Tel Aviv University, Leiden University, and Forschungszentrum Jülich, published the results of several studies using SAXS to show how to improve the packaging and delivery of RNA into human cells.[49, 50, 51] These studies paved the way for the development of a new class of vaccines that use lipid nanoparticles to deliver messenger RNA (mRNA) into cells. In less than a year, this research resulted in a pioneering mRNA vaccine against COVID-19, which is now available in over 116 countries worldwide.[7,52] The work showcases EMBL's important role in supporting industry and academic collaborations to accelerate innovation in technology and medicine. Scientists at EMBL are also using SAXS to model the structure of coronavirus to develop new tests and treatments in collaboration with other researchers.[53]

What the future holds

EMBL continues to push boundaries, expanding its offer of new applications and its role as a 'one-stop shop' for integrative structural biology services for the scientific community.[54,55] The future arrival of PETRA IV, an even more powerful X-ray source, at EMBL Hamburg in 2025 "will offer a unique opportunity to start an entirely new era of services in structural biology", said Matthias Wilmanns, Head of EMBL Hamburg. Integrated with other techniques, SAXS will continue to play an important role in the comprehensive structural analysis of biological molecules in solution.

46. EMBLEM (2021). BIOSAXS. https://embl-em.de/company/portfolio-companies/biosaxs/
47. Badowska D (2020). EMBL facilities support development of RNA vaccines. EMBL News, 1 December 2020. https://www.embl.org/news/science/biontech-uni-mainz-embl-hamburg/
48. BioNTech. Project Lightspeed. https://biontech.de/covid-19-portal/project-lightspeed
49. Siewert CD et al. (2020). Hybrid biopolymer and lipid nanoparticles with improved transfection efficacy for mRNA. Cells 9(9):2034. DOI: 10.3390/cells9092034
50. Nogueira SS et al. (2020). Polysarcosine-functionalized lipid nanoparticles for therapeutic mRNA delivery. ACS Applied Nano Materials 3(11):10634–10645. DOI: 10.1021/acsanm.0c01834
51. Uebbing L et al. (2020). Investigation of pH-responsiveness inside lipid nanoparticles for parenteral mRNA application using small-angle X-ray scattering. Langmuir 36(44):13331–13341. DOI: 10.1021/acs.langmuir.0c02446
52. Holder J (2021). Tracking coronavirus vaccinations around the world. New York Times, 28 October 2021. https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html
53. Gristwood A (2020). Shining high-brilliance beams on coronavirus structure. EMBL News, 9 June 2020. https://www.embl.org/news/science/shining-high-brilliance-beams-on-coronavirus-structure/
54. EMBL (2007) New facility for structural biology to investigate the molecules of life with powerful synchrotron radiation. Press release, 1 February 2007. https://www.embl.org/news/lab-matters/new-facility-for-structural-biology/
55. Badowska D (2021). Shaping the future of structural biology and X-ray imaging at EMBL Hamburg. EMBL News, 12 May 2021. https://www.embl.org/news/events/shaping-the-future-of-structural-biology-and-x-ray-imaging-at-embl-hamburg/

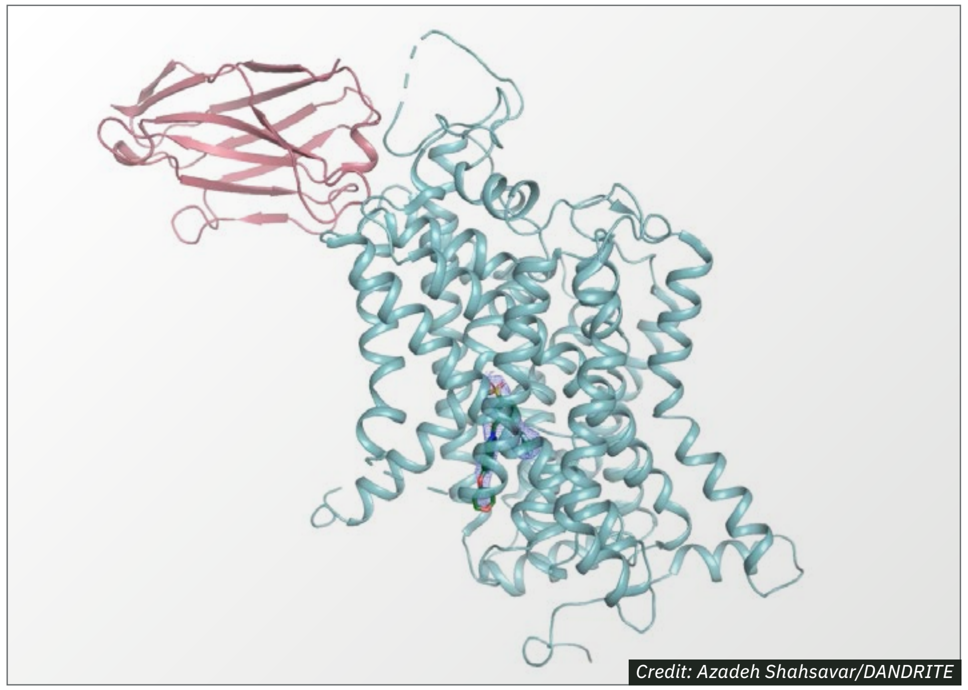
APPENDIX D: CASE STUDIES

D.3 EMBL enables academia and industry to find new avenues in developing drugs for psychiatric disorders

Introduction

Schizophrenia is a chronic and debilitating mental health disorder affecting approximately 20 million people worldwide.[56] Designing drugs to target glycine transporter 1 (GlyT1) could provide new treatments for schizophrenia and other psychiatric disorders. However, developing successful drug candidates has been hampered by the lack of knowledge of the GlyT1 structure.

To reveal the 3D structure of GlyT1 and gain insights into new strategies for drug design, researchers from F. Hoffmann-La Roche (known as Roche), Linkster Therapeutics, and the Danish Research Institute of Translational Neuroscience (DANDRITE) at Aarhus University, which is part of the Nordic EMBL Partnership for Molecular Medicine, collaborated with EMBL Hamburg.[57]



3D molecular structure of glycine transporter 1 (GlyT1).

How it started

Roche had been investing in drug discovery projects to develop small-molecule inhibitors for GlyT1 for over a decade. One of its most promising drug candidates, bitopertin, had reached phase III clinical trials but failed to show any efficacy compared to placebo.[58]

56. World Health Organization (2019). Schizophrenia. WHO, 4 October 2019. https://www.who.int/news-room/fact-sheets/detail/schizophrenia.
57. DANDRITE (2021). About the Nordic EMBL Partnership. https://dandrite.au.dk/about-dandrite/the-nordic-embl-partnership/about-the-nordic-embl-partnership/
58. Bugarski-Kirola D et al. (2017). Bitopertin in negative symptoms of schizophrenia – results from the phase III FlashLyte and DayLyte studies. Biological Psychiatry 82(1):8–16. DOI: 10.1016/j.biopsych.2016.11.014

One of Roche's lead researchers, Roger Dawson (now founder and Chief Executive Officer of Linkster Therapeutics), wanted to understand why the drug had failed, as this could provide new insights to design better drugs.

What happened

Dawson initially teamed up with Poul Nissen and postdoc Azadeh Shahsavar from DANDRITE. The Nissen Group set out to resolve the structure of GlyT1 in combination with bitopertin using X-ray crystallography, a powerful technique that provides detailed 3D models of proteins to gain insights into their structure and function.

When standard methods to resolve the structure of GlyT1 failed, the research team brought in EMBL's expertise in developing advanced methodologies. The EMBL Interdisciplinary Postdoctoral (EIPOD) programme was an important enabler of the collaboration; EIPOD supports postdocs to work on research projects involving academic and industry partners in collaboration with scientists at EMBL.

> ***"The EIPOD programme helped open up and accelerate discussions with Roche now that we were putting the project in a cutting-edge collaboration with EMBL,"***

commented Nissen, Director of DANDRITE and senior researcher on the study.[59] Shahsavar was able to collect the data for the study during her time as a postdoc in the EIPOD programme, during which she worked at EMBL Hamburg, DANDRITE, and Roche.

At EMBL Hamburg, Shahsavar worked in the Schneider Group, which developed the Serial Synchrotron Crystallography approach that allowed her to collect data from hundreds of microcrystals using EMBL Hamburg's state-of-the-art P14 beamline. The Schneider Group then developed software to combine data from microcrystals to reveal the full picture of GlyT1 at high resolution.

> ***"The game changer was when EMBL joined and brought the advanced methodology and software to enable this project to [reach] the end stage," said Dawson.***[60]

Thomas Schneider, Joint Head of EMBL Research Infrastructures, commented: "For challenging projects like this, we are happy to put the methodological expertise of our staff to work and to make full use of the technological capabilities of our beamlines and sample preparation facilities."[61] Nissen agreed:

> ***"EMBL has proved time and time again they can really drive developments in imaging and bioinformatics."***[59]

59. Interview with Poul Nissen conducted by Technopolis in September 2021.
60. Interview with Roger Dawson conducted by Technopolis in September 2021.
61. Badowska D (2021). New perspectives for treating psychiatric disorders. EMBL News, 6 April 2021. https://www.embl.org/news/science/glyt1-structure-psychiatric-disorders/

APPENDIX D: CASE STUDIES

What the future holds

The structure of GlyT1 was published in the leading scientific journal Nature.[62] The study highlights the importance of both scientific excellence and the availability of cutting-edge infrastructure, advanced methodology, and software for progressing research – all of which are provided by EMBL Hamburg.

Findings from the study provided insights into why the drug candidate bitopertin failed to inhibit GlyT1: "This structure provides a blueprint for developing new inhibitors of GlyT1, be they organic molecules or antibodies," explained Dawson. The study also uncovered a binding site on GlyT1 that inhibits its function; this knowledge can be used to develop drugs targeting GlyT1 and other membrane transport proteins.

DANDRITE continues to benefit from being part of the Nordic EMBL Partnership. As Nissen explained, "We [DANDRITE] are more interesting to the outside world and to industry by being so tightly connected to EMBL through a partnership. The EMBL brand has opened opportunities for many other grant applications and collaborations."[59] Shahsavar added:

> ***"As an external user, I keep thinking of ways to keep my link to EMBL. It's not just the infrastructure, it's the science-focused mentality. I haven't seen that in many places."***[63]

D.4 EMBL supports the 'impossible': Mapping the ribosome

Cells use large molecular 'machines' – assemblies of molecules called ribosomes – to turn their genetic code into protein. This process of translation is essential for life and is present in all organisms. While their basic working mechanisms are similar, ribosomes in bacteria (prokaryotes) and higher organisms (eukaryotes) have different structures. These differences present an important opportunity: around half of the antibiotics currently in use selectively target the prokaryotic ribosome to disrupt protein synthesis and stop microbial attack.[64] Understanding the structure and mechanism of the translational machinery can provide key information for research on new antibiotics and on antibiotic resistance – an issue of critical importance that is threatening effective prevention and treatment of infectious diseases.

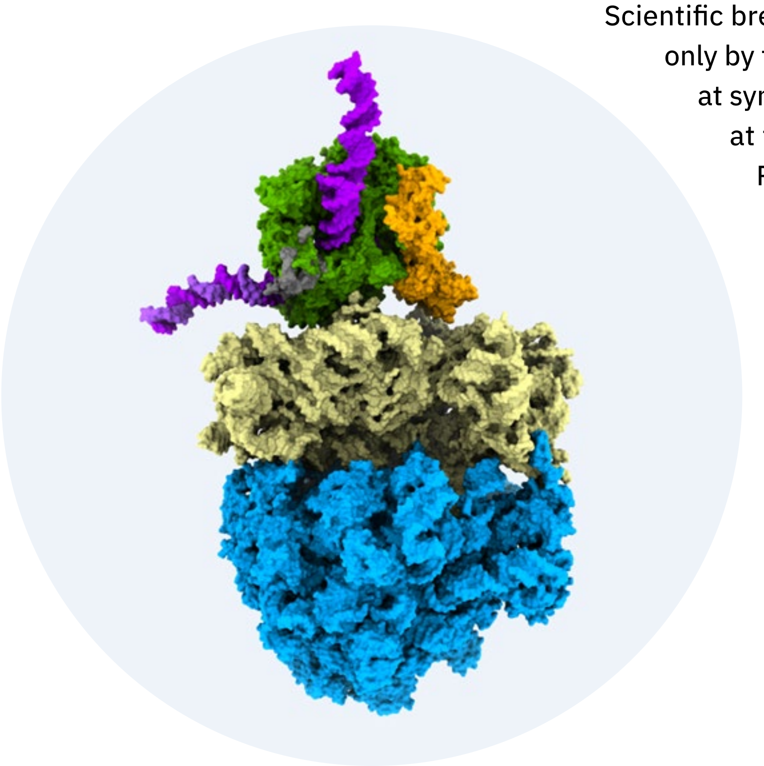
Ada Yonath gives Jentschke Lecture
Credit: Marta Mayer/DESY

62. Shahsavar A et al. (2021). Structural insights into the inhibition of glycine reuptake. Nature 591(7851):677–681. DOI: 10.1038/s41586-021-03274-z
63. Interview with Azadeh Shahsavar conducted by Technopolis in September 2021.
64. Wei Y, Daunert S (2010). Enabling technologies in discovery: the 2009 Nobel Prize and its implications in antibiotic design. Analytical and Bioanalytical Chemistry 396(5):1623–1626. DOI: 10.1007/s00216-009-3427-z

Ribosomes were first described as cellular organelles in the 1950s.[65] Over the next decade, scientists managed to work out the central role that ribosomes play in all living cells, but they were unable to determine their structure or precise mechanism. In the 1970s, studies using classical electron microscopy provided the first views of the ribosomal architecture, albeit at fairly low resolution. To improve on the 'blobby' electron microscope image, the researchers would need to use X-ray crystallography. This technique requires the large molecular assembly of the ribosome to be arranged into a regular order – a crystal – a feat that seemed well beyond the achievable at the time.

In the late 1970s, Israeli crystallographer Ada Yonath decided to tackle ribosomal crystallography, more than a decade before others entered the field.[66] Throughout the 1980s and early 1990s, Yonath worked to coax ribosomes into more ordered lattices and tested the resulting crystals using powerful X-rays. This is where scientists at EMBL Hamburg and EMBL Grenoble were able to help Yonath to tackle this seemingly impossible task.

Scientific breakthroughs are often made possible only by technological innovation. Using beamlines at synchrotrons, such as the EMBL beamline at the German Electron Synchrotron Radiation Facility (DESY) in Hamburg, Yonath not only showed success in growing ribosomal crystals, but also developed a method for freezing biological crystals that allowed them to survive the intense beams for longer.[67,68] The technique, termed cryo-crystallography, enabled Yonath to obtain crystallographic data on ribosomes – and has since become routine in structural studies of macromolecules.



Molecular structure of the ribosome (pale yellow and blue) as imaged by EMBL Group Leader Julia Mahamid in 2020. Credit: Liang Xue, Julia Mahamid/EMBL

65. Puglisi JD (2009). Resolving the elegant architecture of the ribosome. Molecular Cell 36(5):720–723. DOI: 10.1016/j.molcel.2009.11.031
66. The Nobel Prize (2009). Ada E. Yonath. https://www.nobelprize.org/womenwhochangedscience/stories/ada-yonath
67. Hope H et al. (1989). Cryocrystallography of ribosomal particles. Acta Crystallography B 45:190–199. DOI: 10.1107/s0108768188013710
68. Berkovitch-Yellin Z et al. (1991). Crystals of 70S ribosomes from thermophilic bacteria are suitable for X-ray analysis at low resolution. Journal of Crystal Growth 110:208–213
69. The Nobel Prize (2009). The Nobel Prize in Chemistry 2009. https://www.nobelprize.org/prizes/chemistry/2009/summary/
70. Wilson R (2014). Dinner with a Nobel Laureate. EMBL News, 11 December 2014. https://www.embl.org/news/lab-matters/1412_yonath/
71. "These studies could not be performed without the cooperation, assistance and advice of the staff of the synchrotron radiation facilities at EMBL and MPG at DESY, ID14 at EMBL/ESRF, and ID19/APS/ANL." From the Acknowledgments section of Professor Ada Yonath's Scientific Activities webpage at the Weizmann Institute of Science. http://www.weizmann.ac.il/csb/faculty_pages/Yonath/00Sc_activities.html
72. Written quote provided by Ada Yonath to Technopolis in September 2021.
73. Matzov D et al. (2017). A bright future for antibiotics? Annual Review of Biochemistry 86:567–583. DOI: 10.1146/annurev-biochem-061516-044617
74. Polikanov YS et al. (2018). The mechanisms of action of ribosome-targeting peptide antibiotics. Frontiers in Molecular Biosciences 5:48. DOI: 10.3389/fmolb.2018.00048
75. Martin B (2017). Designing selective antibiotics can reduce drug resistance, says Nobel laureate. Imperial College London, 24 March 2017. https://www.imperial.ac.uk/news/178380/designing-selective-antibiotics-reduce-drug-resistance/

The breakthrough occurred in 2000 and 2001, when the hard work of Yonath and other groups paid off: together, they revealed the structure of ribosomal particles at atomic resolution.[65] In recognition of this achievement, Yonath was awarded the 2009 Nobel Prize in Chemistry alongside two other crystallographers.[69] Yonath worked on the EMBL beamlines during her time as head of a unit of the Max Planck Institute for the Structure and Dynamics of Matter at DESY from 1986 to 2004.[70] She highlighted the crucial contribution of EMBL in providing experimental equipment for her studies:

> ***"EMBL provided the equipment needed for our biochemical preparations and storage."***[71,72]

Yonath continues to conduct research on ribosomes. Today, she focuses on how structural changes in the ribosome, as a result of mutations in the bacterial genome, make them resistant to antibiotics.[73] This knowledge is paving the way for the design of new and improved antibiotics.[74,75]

The following year after being awarded the Nobel Prize, with the basic structure in hand, Yonath was able to solve the structures of five antibiotics bound to the ribosome. The structures demonstrated how these drugs stop translation – and thereby kill the organism.[76]

EMBL researchers are also addressing the issue of antibiotic resistance. For example, a group led by Orsolya Barabas at EMBL Heidelberg reported the first crystal structure of a protein-DNA machine that inserts transposons into the bacterial genome.[77,78] In this way, transposons can transfer antibiotic resistance genes between bacteria, a key mechanism by which resistance spreads. The group then designed ways to help control the spread: based on the crystal structure, Barabas and colleagues developed molecules and provided proof of principle for how they could block the transposons' movement.

D.5 EMBL supports transfer of innovative technology to industry and academia

Introduction

The interplay between EMBL's external users and EMBL facility scientists has inspired numerous developments in experimental techniques and instruments. EMBL is committed to maximising the social value derived from these developments through its technology transfer partner, EMBLEM. Many spin-offs have been established and scaled up to make experimental services developed at EMBL widely available to academia and industry. EMBLEM has also facilitated partnerships with industry to commercialise instruments developed at EMBL.

The following subsections describe three examples of how EMBL experimental services have been scaled up and disseminated to make these technologies available to the wider scientific community.

76. Schlünzen F et al. (2001). Structural basis for the interaction of antibiotics with the peptidyl transferase centre in eubacteria. Nature 413(6858):814–821. DOI: 10.1038/35101544
77. Rubio-Cosials A et al. (2018). Transposase-DNA complex structures reveal mechanisms for conjugative transposition of antibiotic resistance. Cell 173:208–220. DOI: 10.1016/j.cell.2018.02.032
78. EMBL (2018). Potential new way to limit antibiotic resistance spreading. Press release, 15 March 2018. https://www.embl.de/aboutus/communication_outreach/media_relations/2018/0315_Cell_Barabas/

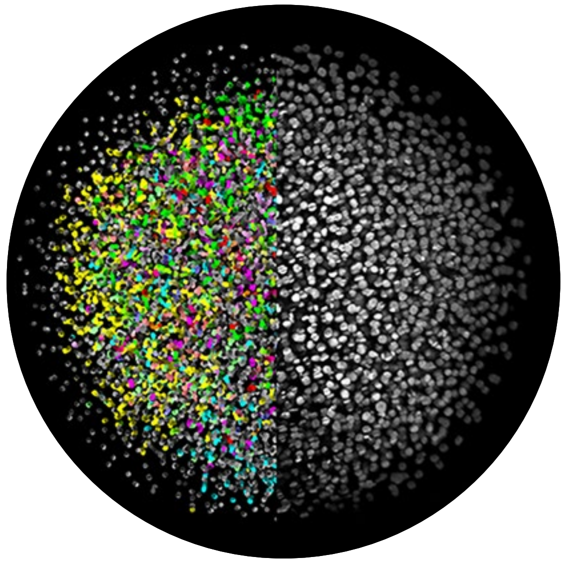
Luxendo

Development of SPIM technology

The invention of single plane illumination microscopy (SPIM) technology started in Ernst Stelzer's lab at EMBL in the early 2000s.[79] SPIM allows minimally invasive 3D imaging of multicellular specimens at high resolution and has many applications, such as modelling tissue development and disease progression.[80] Almost two decades on, the Stelzer lab at EMBL developed a fluorescence SPIM microscope that allowed scientists for the first time to watch a living embryo develop at the cellular level.[81] The SPIM technology was further developed by Lars Hufnagel, a former group leader in the Cell Biology and Biophysics Unit at EMBL, so that larger samples could be studied at high resolution. Hufnagel described the key advance in a Nature Methods paper, which was later recognised by Nature as Method of the Year 2014.[82] The development of this new technology sparked a lot of interest from the research community: "We were contacted by a number of labs that wanted to get access to this disruptive technology," said Jürgen Bauer, EMBLEM's deputy managing director. The demand for SPIM technology inspired EMBLEM to create the company Luxendo to make the technology widely available to the scientific community.

Scaling up SPIM for the scientific community

Luxendo was founded in 2015 to commercialise the novel microscopy technique. The start-up, which is based at EMBL Heidelberg, benefited from both external investment and internal scientific expertise and access to EMBL users, who provided feedback on prototypes and early versions of commercial products. In October 2015, Luxendo raised €8 million in venture capital funding from EMBL Ventures and Life Science Partners to further scale and commercialise SPIM microscopes. The rapid success of the company increased the need to find an external partner to help with the distribution channel and increase Luxendo's international presence. In 2017, Bruker (a USA-headquartered public limited company manufacturing a wide range of scientific instruments for health and life sciences applications) acquired Luxendo with a valuation of €17 million.



Keller's digital zebrafish – the first complete developmental blueprint of a vertebrate. Credit: Keller et al./EMBL

Hufnagel joined Bruker as Vice President and General Manager of Luxendo to take the "brainpower from EMBL to Bruker" and continue innovating the technology.[83] He has since developed several new SPIM products and has kept the EMBL tradition of fostering an open science:

79. Lemonick S (2015). SPIM doctors. EMBL News, 17 December 2015. https://www.embl.org/news/science/1512-spim/
80. Hinton-Sheley P (2018) Single plane illumination microscopy. News-Medical, 11 September 2018. https://www.news-medical.net/life-sciences/Single-Plane-Illumination-Microscopy.aspx
81. Keller PJ et al. (2008). Reconstruction of zebrafish early embryonic development by scanned light sheet microscopy. Science 322(5904):1065–1069. DOI: 10.1126/science.1162493
82. Nature Methods (2014). Method of the Year 2014. Nature Methods 12:1. DOI: 10.1038/nmeth.3251

> ***"We play an active role in supporting the open-source community by integrating and maintaining data processing tools."***

This declaration reflects the willingness of the private instrumentation sector to support a hybrid distribution model, where private companies sell their products at commercial rates while making software and tools openly available.

What the future holds

As a result, EMBL's SPIM technology has come into widespread scientific use, and EMBL has been able to invest the proceeds from the trade sale into the launch and early-stage funding of several other EMBL spin-offs. Through Bruker, SPIM microscopes are now available in more than 100 laboratories worldwide (including across the USA, Europe, and Asia). Most customers (90%) are based at research universities or institutions and work in one of several application areas (such as biology, stem cells, brain neuroscience, and clear tissue). Over the past two years, however, this technology has been also requested more frequently by contract research organisations and pharmaceutical companies.

Most recently, Memorial Sloan Kettering Cancer Center (MSKCC) in New York City has purchased SPIM microscopes from Bruker to visualise how cancer cells develop, with the aim of discovering new cancer treatments.

> ***"Instruments such as these [SPIM microscopes] are useful for imaging [cancer cells] (...) and processes that enable [them to spread],"***

explained Anna-Katerina Hadjantonakis, Chair of the Developmental Biology Program, at MSKCC.[84]

ALPX

Development of fully automated macromolecular crystallography

Over the past two decades, automation has been introduced in macromolecular crystallography at a rapid pace, revolutionising both crystallisation procedures and the use of beamlines. Nonetheless, crystal harvesting continues to be a relatively slow process, with potential implications for crystal quality, speed, reliability, and throughput. To address these shortcomings, in 2008, Jose Marquez and Florent Cipriani, scientists at EMBL Grenoble, developed the CrystalDirect technology and the web-based Crystallographic Information Management System (CRIMS) software.[85] Together, these technologies enable a fully automated protein-to-structure pipeline that can be piloted remotely from any computer anywhere in the world.

83. Interview with Lars Hufnagel conducted by Technopolis in September 2021.
84. Bruker (2021). Bruker light-sheet microscopes at major comprehensive cancer center. Press release, 24 March 2021. https://www.bruker.com/ja/news-and-events/news/2021/bruker-light-sheet-microscopes-at-major-comprehensive-cancer-center.html

EMBL has played a critical role in translating the initial idea behind CrystalDirect technology into direct applications in structure-based drug design.

> ***"[EMBL is] a fantastic place to do research and development, [it was] almost like an incubator because we started with the technological development and then applied it to different project cases,"***

said Irina Cornaciu, co-founder and Chief Executive Officer of ALPX. "Over the course of a few years, the attention and requests for services from third parties has increased to a level where spinning off the commercial CrystalDirect services into a separate company became the logical next step" to ensure that demand could be satisfied at a rapid pace, Cornaciu explained.[86]

Scaling up CrystalDirect and CRIMS for industry

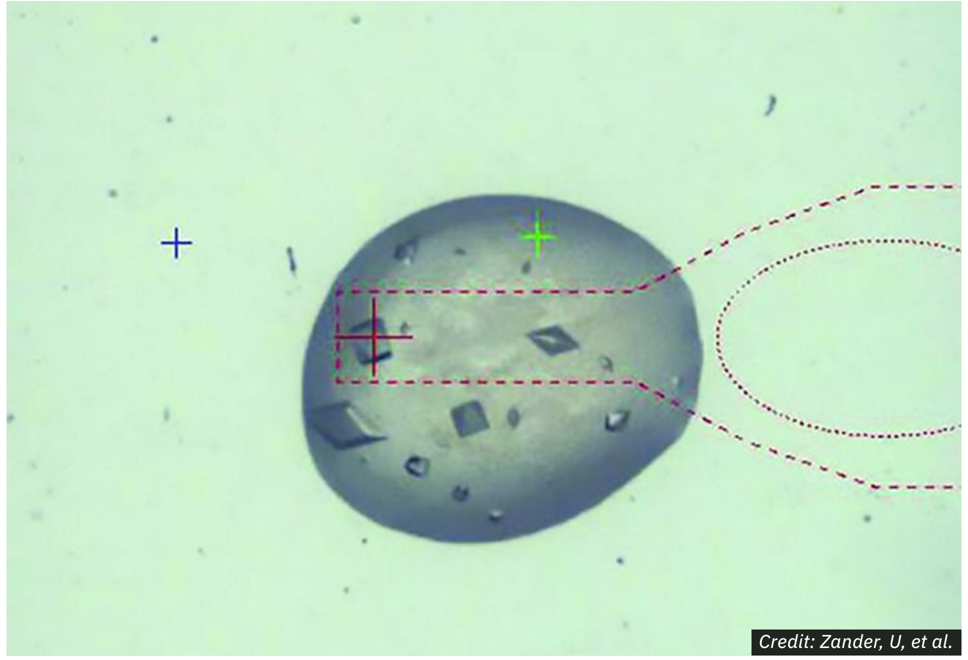
ALPX was founded in 2019 at EMBL Grenoble. It provides industry users with access to its high-throughput crystallisation and fragment screening facility, the HTX Lab, based on the CrystalDirect technology. CRIMS can be operated remotely to fully automate crystallography pipelines. It is capable of screening small-molecule libraries of more than 1,000 fragments, over multiple projects. CrystalDirect technology and CRIMS is in high demand among academic and industry users, with particular interest from the pharmaceutical industry, which uses the screening facility to support structure-based drug development programmes.

Throughout the development process, EMBLEM has been working and supporting the scientists behind the technology. "EMBLEM not only took care of securing intellectual property rights, such as patents, trademarks, and copyrights associated with the technology, but also helped to establish CrystalDirect services for industrial partners," said Jürgen Bauer, Deputy Managing Director of EMBLEM.[86]

What the future holds

ALPX's services are increasingly critical to industry's – and academia's – efforts to improve and accelerate the drug development pipeline through faster screening of much larger numbers of candidate molecules and targets. This in turn could help to combat the spiralling cost of drug development and the resultant increase in the price of medicines. From this perspective, EMBL is supporting a strategic European industry and contributing indirectly to European Union policy commitments in the health sector around the affordability and equality of access to medicines and to Europe's Beating Cancer Plan. In addition, while ALPX is working mainly with the healthcare sector initially, its technology might also have important agricultural applications – such as developing new pesticides and fertilisers, which could bring environmental benefits in the long term.

85. Cipriani F et al. (2012). CrystalDirect: a new method for automated crystal harvesting based on laser-induced photoablation of thin films. Acta Crystallographica Section D, Biological Crystallography 68(10):1393–1399. DOI: 10.1107/S0907444912031459
86. Jäger M (2020). ALPX – smart crystallography. EMBL News, 8 July 2020. https://www.embl.org/news/lab-matters/alpx/



CrystalDirect robot control software: signal from a video camera monitoring the laser working area.

Arinax

Development of instrumentation for synchrotron X-ray and neutron beamlines

Scientific breakthroughs are often made possible only by innovative technological developments. The Instrumentation Team at EMBL Grenoble has developed innovations to further advance the capabilities of EMBL technologies, such as X-ray crystallography.

X-ray crystallography involves shining intense X-ray beams at protein crystals to determine their structure. When the high-brilliance, third-generation synchrotron source at the ESRF opened in 1994, the entire operation of sample handling on crystallography beamlines was done manually.[87]

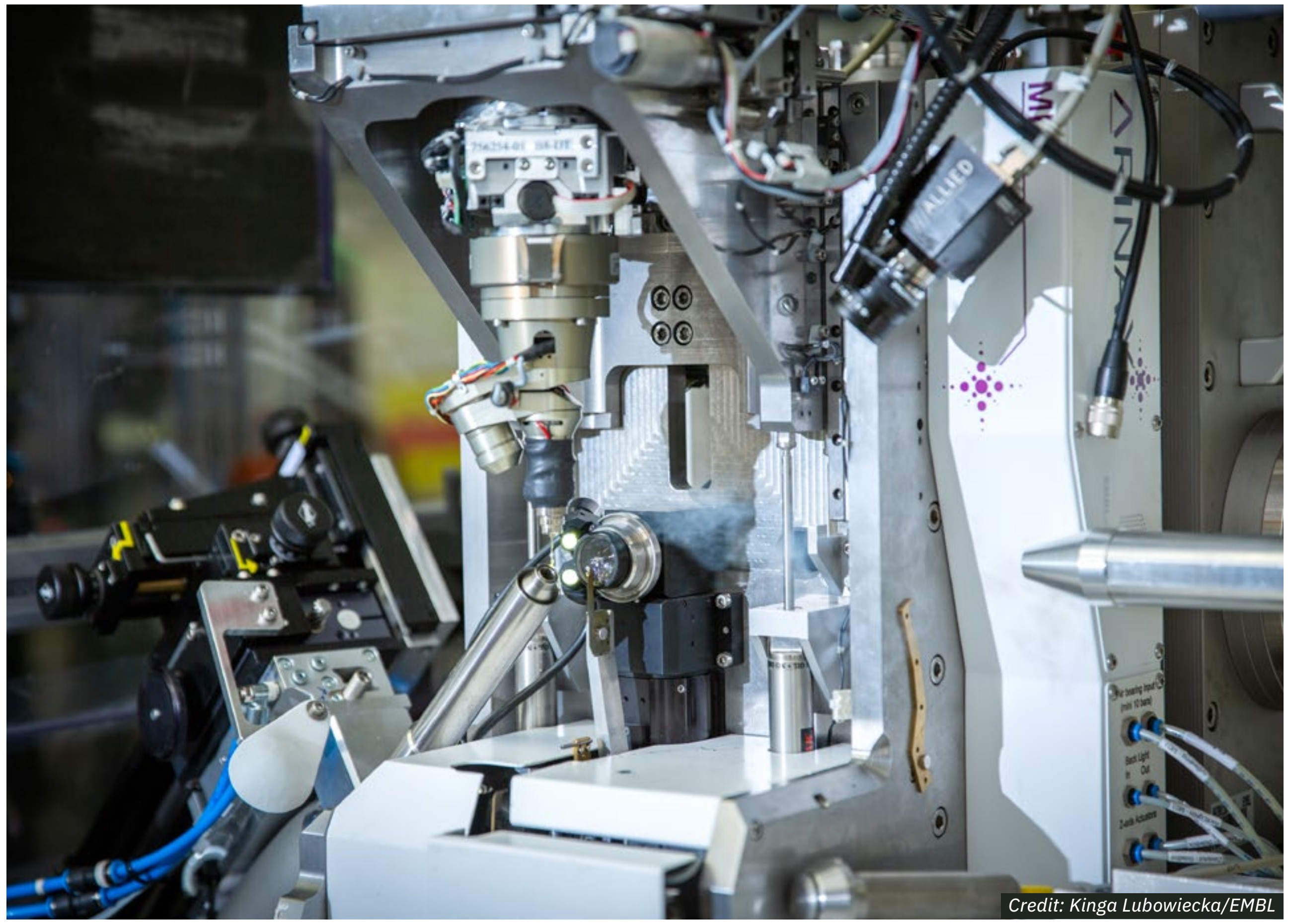
Since the opening of the synchrotron source at the ESRF, the Instrumentation Team at EMBL Grenoble has worked closely with the ESRF Structural Biology Group to pioneer instruments and automate crystallography beamlines to increase the efficiency of structure determination processes, from sample preparation to data collection. Two of the most notable inventions are micro-diffractometer devices (called MD2 and MD3), which are goniometer devices that enable the automated and high-precision positioning of protein crystals in an X-ray beam, significantly increasing the efficient use of beamtime at synchrotrons.

87. André M (2021). Structural biology at EMBL: driving technology development. EMBL News, 13 April 2021. https://www.embl.org/news/lab-matters/structural-biology-at-embl/

Scaling up the instrumentation techniques for the scientific community

With the support of EMBL's technology transfer partner, EMBLEM, micro-diffractometer devices – MD2 and MD3 – have been patented and, through partnering with scientific instrumentation manufacturer Arinax, commercialised to academia and industry. Ralf Siebrecht, Chief Executive Office of Arinax, underlined the importance of the trust and values shared with EMBL Grenoble: "At Arinax, we are aware of this symbiosis that works very well with EMBL." He also emphasised the special working environment at EMBL, which has enabled the Instrumentation Team to grow and support the needs of the technology development cycle: the emergence of a need from a scientist, the development of an innovation, use by the research community, and validation of the new technology. [87]

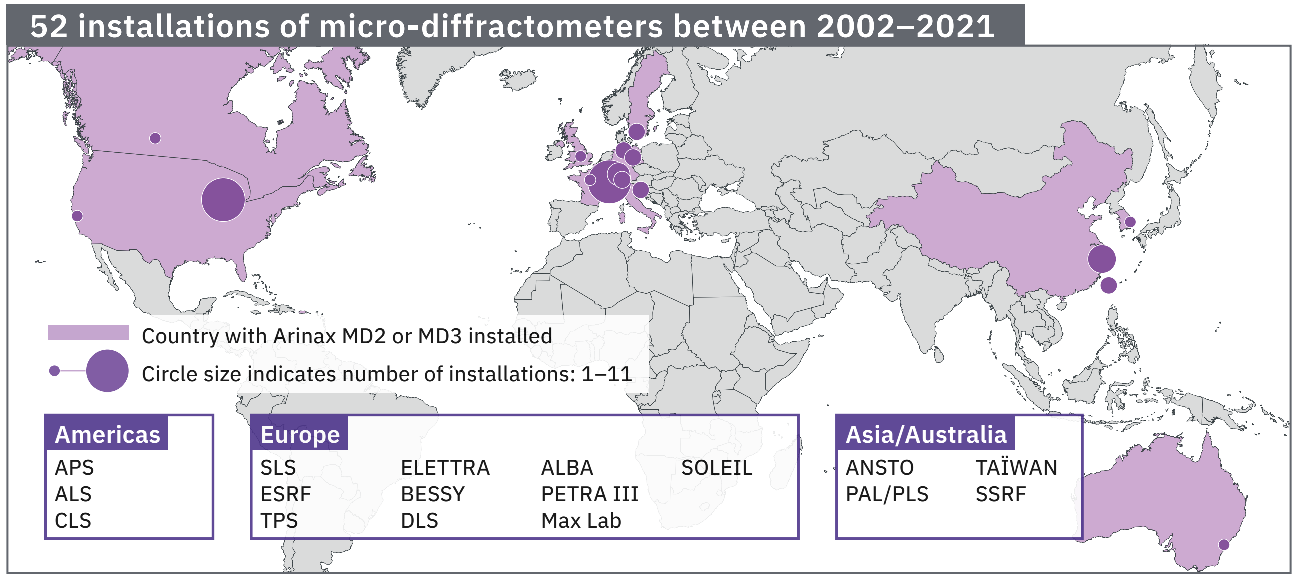
Arinax has frequent discussions with EMBL about development projects based on feedback on device testing from other synchrotrons to fuel new innovations, such a MD2S, a follow-up to MD2. MD2S plays an important role in high-throughput crystallography, e.g. in ligand and compound screening for drug discovery. MD3, by contrast, provides new opportunities for conducting experiments to understand protein dynamics at biological temperatures.



EMBL Hamburg P14 beamline installed with ARINAX micro-diffractometer.

"This device opens windows for cutting-edge research in structural biology. Today's protein micro-crystals would be impossible to align by simply doing it manually. The MD3 is doing this job automatically and with nanometre precision," said Siebrecht.[88]

As of 2021, Arinax has installed micro-diffractometers in over 20 synchrotrons around the world (including in Europe, USA, Canada, Korea, China, Taiwan, and Australia). MD2S and MD3 micro-diffractometers cost around €450,000 and €600,000, respectively (depending on the options and services that customers choose), which is a sizable investment that synchrotron facilities are willing to pay to keep their services at the cutting edge.



What the future holds

EMBL, through Arinax, will continue to support the scientific community around the world and to improve the quality of research through this valuable technology. The ability to adjust technologies to researchers' needs is one of the reasons why instruments developed at EMBL are – and will continue to be – widely used by the scientific community. "This is a service for the whole science community," said Thomas Schneider, Joint Head of EMBL Research Infrastructures at EMBL Hamburg.[87]

88. Written quote from Ralf Siebrecht provided to Technopolis in October 2021.

About EMBL

Europe-wide, global impact, infinite curiosity. The European Molecular Biology Laboratory is a powerhouse of biological expertise.

EMBL performs fundamental research in molecular biology, studying the story of life. EMBL offers services to the scientific community; trains the next generation of scientists and strives to integrate the life sciences across Europe.

EMBL is international, innovative and interdisciplinary. There are more than 1900 people, from over 90 countries, operating across six sites in Barcelona (Spain), Grenoble (France), Hamburg (Germany), Heidelberg (Germany), Hinxton (UK) and Rome (Italy). EMBL scientists work in independent groups and conduct research and offer services in all areas of molecular biology. EMBL research drives the development of new technology and methods in the life sciences. EMBL works to transfer this knowledge for the benefit of society.

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