

Integrated structural biology infrastructure





Instruct provides access to high quality structural biology infrastructure for European researchers. Access is provided free at Instruct centres and includes expert support

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What is Instruct?

Instruct is a pan-European research infrastructure in structural biology, making high-end technologies and methods available to scientists.

Structural biology is one of the key frameworks on which we interpret molecular and cellular functions. The main experimental technologies are complementary, and increasingly link detailed atomic structure with cellular context.

Structural biology is currently in the middle of a revolution enabled by significant advances in the tools (direct electron detectors in EM, advances in synchrotron sources and detectors, XFELs, ultra-high field NMR, super-resolution cryo-light microscopy).

Who can gain access to Instruct infrastructure?

Access to the Instruct infrastructure, expertise and methods is available to all researchers from Instruct Member countries.

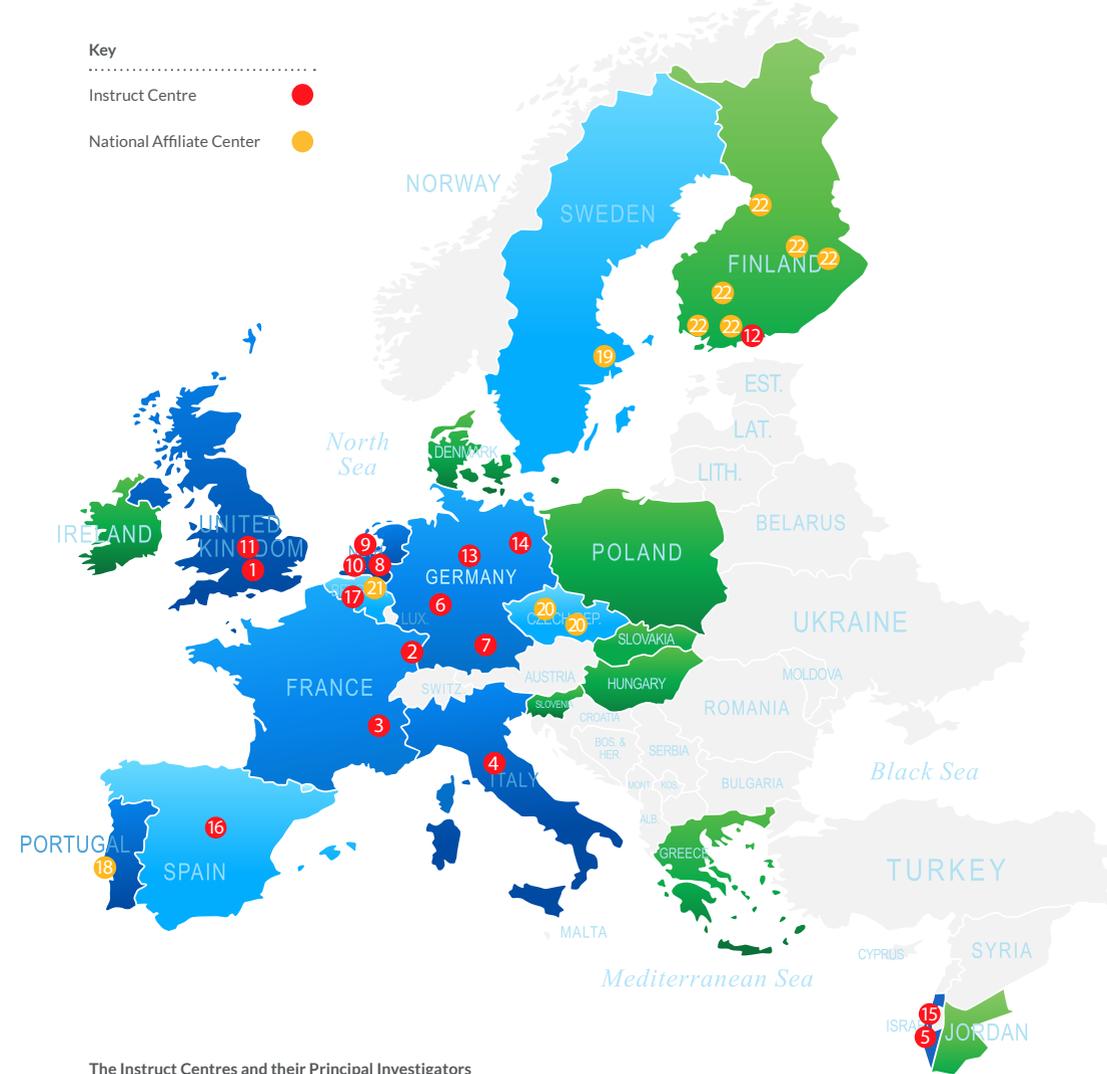
Access is granted subject to scientific peer review and is available either :

1. for basic or pre-competitive research (users agree to publication of data; access is funded by Instruct)
2. on a service basis for commercial use (user access is on a fee for service basis; no obligation to disclose or publish data)

Access to Instruct infrastructure can help advance your research – 67 peer reviewed publications acknowledge Instruct infrastructure. **Apply now.**

Key

- Instruct Centre (Red dot)
- National Affiliate Center (Yellow dot)



The Instruct Centres and their Principal Investigators

- | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
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Full profiles of the centres can be found at www.structuralbiology.eu



Integrated structural biology

Instruct aims to ensure that structural biology contributes to meeting some of the challenges faced by society, an ambition that reflects the achievements and potential of a relatively little known field of scientific research.

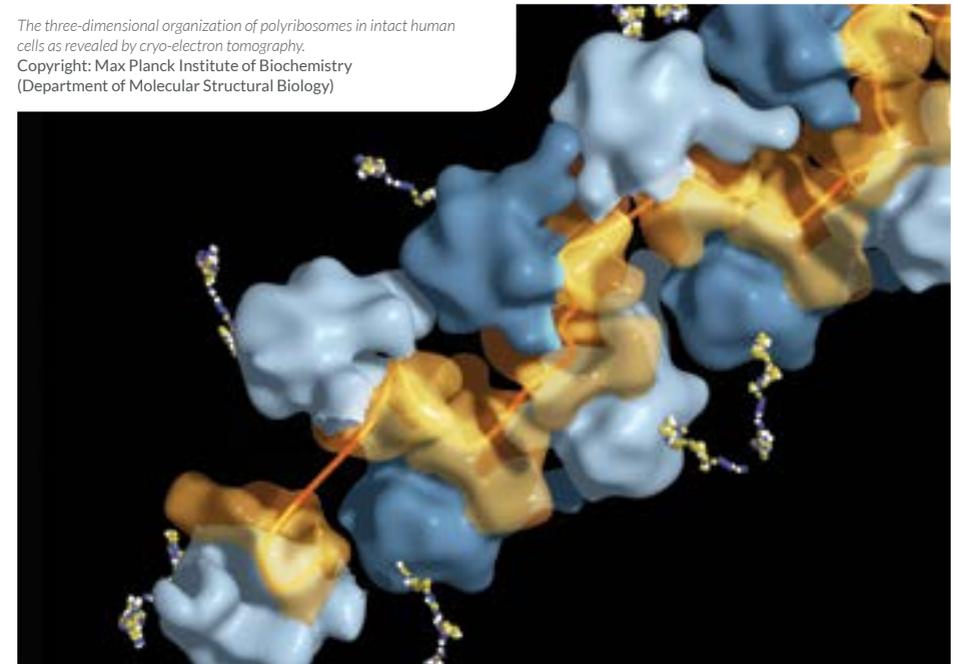
It's the small things that matter in life. In structural biology the small things include proteins, enzymes and viruses. A single change in their molecular structure can mean the difference between function and malfunction, health and illness. The three-dimensional shape of a molecule helps us to understand how it functions and its impact on the cell and the organism.

The science of structural biology is barely a hundred years old. Its origins lie in the discovery of X-ray diffraction early in the 20th century and its subsequent use to determine molecular structures. Since then, there has been continuous progress and structural biology has had an immeasurable impact on science and medicine. The discovery of the structure of DNA is the most famous advance, which helped scientists understand how the cell mechanisms drive evolution through

information transfer and how genes play a role in illness. There have been other key milestones, including the visualisation of haemoglobin and the first determination of an enzyme structure in the 1960s.

The advances in structural biology have been dependent on the technology available to scientists to study molecular structures. Synchrotrons were the first large-scale technology to have a major impact on structural biology, meanwhile nuclear magnetic resonance and electron microscopy joined X-ray diffraction in the structural biology toolbox. These three technologies, still the principal tools of structural biology, have been steadily improved by innovative scientists and are now immensely powerful. Work that might once have taken years can now be completed in just days or even hours.

The three-dimensional organization of polyribosomes in intact human cells as revealed by cryo-electron tomography.
Copyright: Max Planck Institute of Biochemistry (Department of Molecular Structural Biology)

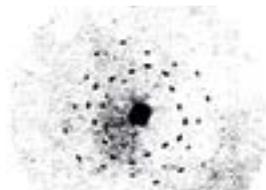


Structural biology continues to have a significant impact on molecular medicine. The early drugs developed to treat HIV were structurally designed to stop the virus multiplying in the body. They were very effective until the virus mutated. New structure-based drugs to combat HIV are continually being developed. Tamiflu, which is used to treat influenza, is another example of a structurally designed drug.

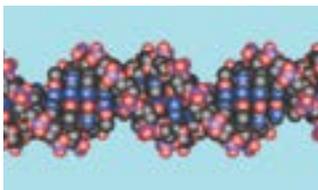
Reaching this objective will require a new approach, based on integrating the methodologies and technologies that individually are not sufficient. Scientific researchers will need the knowledge and practical skills to harness the range of technologies available. They will be guided by the needs of the science rather than constrained to a single specialism. They will also seek to collaborate more broadly with colleagues with complementary skills.

The new challenge in structural biology is to study systems of proteins in situ, in real-time. Achieving this will make it possible to understand how the targeted protein interacts with its environment. It will integrate determination of structure and understanding of function. The ultimate aim is to create a detailed map of the cell that shows not just the proteins within, but the interactions and interdependencies as well.

The potential benefits of an integrated structural biology approach are huge. Properly developed integrated structural biology will allow European researchers, institutes and companies to remain world leaders. It will also drive further developments in medicine such as more effective screening of drugs. Ultimately, it will take us closer to meeting the grand challenges facing society; hunger, disease and ageing.



The beginnings of X-ray crystallography, one of the first X-ray diffraction patterns recorded by Friedrich, Knipping and von Laue in 1912 obtained by irradiating a crystal of copper sulphate.
Copyright: The Nobel Foundation



This is a molecular model of DNA obtained from X-ray diffraction data. Carbon atoms are shown in black, nitrogen atoms in blue, oxygen atoms in red and phosphorus atoms in purple. This is the standard "B" form double helix.
Copyright: Peter Artymiuk, Wellcome Images



A microscope image of protein crystals grown from a 100 nanolitre drop of protein solution. The crystals are of a fragment of an antibody which shows enhanced effector functions.
Copyright: Dr Thomas A. Bowden

Instruct Spotlight

Nanobodies4Instruct

Nanobodies4Instruct is a new flagship technology offered through the Instruct access network. Jan Steyaert explains what nanobodies are and why they are in such high demand:

Nanobodies are the small (15 kDa) and stable single-domain fragments harboring the full antigen-binding capacity of camelid heavy chain-only antibodies. Nanobodies are exquisite chaperones for crystallizing membrane proteins, multiprotein assemblies, transient conformational states and intrinsically disordered proteins. Nanobodies can also be used for other applications in structural biology. Domain-specific Nanobodies have been used in single-particle electron microscopy (EM) to track these domains in particle projections. Because Nanobodies can be functionally expressed as intrabodies in eukaryotic cells, these single-domain antibodies can also be used to track their targets inside a living cell.

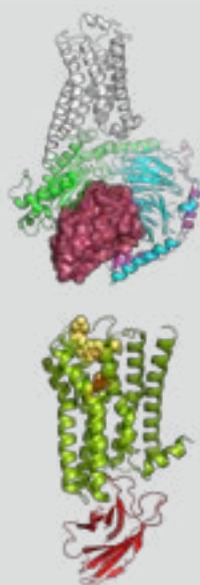
The active-state conformations of GPCRs are unstable in the absence of specific cytosolic signaling partners representing key challenges for structural biology. In collaboration with Brian Kobilka, Nanobodies4Instruct generated Nanobodies against the β 2 adrenergic receptor (β 2AR) and the muscarinic acetylcholine receptor (M2R) that exhibit G protein-like behaviour, and obtained agonist-bound, active-state crystal structures of receptor•Nb complexes of β 2AR and M2R.

Other Nbs were developed that stabilize the β 2AR-Gs complex. One of these nanobodies that inhibits the GTP driven dissociation of β 2AR-Gs was instrumental for obtaining the high-resolution crystal structure of this complex, providing the first view of transmembrane signaling by a GPCR.



Jan Steyaert

Els Pardon



Apply to visit Jan and Els at [structuralbiology.eu](http://www.structuralbiology.eu)

The Hub

Our activities are coordinated through the Hub. It is a thriving online community of scientists interested in integrated structural biology.

The application process for access to the technologies is completed entirely via the Hub, which is key to our commitment that the process be straightforward, transparent and quick. The expert support that accompanies access will also be coordinated through the Hub. The Hub holds a comprehensive catalogue of technologies that can be accessed for research as well as extensive information about each of the Instruct Centres.

Scientists and others use the Hub to keep up to date with the latest developments in integrated structural biology. A full calendar of events, seminars and conferences is updated regularly. Instruct training courses are booked through the Hub. The site's simple registration process encourages users to create profiles and prioritise areas of interest about which they would like to receive information.

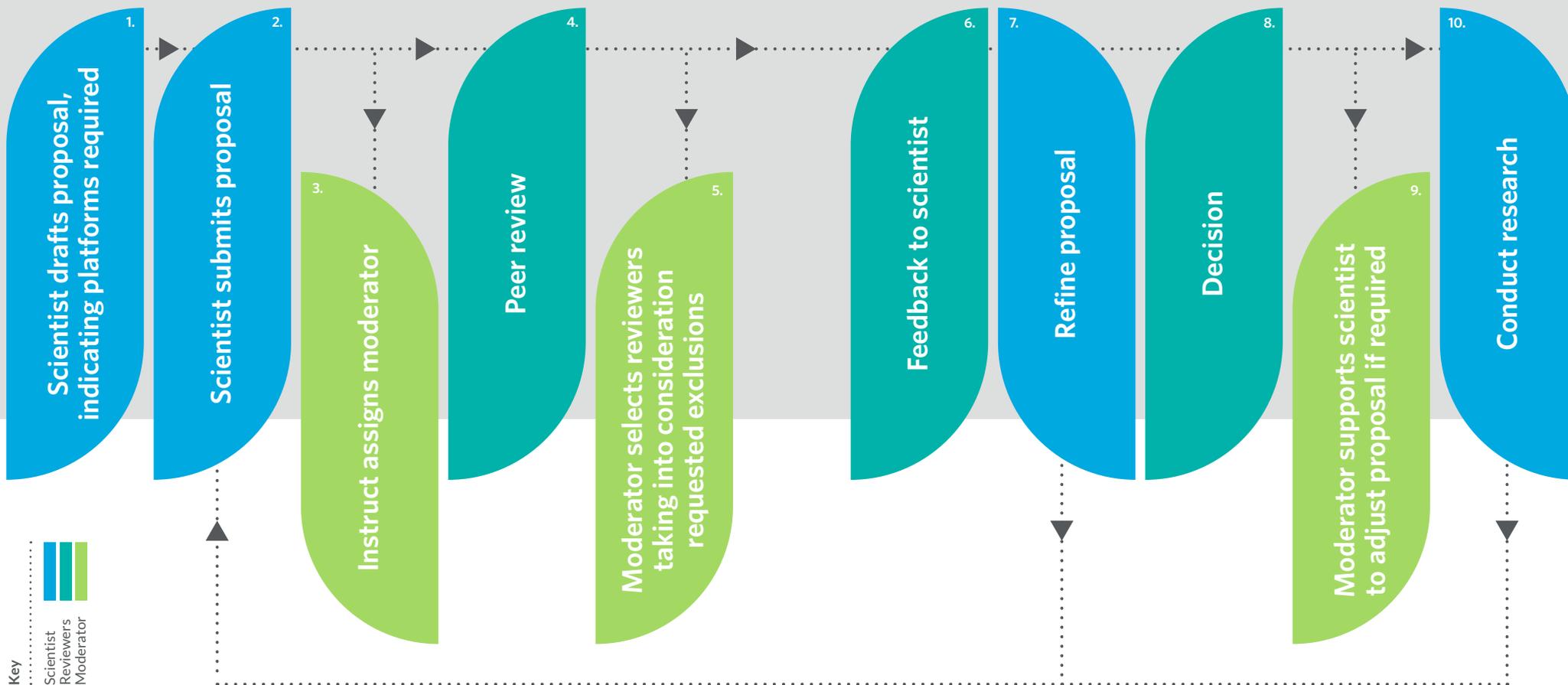
The Hub also provides a forum for discussions and idea sharing that will help shape the future of structural biology. Those involved in collaborative projects can use the Hub's secure virtual workspaces. There will be opportunities to promote research projects, institutions and publications online.

We provide monitoring tools through the Hub so that anyone involved can see clearly what Instruct is achieving in practical and measurable ways. For example, how many research applications has Instruct received, assessed and accepted? We are open about our work because we believe that is critical to building trust and maintaining credibility.

Join the Hub at www.structuralbiology.eu

Follow us on Twitter @instructhub

“The Hub also provides a forum for discussions and idea sharing that will help shape the future of structural biology”



Conducting research – Access

We have made it as easy as possible for you to further your research through Instruct. The application and review process is both efficient and transparent, drawing from worldwide expertise to review and advise.

Every application is carefully evaluated on its scientific merit; we are looking for research projects that demonstrate innovative approaches within integrative structural biology.

Alongside reviewing it is our goal to help advise and strengthen scientific proposals, and align your specific science with the correct cutting edge techniques.

Conducting research – The technology

Through our Instruct Centres, we provide access to cutting-edge technology and scientific expertise. We offer all the core technologies needed to further structural biology research. A comprehensive, up-to-date catalogue of the technologies is available on the Hub.

We are focused on ensuring that we offer the very best and most innovative technology.

For example, we provide the specialist sample preparation for cryo-electron tomography using ion beam milling housed at the Max Planck Institute Martinsried and the automated system for mammalian expression housed at Oxford, both of which are at the frontier of current technology.

Our aim is to offer access through Instruct to new technologies as they are developed. For example, we intend to offer access to the NMR grid providing high-capacity, fast data analysis for NMR through interaction with the Magnetic Resonance Center (CERM/CIRMMP) in Florence.

Information technology for structural biology

Information technology is an important tool for structural biology. Imaging techniques are generating huge amounts of data, which takes time to analyse and interpret. The different methods and formats associated with the core technologies are a barrier to integrated structural biology.

Standardisation across technologies could significantly benefit both individual

scientists and the research community as a whole. Scientists need not be familiar

with multiple computational methods and formats. It will also be substantially easier for researchers to combine technologies as the data generated can be integrated.

“Our aim is to offer access through Instruct to new technologies as they are developed.”

The deposition of data and structures in public databases will be facilitated through the widespread use of common formats. Scientists will no longer need to adapt their depositions to suit different formats, and those viewing the depositions will be able to do so with a uniform set of skills. This will encourage more scientists to make depositions and broaden their use.

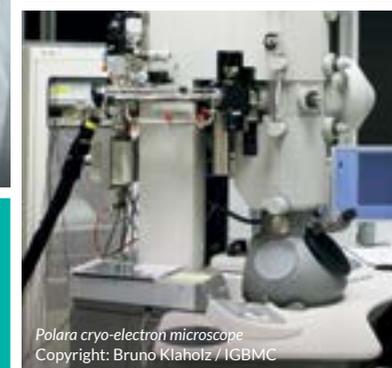
Standardisation is also a major step in quickening progress towards real-time analysis using more than one technology; a key development for integrated structural biology.



Insertion of the sample in the 700 MHz NMR spectrometer at CERM
Copyright: Federico De Luca



A macromolecular crystallography beamline at the Diamond Light Source
Copyright: Dave Stuart



Polara cryo-electron microscope
Copyright: Bruno Klaholz / IGBMC

The main technologies that can be accessed through Instruct are:

- 1. X-ray crystallography:** access to a pipeline process from sample production, crystallization to X-ray diffraction for many proteins and complexes. X-ray crystallography determines the three-dimensional shape of proteins at the atomic level and can define interaction surfaces, conserved structural regions and show non-protein modifications such as glycosylation and methylation.
- 2. Nuclear magnetic resonance (NMR):** provides three-dimensional structural and dynamic information at atomic resolution in conditions similar to physiological ones. It allows functional process to be followed, even in living cells, and can investigate transient and weak protein-protein interactions.
- 3. Electron microscopy (EM):** access to cryo-electron microscopy and tomography. Cryo-EM builds a three-dimensional image from a number of projections of sub-cellular objects. Electron tomography is particularly powerful for capturing transient structures.

Other methods that complement these three main technologies are:

- 1. Mass spectrometry:** this technique can provide information on the stoichiometry (the quantitative measurement of the component parts of complexes), sub-unit interactions and organisation of molecular assemblies.
- 2. X-ray imaging:** non-destructive imaging of biological samples at μm range. Particularly good for spatial resolution of structures within a sample.
- 3. Solid state NMR:** provides structural and dynamic information at the atomic level of microcrystalline samples, protein aggregates and membrane-embedded biomolecules.
- 4. Small angle X-ray scattering (SAXS)** is a technique for studying nanoscale structural features of biological samples. The technique yields information on particle size, shape and orientation and is particularly useful for examining molecular complexes.

Conducting research – Expert support

Biophysical characterisation of structural proteins at University of Oxford
Copyright: Paul Wilkinson Photography

Pursuing research through Instruct is an opportunity to develop your scientific knowledge and skills, as well as further your research project. You will receive advice and support from scientists who are recognised leaders in their field.

As part of the application process, you will receive scientific and technical support to ensure that your proposal is fully developed and that you are fully prepared to conduct

effective research. A technical feasibility assessment will ensure that the appropriate technologies are used. After the assessment we may recommend a wider or different range of technologies. We may offer use of the more innovative platforms, or even invite you to participate in technology development projects.

At Instruct Centres, experts support researchers to ensure that their work on site is effective and productive. This includes training on the advanced technology platforms available, if relevant. We want researchers to acquire the scientific skills needed to advance their research. The Instruct Centres will also provide logistical support such as advice on accommodation and travel.

Research funding

Access to technologies is possible because Instruct Centres have made up to 20% of their technology resources available through Instruct. We are able to allocate access to high-impact research proposals that we select according to agreed scientific priorities.

We allocate a proportion of our financial resources to funding access visits. However, this is not sufficient for all successful access proposals. We hope that there will be increased future funding for structural biology that will be channeled through Instruct, which would allow us to provide funding for all successful applications. In the meantime, the Hub offers extensive information about other sources of funding which can cover additional access costs such as travel.

We will facilitate access for, and support with expertise, proposals that have already received funding from other sources.

In addition, we will fund a small number of innovative proposals that require preliminary work or further development before they can be submitted to funding agencies. This will be subject, of course, to peer review, scientific priorities and potential impact.

Instruct training



Training session at the cryo-electron microscope
Copyright: Paul Wilkinson Photography

Our education programme is helping to train a cadre of European structural and cell biologists who are proficient in a raft of technologies, not just one specialism. They will be able to integrate different technologies to open up new areas of research. These scientists, and their work, enhance the reputations of their research institutes and companies.

We offer a range of workshops delivered at Instruct Centres by internationally recognised experts.

There are advanced practical courses in the 'core' techniques of X-ray, NMR and electron microscopy, as well as courses in key emerging techniques such as native mass spectrometry and correlative microscopy. Each course will have an associated forum to support ongoing networking and knowledge sharing.

We are determined to respond to the training needs of all our academic and industry users. Suggestions for training courses can be made through the Forum on the Hub.

We also organise PhD and Fellowship programmes and work exchanges. More information about these and the full programme of workshops is available through the Hub.

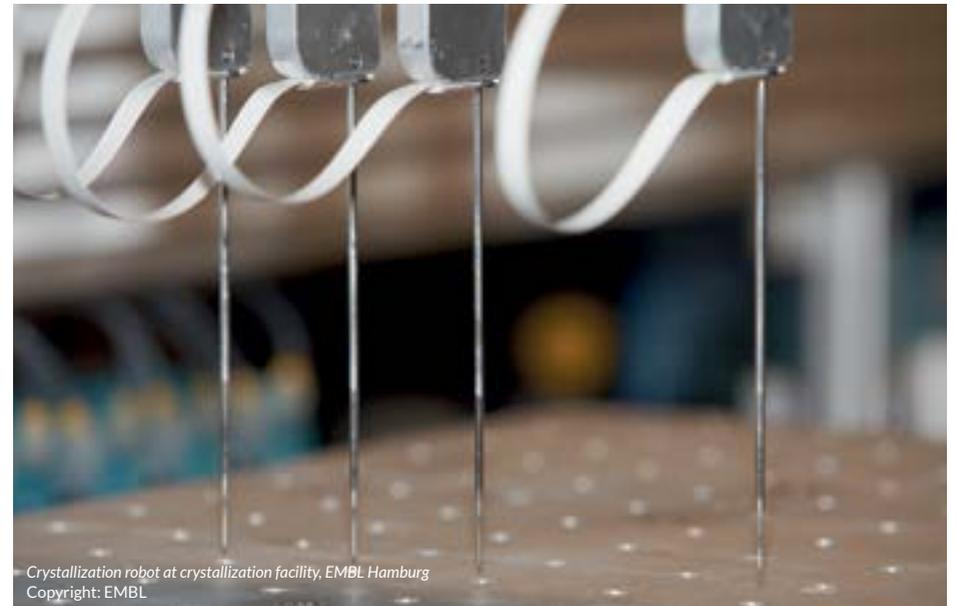
Our education work is distinct from the training provided in support of access and is open to all scientists, not just those who have submitted access proposals.



Performing a NanoDrop crystallization experiment
Copyright: Paul Wilkinson Photography



Scientists working together in the lab
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Crystallization robot at crystallization facility, EMBL Hamburg
Copyright: EMBL



Automatic platform for cell-free expression screening
Copyright: IBPC-GUF



Tecan liquid handler used at the ISPC for HTP protein expression tests
Copyright: Weizmann Institute

The socio-economic potential of integrated structural biology

We realise that Instruct must deliver an economic benefit for Europe and add value to the work of structural and cell biologists if it is to justify its existence. We believe that integrating structural biology through a distributed infrastructure of cutting-edge technologies, expert support and training will reap huge rewards.

Facilitating access to the most advanced technologies provides an invaluable resource for pharmaceutical and biotech companies. At a time when companies find investing in expensive technology difficult, we are providing cost-effective access through a single organisation. Our specialized training courses are another important resource for European companies.

While providing access and training, we also aim to build meaningful long-term collaborations that lead to translatable scientific advances. We offer an opportunity to work with world-leading scientists and use cutting-edge techniques. We know that collaboration between commercial and not-for-profit organisations can be difficult, so we will advise academic researchers on how best to form effective partnerships with the commercial sector.

Instruct already has well-developed partnerships with manufacturers of the technology used in Instruct Centres, including Bruker, Agilent, Rigaku, FEI, Qiagen and Leica Microsystems. These companies have worked with Instruct scientists because they need to understand where the next advances will come from and what technology will be relevant. We are also well placed to assist in the development and testing of new technologies.

We fund a rolling programme of a small number of pilot research projects that focus on innovative technology. The funding will progress projects from initial ideas to the point where they can be submitted for funding from other agencies.

If you or your company are interested in working with us, please contact the Instruct Coordinator;
coordinator@structuralbiology.eu

Raising the game in the European Research Area

The fostering of truly integrated structural biologists with access to the most advanced technology available will help make Europe the leading force in structural biology. Researchers working from small groups or institutes will be able to take on bigger scientific challenges thanks to Instruct. The new areas of research opened by integration and collaboration will generate scientific breakthroughs. We also believe that promoting high-impact research will attract the best scientists to Europe.

We believe that we can raise the standard of scientific work by making integrated approaches to science more accessible. Structural biology is not the only field that requires investment in expensive technology infrastructures and risks developing researchers with specialist but overly narrow skills. We

know more integrated approaches can deliver significant advances in structural biology. The same should be true in a wide range of sciences.

Fragmentation of research inhibits Europe's potential for innovation, makes investment less effective, and reduces our ability to solve problems such as ageing populations, pandemics and climate change. Part of the solution is the establishment of the European Research Area. This will foster greater cooperation and collaboration across European Union member states and encourage the region's sustainable development and competitiveness. Instruct is one of the biomedical sciences projects that contributes to making the European Research Area a reality.

Finance and resources

The Centres provide the technology and expertise that scientists access through Instruct. These multi-million Euro resources are critical to our success.

Instruct is operationally funded through membership of participating countries. The subscription pays for their scientists to have full access to Instruct: including its Centres and technologies, expert support and training programmes. We believe that this payment mechanism will allow a wide range of scientists to advance their research based on merit, not geography. The membership also gives a representative of each participating country the right to sit on the Instruct Council and have a role in setting the strategic direction and budget of the organisation.

In future, Instruct may manage grants for structural biology, funds that would be used to support access to technology. We also seek funding for other aspects of our work, such as the PhD programme.

Building productive partnerships with commercial enterprises is important for us and we aim to provide access and collaboration that is attractive to business. The fees paid by our commercial partners for access and training are an additional source of income.

*Petra III experimental hall on the DESY Campus, Hamburg
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*IGBMC building Strasbourg Illkirch-Graffenstaden France
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*Research Complex, Harwell
Copyright: STFC*

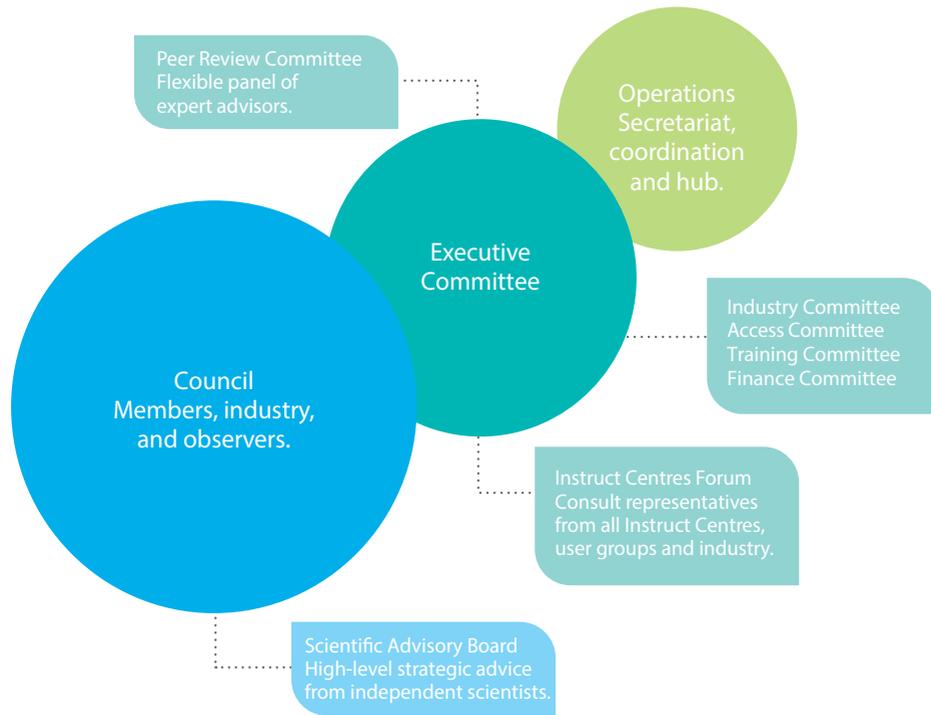


*EMBL Grenoble
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*Helmholtz Centre for Infection Research, Braunschweig, Germany
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Governance



Instruct’s objectives are set by the Instruct Council and Executive Committee. The Independent Scientific Advisory Board, the Peer Review Committee, the Instruct Centres Forum and user groups all provide advice. This structure provides all stakeholders, from funding agencies to individual scientists, with the channels and opportunity to shape the future of Instruct.

The management and operation of Instruct is delivered through Instruct Academic Services, a not-for-profit organisation.

Led by the Instruct Director, it employs the management team and establishes contracts on behalf of Instruct.

Instruct is part of the European Strategic Forum on Research Infrastructures (ESFRI) roadmap, which contributes to the realization of the European Research Area. The competitive and open access to high quality research infrastructures supports the activities of European scientists and attracts the best researchers from around the world.

Instruct

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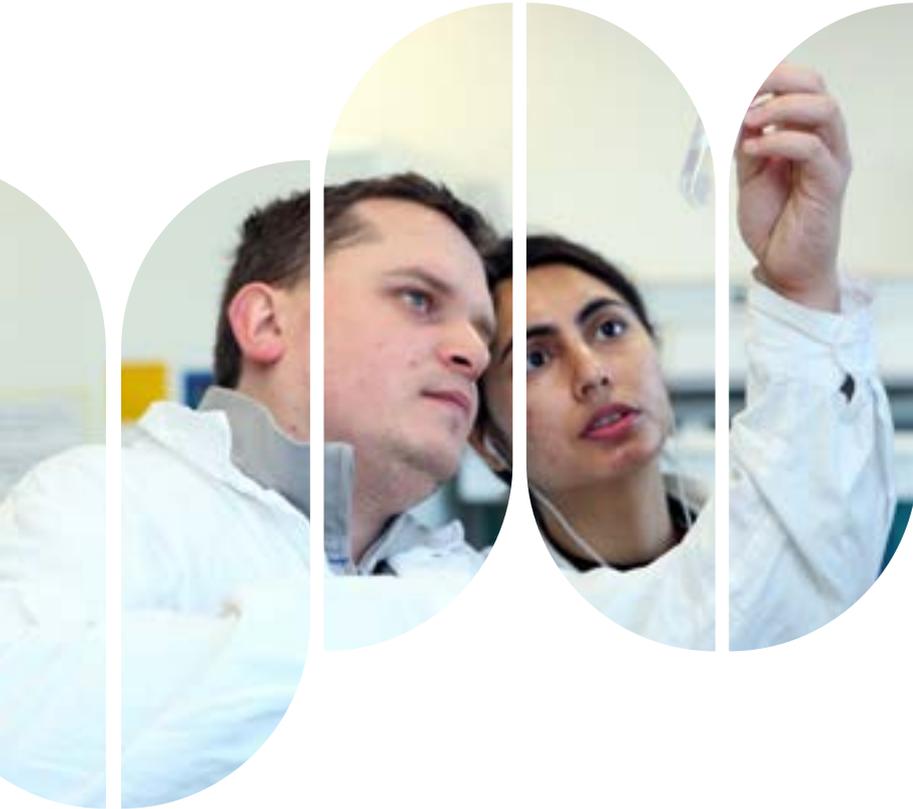
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Where better to find the talent that will support your work or look for the opportunity that will help shape your future than the Instruct Hub?



The Hub is a dynamic online community of scientists interested in integrated structural biology.

Whether you are looking to attract an experienced researcher or a graduate, or are a biochemist or molecular biologist seeking a new exciting role, never has it been simpler.

Jobs available and jobs wanted, for free,
at the Hub www.structuralbiology.eu

