Integrated Structural Biology Infrastructure for Europe



Integrated structural biology infrastructure

2010-

European Strategy Forum on Research InfrastructuresInitiated in 2008

Sur les bases de SPINE, SPINE2 (2002-2010)



Provide infrastructure for structural biology, to accelerate the development of integrated structural biology, bringing molecular and atomic explanations to the cellular context

European hub of structural biology providing:

- integrated infrastructure with cutting-edge technologies
- scientific expertise
- training
- peer review access for academia and industry

http://www.structuralbiology.eu/

Instruct Centre National Affiliate Center FINLAND POLAND

What is Instruct?

a pan-European Research Infrastructure

11 Countries, 17 European Centers, 171 Platforms

providing expertise and access to high quality instruments for structural cell biology researchers.

- University of Oxford: David Stuart & Carol Robinson
- 2. IGBMC-CERBM: Alberto Podjarny 3. PSB. Grenoble:
 - Darren Hart & Eva Pebay-Peyroula
 - Magnetic Resonance Center (CERM/CIRMMP), Florence: Lucia Banci
 - Weizmann Institute of Science:
 Joel Sussman & Gideon Schreiber
 May Planck Institute of Biophysics
 - MOLDON 6. Max Planck Institute of Biophysics & Goethe University Frankfurt IBPC: Hartmut Michel & Frank Bernhard
 - Max Planck Institute of Biochemistry: Patrick Cramer

- Instruct NL & Utrecht University: Albert Heck & Rolf Boelens
- Protein Facility NKI: Anastassis Perrakis
- 10.NeCEN LU: Bram Koster
- 11.CCISB, Harwell: Martyn Winn
- 12.University of Helsinki Dennis Bamford
- 13.Helmholtz Centre for Infection Research: Joop van den Heuvel
- 14.Leibnitz Institute for stry: Molecular Pharmacology: Hartmut Oschkinat

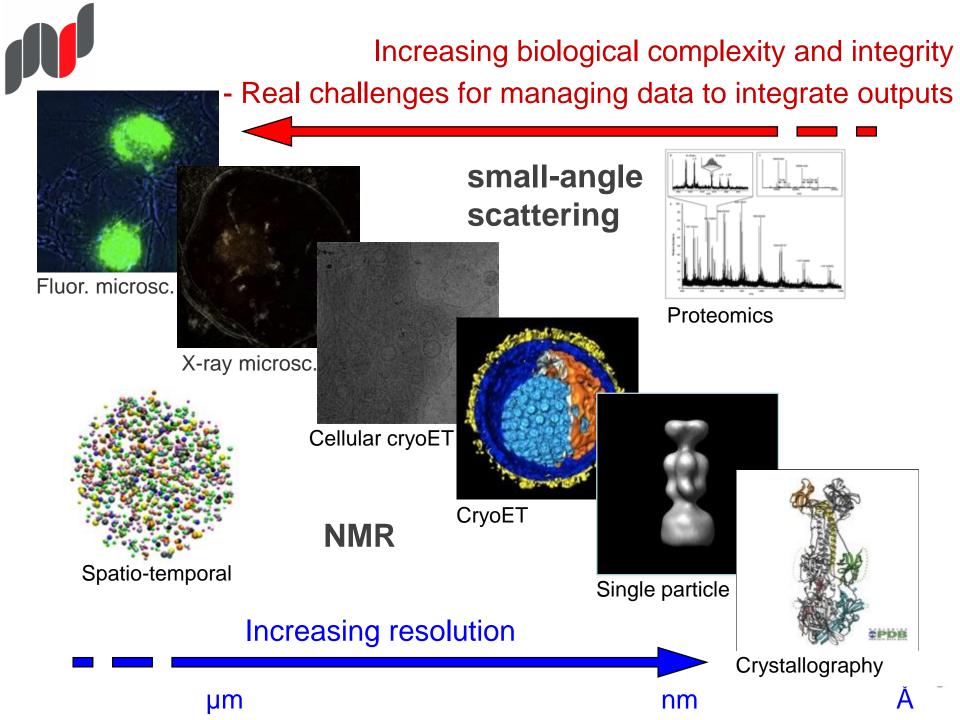
- 15.University of Tel Aviv: Haim Wolfson
- 16.Centre Nacional de Biotecnologia: Jose-Maria Carazo
- 17.Nanobodies4Instruct, VUB, Belgium: Jan Steyaert
- 18.PCISBIO, Portugal
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- 19.SWEDSTRUCT, Sweden Gunter Schneider
- 20.CEITEC & BIOCEV, Czech Republic Jan Dohnálek & Vladimír Sklenár
- 21.BIACe, Belguim Jan Steyaert & Han Remaut
- 22.Biocenter Finland Rik Wierenga & Sarah Butcher

Black Sea

TURKEY

Access is free at Instruct Centres support for travel, accommodation and consumables may be available.





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.

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:

- 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.
- X-ray imaging: non-destructive imaging of biological samples at μm range. Particularly good for spatial resolution of structures within a sample.
- Solid state NMR: provides structural and dynamic information at the atomic level of microcrystalline samples, protein aggregates and membraneembedded biomolecules.
- 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.





Training

Delivering workshops by internationally recognised experts

Internships

Funding 6-month student placements in cutting-edge laboratories

https://www.structuralbiology.eu

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

Access

Providing access to innovative equiptment to scientists worldwide

Access open now **3**

Pilot Project Award

Supporting novel ideas and building strong science

Structural Biology Hub

Fostering collaborative science and driving communication





































Instruct

Instruct enables European users to **access cutting edge technologies** with excellent scientific and technical guidance

The **national funders** provide for Instruct:

- the key infrastructure at Instruct Centres
- the costs of using their best equipment for access as part of the Instruct infrastructure.
- Nominated consumable costs for standard access units
- Key support staff to ensure the best outcome

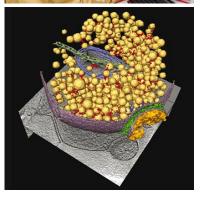
Instruct provides:

- The access process proposal submission, review, scheduling, reports
- Funds to support users to visit Instruct Centres for access (travel and accommodation; some consumable costs) up to a maximum of €1500 per access unit.

Access is internationally open to all researchers from Instruct member countries and awarded on the basis of scientific peer review.





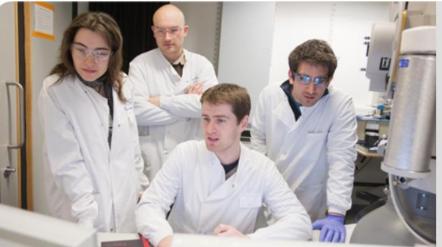






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Integrating Structural Biology

Search...

Instruct is a pan-European Research Infrastructure providing expertise and access to high quality instruments for structural cell biology researchers. Access is free at Instruct Centres and support for travel, accommodation and consumables may be available. Proposals are being accepted now for access projects requiring one or more Instruct facilities.

Starting Points: Platform Catalogue Training & Events Jobs Instruct Centres Contact Us



Instruct Internship Programme

The instruct Internship Programme funds research visits of 3-6months duration to Instruct Centres in Europe. The aim is to facilitate valuable collaborations with Instruct research groups. Submit an internship proposal for the programme before the deadline to apply for this opportunity.

Deadline for Submission: June 12th, 5PM CET

R&D Pilot Project Award

Instruct is supporting a limited number of pilot studies proposed by researchers from Instruct member countries. The intent of this support is to help researchers develop external funding projects. Pilot projects may be funded up to a maximum of €20,000. Submit an R&D proposal by the deadline to apply for these funds.

Deadline for Submission: June 12th, 5PM CET

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Sample Preparation

Bacterial expression

Baculovirus expression

Biobank sample

Cell-free Expression

Library Methods

Mammalian expression

Nanobody Production

Purification:

chromatographic system

Purification: Lysis system

Virus purification

Yeast expression



Biophysical Characterisation

Analytical Ultracentrifugation (AUC)

Calorimetry

Circular dichroism (CD)

Crystallisation

Flow Cytometry

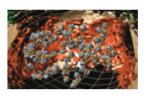
Microscale Thermophoresis

Multi Angle / Dynamic Light Scattering (MALS)

Proteomic Mass Spectrometry

Surface Plasmon Resonance (SPR)

Thermal shift assay



Structural Analysis

Correlative Light and Electron Microscopy

Electron microscopy

Electron Paramagnetic Resonance

Fast field cycling relaxometry

In-house X-ray source

Ion Mobility Mass Spectrometry

Labelling Mass Spectrometry

Light microscopy

Native Mass Spectrometry

Small angle scattering

Solid State NMR

Solution NMR

X-ray crystallography beamline



Data Analysis

Bioinformatics

Computational software

Image Processing

Filter Catalogue

Search...

Select Funding Route

Bio-NMR

■ BioStructX

FRISBI

Instruct

PRIME-XS

WeNMR

Select Centre

Bijvoet Center - UU

Centre for Bioinformatics

Centre for Computational Biology

Centre for Image Processing

Centre for Protein Production

Centre for Solid State NMR

Centre for Virus Production

Diamond Light Source

Goethe University - Frankfurt

Instruct Centre - CFRM/CIRMMP Italy

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X-ray data collection

X-ray data collection within Instruct includes the techniques of x-ray crystallography, small angle scattering and x-ray imaging on synchrotron sources. X-ray crystallography is also available on in house x-ray sources.

X-ray crystallography allows the determination of the three-dimensional shape of proteins at the atomic level and can define interaction surfaces, conserved structural regions and show protein modifications such as glycosylation and methylation. The first step after crystallisation is X-ray data collection, followed by phase determination, calculation of the electron density, model building and model refinement.

In-house X-ray source



Micro-focus rotating anode X-ray generators equipped with CCD camera or image plate detector are typically used as in-house X-ray source for protein crystallography.

Small angle scattering



from biological macromolecules in solution

X-ray crystallography beamline



3D images of molecules at atomic scale for insights into molecular interactions and biological processes

X-ray imaging beamlines

Search...

3D images of biological cells at a resolution superior to the light microscope with specimens much thicker than possible with electron microscopy

Instruct has 2 centres offering
In-house X-ray source across
Europe. Navigate the map and click
on the pins to discover centres near
you.



In-house X-ray source Details

Micro-focus rotating anode X-ray generators can be endowed with stations adapted either to crystal screening or data collection:

Especially in case of membrane proteins for crystal screening the X-ray power has to meet highest demands. Big wheel rotating anode X-ray generators allow a power at the focal spot of twice the brilliance than generators with normal sized anodes. Use of multilayer optics can help to further increase the flux at the crystal. These optics can be constructed with high acceptance angles for the incident radiation on the cost of a high beam divergence. As a consequence, reflections of longer lattice constants can not be properly resolved. Such a station is therefore optimized for crystal screening and less well suited for data collection.

On the other hand, optics with smaller acceptance angles and long focal distance result in a much smaller divergence of the emitted X-ray beam. Even reflections of membrane protein crystals which often exhibit very large lattice constants do not overlap with such an optic. This station is therefore much better adapted to data collection.

Since the flux of a rotating anode generators is sometimes not powerful enough to avoid synchrotron trips for crystals screening, both kinds of stations are necessary for an in-house X-ray lab of high standard. CCD cameras are by a factor of 3 to 4 more sensitive to X-rays compared to Image plate detectors and thus give room for further optimization of in-house sources.

User Guide

Instruct currently provides stations adapted to crystal screening and stations better suited for data collection of crystals with large unit cell dimensions, according to the optics connected to the rotating anode X-ray generators within their labs. Crystal screening stations can be equipped with crystal mounting robots for higher throughput. Basic automatic centring can be provided based on the centre of the loop. Improvement is planned by means of UV-light to detect micro crystals off the loop centre.

Technical Specifications

Platform Instances

Data collection station at the MPI of Biophysics in Frankfurt, Germany - Instruct Centre Frankfurt - CCMP

Crystal Screening Station at the MPI of Biophysics in Frankfurt, Germany - Instruct Centre Frankfurt - CCMP

In-house X-ray source at IGBMC-CERBM Strasbourg-Instruct Centre - France 1

Platform Contacts



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Juergen Koepke Max Planck Society juer...@biophys.mpg.de Instruct has 5 centres offering Electron microscopy across Europe. Navigate the map and click on the pins to discover centres near you.



Electron microscopy Details

Since the development of the electron microscope through Ernst Ruska and colleagues in the 30's electron microscopy greatly contributed to the structural analysis of cells, organelles, viruses and proteins. Electron microscopes have a greater resolving power than light optical microscopes, because electrons have wavelengths about 100,000 times shorter than visible light (photons), and can achieve better than 50 pm resolution and magnifications of up to about 10,000,000x, whereas ordinary light microscopes are limited by diffraction to about 200 nm resolution and useful magnifications below 2000x.

There are two main types of electron microscopes, the scanning electron microscope and the transmission electron microscope.

A scanning electron microscope (SEM) images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition, and other properties such as electrical conductivity.

A transmission electron microscope (TEM) uses a technique whereby a beam of electrons is transmitted through an ultra thin specimen, interacting with the specimen as it passes through. An image is formed from the interaction of the electrons transmitted through the specimen; the image is magnified and focused onto an imaging device, such as a fluorescent screen, on a layer of photographic film, or to be detected by a sensor such as a CCD (charge-coupled device) camera.

Over the past decade, cryo-electron microscopy (cryo-EM) has increasingly replaced the traditional methods of sample preparation for electron microscopy. It was the pioneering work of Taylor and Glaeser and of Dubochet and colleagues that paved the way for this development, which presented a quantum leap of biological electron microscopy as it enabled to obtain images of fully hydrated specimens in a close-to-native state.

The term cryo-EM refers to various electron microscopic imaging modalities when applied to samples embedded in vitreous ice. Three major branches of cryo-electron microscopy are relevant in the context of molecular structural biology: Electron crystallography, single-particle analysis and electron tomography.

Electron crystallography offers the advantage in determining the structure of proteins forming 2D-crystals below 4Å (e.g. as shown with water transporting membrane proteins - aquaporins). Membrane proteins are particularly promising candidates for the formations of 2D-crystals. Resolutions beyond 2\AA have been obtained.

Single-particle analysis is used for isolated and purified larger assemblies of multiple subunits that are often very heterogeneous, metastable and extremely hard to crystallize (e.g. like the ribosome or the 26S proteasome) at a routine resolution of less than 10 Å. Sample size range: 5-50 nm.

Electron tomography can nowadays be used for quasi in vivo studies of non-repetitive structures, such as whole cells or for example giant molecular assemblies like the nuclear pore complex. Tomograms of organelles and cells contain an imposing amount of information at a resolution of \sim 4-5 nm. They are, essentially, 3D images of entire proteomes, and they should ultimately enable us to map the spatial relationships of the full complement of macromolecules in an unperturbed cellular

Platform Instances

Cryo Electron Microscopy at IGBMC-CERBM Strasbourg - Instruct Centre - France 1

Cryo-electron microscopy at the MPI of Biochemistry in Martinsried, Germany - Instruct Centre - Germany 1

Cryo-TEM and cryo-STEM Imaging and Tomography at Weizmann Institute of Science in Rehovot, Israel -Instruct Centre - Israel

Electron cryo-microscopy on Tecnai Polara (FEI) at OPIC in Oxford, UK - OPIC

Electron cryo-microscopy on Tecnai F30 (FEI) at OPIC in Oxford, UK - OPIC

Cryo-electron microscopy on Tecnai F20 at the MPI of Biochemistry in Martinsried, Germany - Instruct Centre-Germany 1

Cryo-electron microscopy on Tecnai F30 Polara at the MPI of Biochemistry in Martinsried, Germany - Instruct Centre - Germany 1

Cryo-electron microscopy on Titan Krios at the MPI of Biochemistry in Martisried, Germany - Instruct Centre-Germany 1

Electron cryo-microscopy on Tecnai T12 (FEI) at OPIC in Oxford, UK - OPIC

Cryo EM on Polara in Grenoble, France - Instruct Centre - France 2

Platform Contacts

Comment accéder à une PF Instruct : 2 modes

Après avoir créer un login, déposer un dossier sur le site Instruct: https://www.structuralbiology.eu/update/

Les projets sont évaluer tout au long de l'année, en continu, sur des bases de qualité scientifique et de faisabilité

Les projets sélectionnés sont financés à hauteur de 1100 € par visite (financement des frais de déplacement, et frais de plate-forme)

Instruct finance de manière ponctuelle :

projets R et D en biologie structurale: un call est en cours (deadline 12 juin)

https://www.structuralbiology.eu/update/submit-randd

TOUS LES LABOS FRANÇAIS PEUVENT BENEFICIER DE CES CALLS

Internship: séjour de 3 à 6 mois dans un centre Instruct.

Call est actuellement ouvert (deadline 12 juin) https://www.structuralbiology.eu/update/submit-internship

INSTRUCT organise des workshops:

Programme

https://www.structuralbiology.eu/support/whats-on/calendar-events



Réseau National de Formation en Biologie Structurale Intégrative

French Infrastructure for Integrated Structural Biology



Establishment of the infrastructure: May 2011 Opening infrastructure June 2012



Infrastructures nationales en biologie et santé PROJET FRISBI



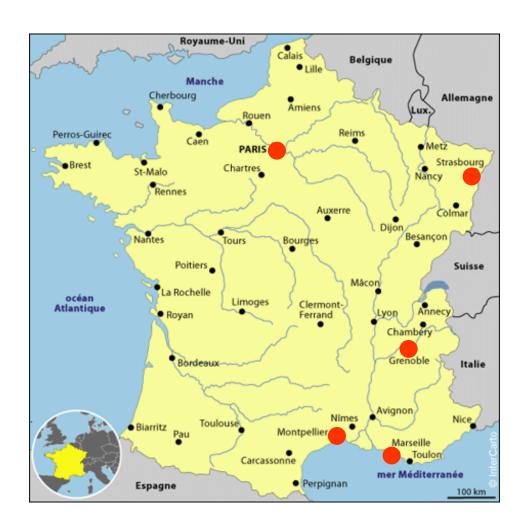
MINISTÈRE DE L'ENSEIGNEMENT SUPÉRIEUR ET DE LA RECHERCHE

COMMISSARIAT GÉNÉRAL À L'INVESTISSEMENT

INTITULE DU PROJET		FRISBI	
COORDINATEUR DU PROJET		CNRS	
FINANCEMENT TOTAL		32 000 000 €	
DISCIPLINE		Biologie structurale	
DESCRIPTION		Coordonner et équiper les équipes françaises de biologie structurale intégrative afin de leur donner les moyens de rester au meilleur niveau d'excellence.	
	LA SCIENCE	Il s'agit d'intégrer les données de biologie structurale provenant de différentes techniques physiques, in vitro et cellulaires, afin de comprendre comment les protéines complexes ou les agents pathogènes (virus, bactéries) interagissent avec leur environnement cellulaire	
APPORTS POUR	LE CITOYEN	Comprendre le fonctionnement cellulaire au niveau des interactions protéine-protéine dans les cellules saines et pathologiques c'est obtenir de nouvelles pistes pour des agents thérapeutiques.	
	LE SYSTEME DE RECHERCHE	Le projet d'infrastructure nationale regroupe les 5 sites d'excellence française en biologie structurale intégrative ; il permettra à la France de rester un des leaders mondiaux de cette discipline et d'entrer comme tel dans le réseau européen.	
	L'ECONOMIE	Cette recherche amont devrait permettre de comprendre les mécanismes de certaines maladies au niveau intracellulaire et ainsi ouvrir de nouvelles voies au développement de médicaments.	
LOCALISATION	REGION(S)	Rhônes-Alpes, Languedoc-Rousillon, Alsace, Provence-Alpes- Côte d'Azur	
	VILLE(S)	Grenoble, Montpellier, Strasbourg, Marseille, Saclay	

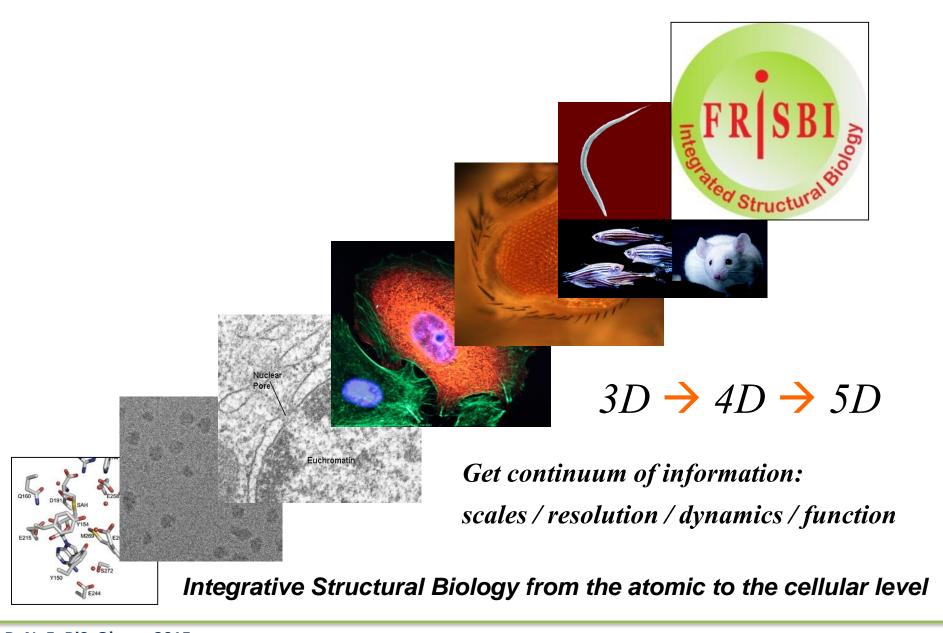


French Infrastructure for Integrated Structural Blology



5 FRISBI centers (Strasbourg, Grenoble, Montpellier, Marseille, South Paris) 2 of them are Instruct centers (Strasbourg and Grenoble)

French Infrastructure for Integrated Structural Blology





French Infrastructure for Integrated Structural BIology

Strategic aims of the infrastructure

- be at the forefront of integrative cellular structural biology
- provide access to state-of-the-art integrated structural biology infrastructures and expertise
- strategic choices for large instrumentations (investments + maintenance; e.g. NMR, EM)
- define & use data standards for storage and integrated analysis of structural information
- stimulate exchange and co-development with industrial partners
- organise training and dissemination of expertise
- develop innovations in the field of biomedical targets involved in human diseases

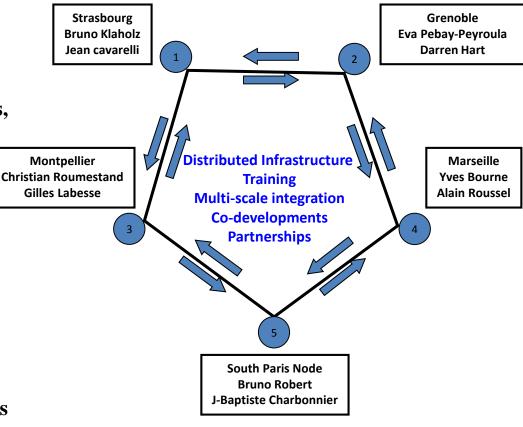


Organisation of the FRISBI infrastructure

Open to national and European, academic and Industrial users.

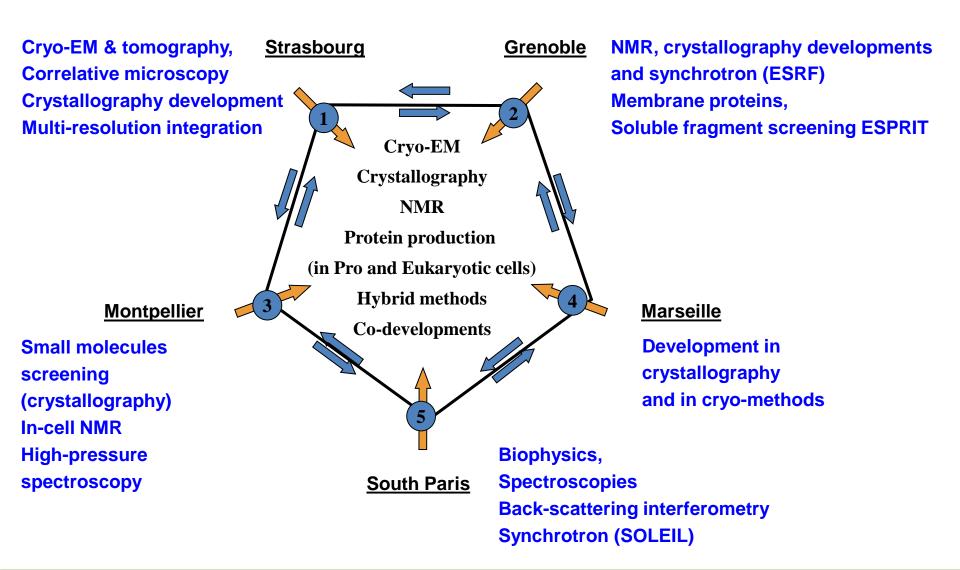
State-of-the-art complementary technologies, organized through working groups:

- crystallization & crystallography, SAXS
- NMR
- cryo-EM & tomography; super-resolution correlative microscopy
- sample production & expression systems (in vitro, procaryotes and eucaryotes)
- protein-protein interactions
- biophysical characterization, spectroscopies





Complementary expertise and synergies within the FRISBI network





French Infrastructure for Integrated Structural BIology

Benefits to the scientific community

- Project-based access & training

to state-of-the-art European structural biology infrastructures and expertise for the national and European scientific community

- <u>Development & Dissemination</u>

of the next-generation structural biology technologies and procedures

- Interdisciplinarity

support new users, favour interactions between structural, molecular and cellular biology communities

- Industrial partnerships

co-developments in electron & optical microscopy, crystallography, computing (FEI, NatX-ray, Xenocs, Bruker, Molecular Sensing, Phycosource ...)



FRISBI website

Web site: http://www.frisbi.eu accessible also via the Instruct, CNRS & ITMO websites, 5700 visitors since February 2013, 65 % of national visitors and 35 % international



Sample Preparation

▼

Sample preparation is not only a key issue for structural and molecular biology studies, but concerns Life Sciences development as a whole. FRISBI offer state-of-the-art infrastructures for the expression and production of biomolecules and their complexes in prokaryotic and eukaryotic system.

 \blacksquare Crystallisation **Bacterial expression** Yeast expression Crystallisation of protein molecule is a crucial step during the course of X-ray structure determination. Insect cells expression Crystallisation under anaerobic conditions Mammalian expression High throughput crystallisation Cell-free production High throughput membrane protein crystallisation Isotopic labelling ▼ Library based construct screening Structural analysis Purification FRISBI offers acces to a range of state of the art structural biology technologies and integrative biological ap-Amino acid analysis/ Nter sequencing proaches and expertise. Mass spectrometry Electron microscopy Biophysical characterisation Light microscopy NMR Spectroscopy Electron spectroscopy Biophysical characterisation EPR FRISBI offers a large panel of state-of-the-art equipment and expertise in bioche FTIR quality control and functional analysis on protein samples. Optical Super Resolution Spectroscopy Resonance Raman spectroscopy AUC ▼ X-ray data collection Calorimetry Small Angle X-ray Scattering Circular Dichroism In-house X-ray crystallography High pressure X-ray crystallography beamline MALS

resources and efficiently extract relevant knowledge.

Bioinformatics

In the framework of integrated structural biology, the goal of bioinformatics is not only to facilitate the determination of a protein's 3D structure, but also to understand its role(s) in the complex, dynamic networks that are responsible for cellular or organismal functions. This requires dedicated computational systems that can handle and store large volumes of heterogeneous data and that can quickly process queries between the different data

♥

Crystallisation

Thermal Shift Assay

SPR SPRI

Microscale Thermophoresis

FRISBI: French Infrastructure for Integrated Structural Biology http://frisbi.eu/

2 mode d'acces

- 1. En continu toute l'année
- 2. Calls ponctuels d'accès avec financement

(1000 € par projet, nombre de projets limité).

Les projets sont évalués sur leur qualité scientifique et leur faisabilité.

Un call est actuellement ouvert jusqu'au 30 juin 2015

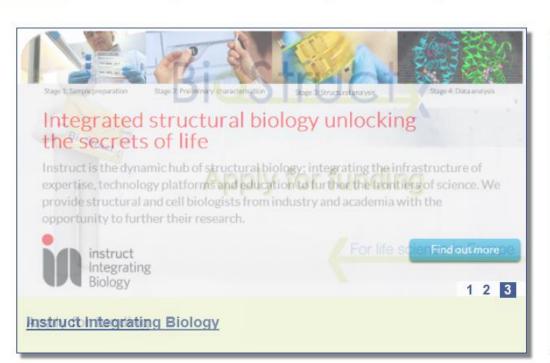
Tous les laboratoires français sont éligibles

FORMATIONS:

FRISBI organise et co-finance des formations en biologie structurale

Un call pour les formations est actuellement ouvert, deadline 1^{ier} septembre 2015





What is Biostruct-X?

BioStruct-X is a project funded by the Seventh Framework Programme (FP7) of the European Commission that establishes a state-of-the-art coordinated and multi-site infrastructure to support access for established and emerging key methods in structural biology. Eleven facilities from across Europe provide 44 installations for applications in small angle X-ray scattering (SAXS), macromolecular X-ray crystallography (MX) biological X ray imaging (XI) protein production and high throughput crystallisation (PP & HTX).

The aim of BioStruct-X is to provide a consolidated platform that brings together all relevant methods in structural biology. Read more

Latest news

IMPORTANT: Access to ESPRIT and MultiBac platforms closed!

9 March 2015

IMPORTANT: BioStruct-X funded access to ESPRIT and MultiBac platforms has now finished and all available units have been allocated. BioStruct-X will... [+]

Upcoming events

BioStruct-X Industry Workshop

15 June 2015 - 17 June 2015 Hamburg, Germany

BioStruct-X Industry Workshop Hamburg, Germany, 15th - 17th June 2015 [+]

more

Apply for funding

Register or login to apply.

Next deadlines Days left

15 September 2015

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Techniques		Platforms				
SAXS						
MX		*Please note that acces to	WP5 PP&HTX platfo	rms is now available!		
XI						
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Upcoming events

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A worldwide e-Infrastructure for NMR and structural biology

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			Chemical Shifts					
			Structure Calculation					
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Highlights News Market Resources			
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2015-04-17 14:39	Fill in the HADDOCK survey		