PSB et al
Partnership for Structural Biology Newsletter

Scientific highlights

Does the Sars-CoV-2 spike protein modulate High-Density Lipoprotein function?

Since the beginning of the COVID-19 outbreak in late December 2019, there has been a lot of talk about how the seriousness of the disease might be connected to the fat levels in people's blood [1]. We were curious about how the Spike protein (S protein) from the virus interacts with High-Density Lipoproteins (HDLs), which are important for transporting cholesterol in the body [2]. In our first study [3], we discovered that the S protein removes fats from model membranes and affects HDL's ability to deal with specific types of fats. This raised questions such as whether the S protein prefers certain fats over others and if an individual's blood fat profile could influence how the S protein affects HDL function.

In our follow-up research [4], we tested this idea using different types of fats (saturated, monounsaturated, and polyunsaturated). We used special techniques to examine the affinities of both HDL and the S protein for these fats: in particular by using selective deuteration and neutron reflection, we could see how HDL removed and deposited fats in detail. Our findings showed that the S protein has a strong preference for saturated fats when cholesterol is present and also for polyunsaturated fats containing for example linoleic acid (Figure 1).

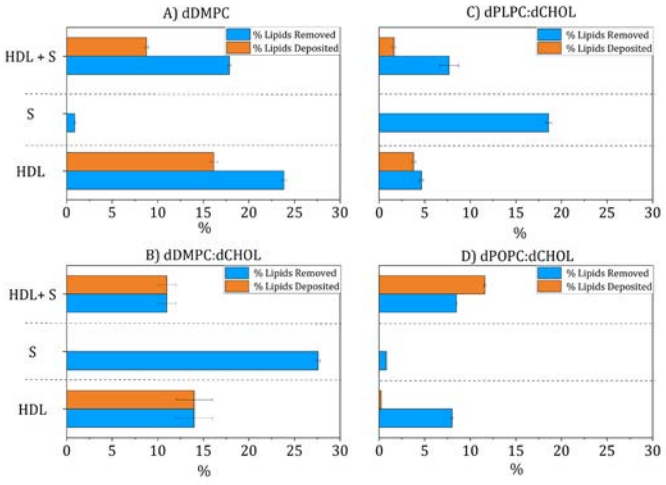

Figure 1: HDL ability to remove and deposit lipids in fluid saturated membranes in the absence (A) and presence of cholesterol (B), as well as in polyunsaturated (C) and monounsaturated (D) membranes in the presence of cholesterol. Data was analyzed after 5 hours of incubation of the SLBs with either HDL (0.132 mg/mL), S protein (0.05 mg/mL) or a mixture of both HDL and S protein (0.132 and 0.05 mg/mL, respectively) in h-TBS at 37 °C.

Next, we looked at how the mixture of fats in the blood, specifically the total amount of triglycerides and cholesterol, influences how the S protein impacts HDL function. Our findings indicate that people with a specific blood fat profile (low triglycerides and high cholesterol) might be less prone to disruptions during a COVID-19 infection or after COVID-19 vaccination. This is because, in such cases, the interaction between the S protein and HDL is not as strong (Figure 2).

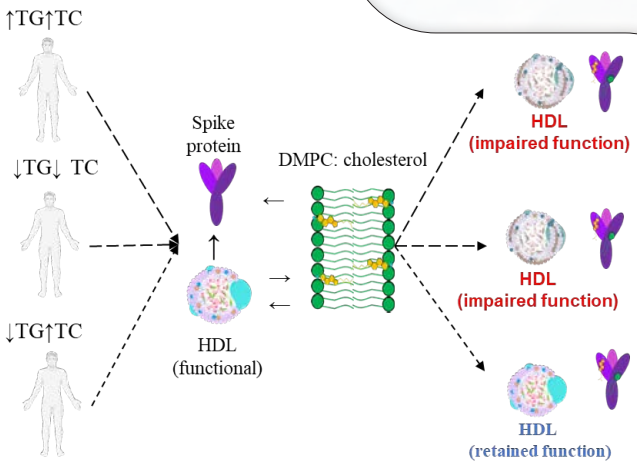

Figure 2: Graphical representation of how an individual's lipid composition affects the relationship between HDL and the S protein. Depending on the donor lipid profile, spike protein modifies HDL activity.

These experiments were conducted in collaboration with deuteration laboratories at the ILL and ANSTO (the Australian Centre for Neutron Scattering).

We were granted beamtime at ILL on Figaro and D17, and at ANSTO on Spatz neutron reflectometers.

Y. Correa (Malmö University)

[1] R.K. Mahat, V. Rathore, N. Singh, N. Singh *et al.* (2021). Clin. Nutr. ESPEN, **45**, 91-101.
[2] M.P. Adorni, N. Ronda, F. Bernini, F. Zimetti, (2021) Cells, **10**, 574.
[3] Y. Correa, S. Waldie, M. Thépaut, S. Micciulla *et al.* (2021) J. Colloid Interface Sci., **602**, 732-739.
[4] Y. Correa, R. Del Giudice, S. Waldie, M. Thépaut *et al.* (2023) J. Colloid Interface Sci., **645**, 627-638.

CONTENTS

Understanding how the cytokine storm propagates

When cells are put under stress from their environment they need to react. To fight stress, such as infection, several coping mechanisms, including the inflammatory response, are used by our bodies. While inflammation is necessary, too much of it can impair cell and organ function. This is the case with cytokine storms – inflammatory cascades during an infection that can spiral out of control and lead to severe disease and even death, as recently highlighted during the COVID-19 pandemic.

When a cell receives the message to start inflammation, the signal is relayed through a series of protein kinases, called the Mitogen Activated Protein (MAP) kinases, that phosphorylate and activate one another. First a MAP kinase kinase kinase (MAP3K) activates a MAP kinase kinase (MAP2K) which in turn activates a specific MAPK. The final MAPK in the chain then enters the nucleus where it modulates gene transcription allowing the cell to react. The chain of kinases allows the signal to be amplified, as each activated kinase can itself activate many more of its target kinases. The individual components of this relay have been studied extensively over 30 years but as the interactions have to be transient in order to transmit the signal, how these proteins interact is largely unknown.

We studied the MAP kinase p38α responsible for activating the inflammatory response, in complex with its upstream activating MAP2K, MKK6 [1]. The key role of p38α in inflammation and the fact that aberrant p38α signaling is involved in numerous diseases, such as arthritis and cancer, but also in the response to infection, make it a highly studied drug target [2]. We used cryo-electron microscopy (cryoEM) to determine the structure of the complex at 4 Å resolution revealing a 'face-to-face' conformation of the kinases with the activation loop (A-loop) of p38α, the region phosphorylated by MKK6, extending towards the active site (Figure 1). The structure reveals new interactions between the kinases and, intriguingly, all contact between the kinases is distal to the MKK6 active site. In order to further our understanding of the system we turned to molecular dynamics simulations, revealing that the observed conformation facilitates the approach of the A-loop of p38α to the active site of MKK6 without compromising the dual specificity of MKK6. The simulations show that both the A-loop threonine and tyrosine can access the active site without specific recognition or binding. Extending these simulations to much longer timescales using a Bayesian/maximum-entropy approach and refinement against SAXS data allowed us to reconstruct the heterogeneous conformational ensemble and understand how the two kinases assemble and initiate phosphorylation (Figure 2). The populations of the main states captured in this ensemble, as well as the paths connecting them, show the importance of the N-terminus of MKK6 and the C-lobes of the two kinases in correctly positioning them for phosphorylation. Cellular assays performed with variants of MKK6 N-termini revealed that the length and structure of the N-terminal linker are important in determining specificity between kinase pairs.

Resolving the architecture of MKK6 activating its target MAPK p38α has identified previously unknown interaction sites between the two kinases and allowed us to model the mechanism of activation. The N-termini of MAP2Ks guide the engagement of specific kinases by being tuned to the correct distance for MAP2K/MAPK pairs. Once bound, rather than acting like a classical enzyme and positioning substrates precisely for catalysis, MKK6 creates a zone of proximity, enabling either the tyrosine or threonine to approach the active site, regardless of their state, allowing dual specificity. Through a comprehensive multidisciplinary approach, the study elucidated the architecture and dynamics of the formation of the MKK6-p38α complex. Many PSB platforms contributed to this work including the EMBL EEF, the macromolecular crystallography and SAXS beamlines of the ESRF-EMBL JSBG and mass spectrometry at the IBS. The findings pave the way for targeted drug development and increase our understanding of essential kinase signaling cascades.

M.W. Bowler (EMBL), E. Pellegrini (EMBL, now IBS) and P. Juyoux (EMBL, now IBS)

[1] P. Juyoux, I. Galdadas, D. Gobbo, J. von Velsen *et al.* (2023). Science, **381**, 1217-1225.
[2] B. Canovas and A. R. Nebreda (2021) Nat. Rev. Mol. Cell Biol., **22**, 346–366.

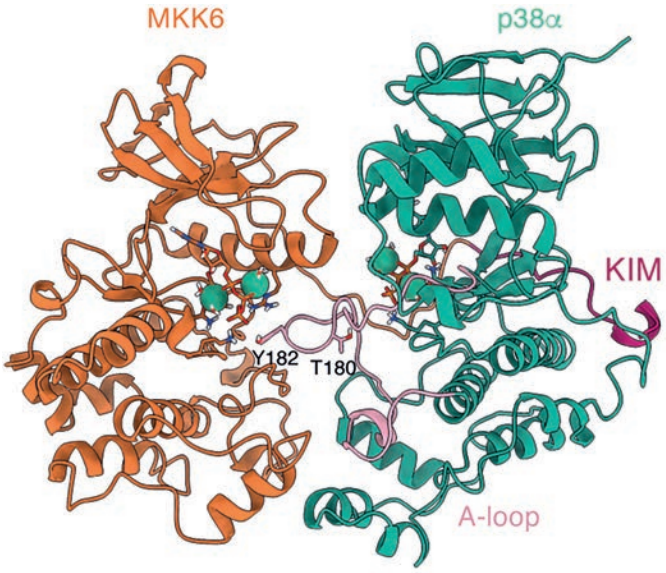

Figure 1: Structure of the MKK6-p38α complex..

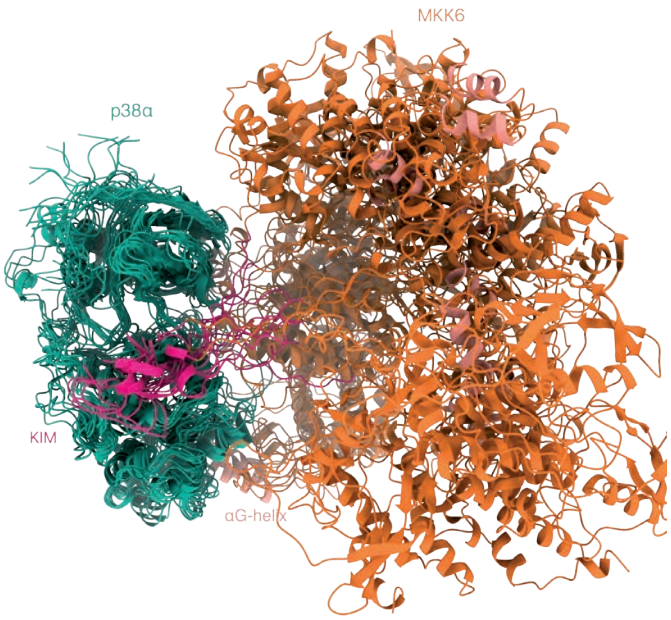

Figure 2: Population of states during the assembly of p38α and MKK6 as derived from the fitting of MD states to the SAXS curve.

Integrative biology furthers the understanding of bioenergetics in Alzheimer's disease

Alzheimer's disease (AD) is an incurable neurodegenerative disease and cases are predicted to rise significantly in the next 30 years. The race is on to find methods to diagnose, treat, and prevent the disease, however, the root causes of AD pathogenesis remain unclear [1]. Mitochondria act as cellular batteries responsible for the generation of ATP via the fatty acid β-oxidation (FAO) and oxidative phosphorylation (OXPHOS) pathways, which are particularly important for energy-demanding neurons. Interestingly, in the brain of AD patients, amyloid-β (Aβ) peptides progressively accumulate within mitochondria and perturb Complex I (CI), the first and largest protein complex in OXPHOS. CI assembly is a complicated process, involving a range of 'assembly factors' responsible for integrating its 45 individual subunits and cofactors to form the functional holoenzyme. A key player is the mitochondrial CI assembly (MCIA) complex, composed of three core proteins – ACAD9, ECSIT, and NDUFAF1. How MCIA contributes to CI assembly is still unclear due to the versatile nature of the individual proteins: ECSIT participates in several signaling pathways whereas ACAD9 is a Flavin cofactor-containing redox enzyme.

We have determined the structures of ACAD9 alone and in complex with the C-terminal domain of ECSIT by an integrative biology approach [2]. Data collected at the IBS EM facility and the CM01 microscope at the ESRF have revealed the interaction site between ACAD9 and ECSIT$_{CTER}$, highlighting a site of functional interest (Figure 1A-B). Upon comparing the bound and unbound ACAD9 structures, a striking conformational change is observed at a site bridging the ACAD9 cofactor pocket and the ACAD9-ECSIT interaction site. A stretch of 20 residues adopts a downward-facing conformation in ACAD9 alone, acting as a barrier between external solvent and the FAD cofactor (Fig. 1A, bottom), however, upon ACAD9-ECSIT$_{CTER}$ complex formation, an ECSIT helix induces the opening of this gatekeeper loop. This loop-flipping mechanism results in deflavination and reassigns ACAD9 from an FAO to an OXPHOS enzyme (Figure 1B, bottom) [2, 3]. In addition, we have conducted cell biology analyses that have revealed that ECSIT undergoes phosphorylation. Remarkably, we have identified an ECSIT threonine residue located at the ACAD9-ECSIT binding interface as a phosphorylation site and our biophysical analyses show that the dephosphorylation of ECSIT seems to be a prerequisite for successful MCIA formation (Figure 1C, left). Furthermore, the exposure of ECSIT to neuronal cells containing soluble Aβ oligomers (before they turn into fibrils) decreases the level of ECSIT phosphorylation (Figure 1C, middle), whereas CI activity is increased (Figure 1C, right). Therefore, our studies suggest that under early amyloidogenic conditions, there is an increased stability of a dephosphorylated MCIA complex, deactivating the fatty acid oxidising function of ACAD9 and assisting to the correct assembly of the CI holoenzyme (Figure 2). However, a sustained overactivity of CI may lead to oxidative stress, boosting the accumulation of Aβ peptides and resulting in a detrimental cycle over time, causing mitochondrial dysfunction and compromising neuronal integrity.

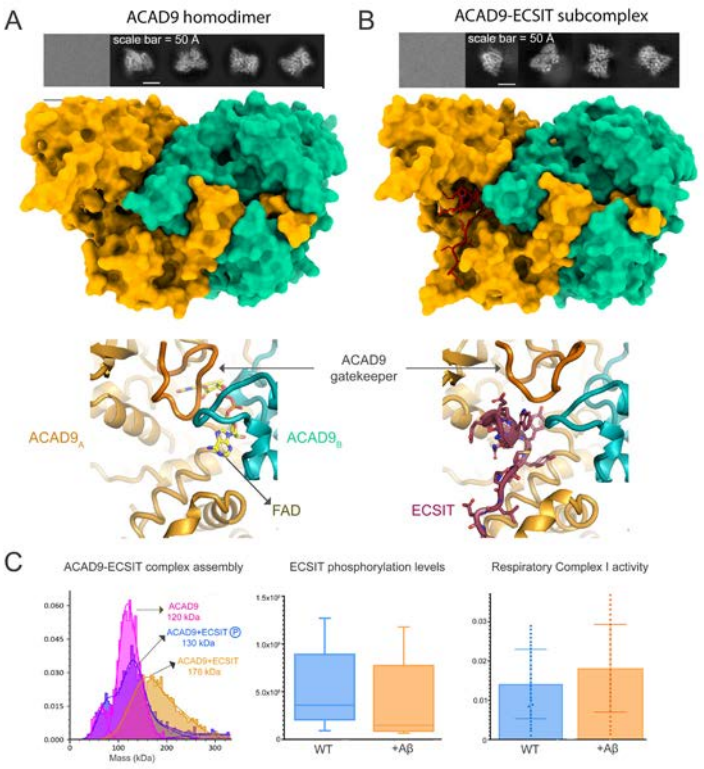

Figure 1: Cryo-EM reconstructions and atomic details of (A) ACAD9 unbound with its FAD cofactor essential for the FAO activity and (B) the ACAD9-ECSIT$_{CTER}$ complex and the conformational arrangement of the gatekeeper loop. (C) Biophysical analyses of the MCIA complex formation upon ECSIT phosphorylation (left) and its effect on amyloid toxicity exposure in neuronal cells (right).

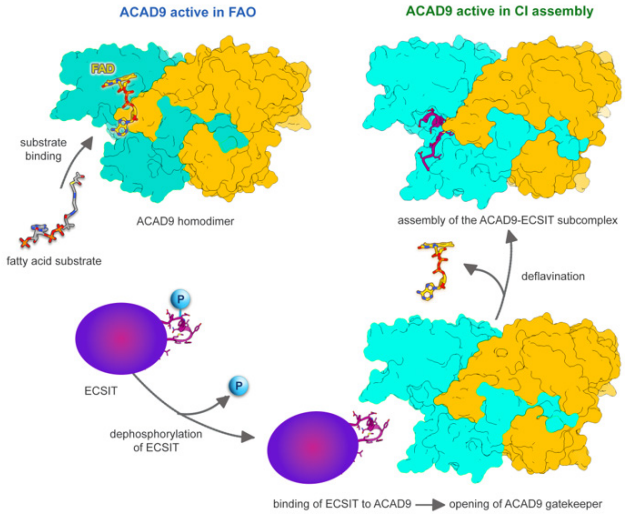

Figure 2: Proposed mechanism of ACAD9-ECSIT assembly and its functional implications in FAO and OXPHOS pathways.

Overall, combining molecular and cell biology, biophysics and structural analysis, we have revealed the interactions within the MCIA subcomplex and how its assembly and activity may be regulated in the presence of amyloid toxicity. These findings will be instrumental in determining whether the MCIA proteins can be used as biomarkers for the early stages of AD.

L. McGregor (ESRF), I. Gutsche (IBS) and M. Soler Lopez (ESRF)

[1] L. McGregor and M. Soler-López (2023) Curr. Opin. Struct. Biol., 80, 102573.
[2] L. McGregor, S. Acajjaoui, A. Desfosses, M. Saïdi *et al.* (2023) Nat. Commun., **14**, 8248.
[3] G. Giachin, M. Jessop, R. Bouverot, S. Acajjaoui *et al.* (2021) Angew. Chem. Int. Ed. Engl., **60**, 4689-4697.

Avian influenza adapts to humans by acquiring multivalency

Avian influenza viruses represent a recurring threat to human health. In particular highly pathogenic zoonotic avian strains, such as the currently circulating H5N1 subtype, can adapt to infect humans with high mortality, posing a catastrophic pandemic threat, in addition to global decimation of wild and domestic bird populations.

Host adaptation is necessary for efficient replication and sustained human-to-human transmission. Amongst other adaptations, replication in human cells requires mutations on the surface of the viral polymerase - the machine responsible for creating new copies of its genetic material. These mutations, located in the terminal domains of one of the subunits of the polymerase (PB2) are known to compensate differences in a host protein, ANP32A, that the virus somehow exploits in the infected cell and that is required for replication.

This enigmatic protein has a long disordered tail, that is 30% longer in birds than in humans, and highly negatively charged, comprising around 70% of acidic amino acids. The molecular origin of the associated compensatory mechanism remains unclear. A recent study from researchers at the IBS, in collaboration with the EMBL, Pasteur Institute and ENS Paris sheds new light on the question.

The Blackledge group at the IBS used high field NMR spectroscopy to demonstrate that avian ANP32A colocalizes two viral proteins, the polymerase domain PB2, and the nucleoprotein (NP). ANP32A interacts with the two proteins using two separate interaction sites on its disordered tail, an interaction that could position copies of NP in close proximity to the newly synthesized RNA as it exits the viral polymerase, allowing for rapid and efficient encapsidation of the viral genome. Such a step is thought to be essential to protect the viral RNA from the host immune system.

Camacho-Zarco and Yu *et al* noticed however that this mechanism would not be possible in human cells, because the disordered tail of the host protein would be too short to accommodate two separate interaction sites and thereby colocalize the NP and the polymerase.

They then demonstrated, using NMR relaxation and exchange, that the mutations present in the viral polymerase provide a new interaction mechanism that allows both viral proteins to simultaneously bind *exactly the same stretch* of the disordered tail of human ANP32A, forming a dynamic ternary complex [1].

The negatively charged flexible tail colocalises the nucleoprotein and the polymerase via highly dynamic and electrostatic interactions [2], rapidly, and crucially multivalently, fluctuating between positively charged surfaces on the two viral proteins. Indeed, the adaptive mutations, in particular PB2 E627K, the signature of all 20th century human flu pandemics, complete the positively charged distribution on the surface of the polymerase domain, thereby promoting the observed multivalency and providing a mechanism to overcome the collapse of the two binding sites that are present in the avian form of the protein.

On this basis, and in comparison with the recent structure of the folded domain of ANP32A in complex with a recently determined structure of a dimer of polymerases of the related influenza C, allowed the authors to speculate on the position of the disordered domain relative to the interacting PB2 domains and the colocalised NP [3].

This remarkable piece of molecular engineering on the part of influenza virus underlines the mechanistic plasticity of the infectious agent to overcome species barriers and achieve zoonosis, but also reveals completely new avenues for the development of potent inhibitory strategies against the ever-present pandemic threat of avian influenza.

A. Camacho-Zarco, L. Yu, M. Blackledge (IBS)

[1] A. R. Camacho-Zarco, L. Yu, T. Krischuns, S. Dedeoglu, *et al.* (2023). J. Am. Chem. Soc., **145**, 20985–21001.
[2] A. R. Camacho-Zarco, S. Kalayil, D. Maurin, N. Salvi, *et al.* (2020). Nat. Commun., **11**, 3656.
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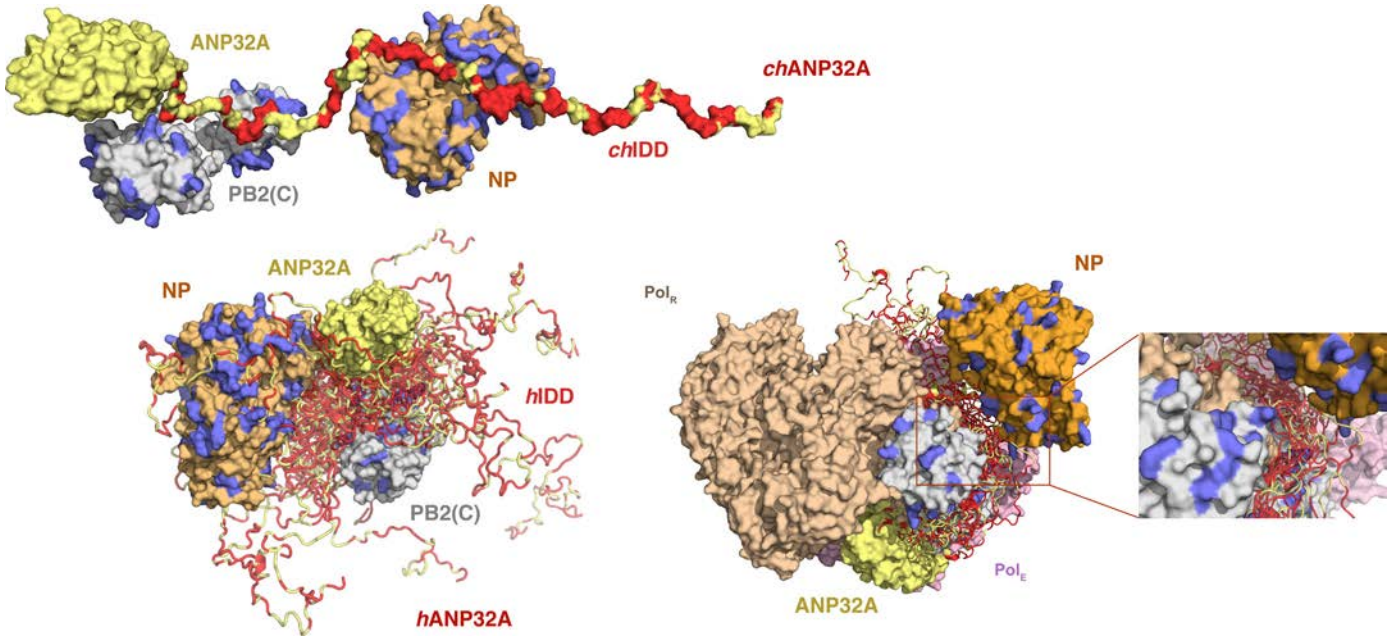

Figure: Top left - Avian ANP32A colocalizes the polymerase domains (PB2(C)) and nucleoprotein (NP) via two distinct interaction sites on the disordered tail. **Bottom left -** In humans the two sites have collapsed. In response the virus mutates residues on the surface of PB2, to promote multivalent, electrostatic interactions that colocalize the two proteins via the identical disordered interface. **Right -** Model of the possible colocalization of NP and the PB2(C) domains in the context of the structure of the folded ANP32A bound to influenza C polymerase dimer [3].

Room Temperature Protein Electron Crystallography

Due to its charge, electron interacts strongly with matter. Electron crystallography can thus be carried out on nanometer-sized crystals that contain fewer unit cells than crystals typically required for X-ray or neutron crystallography. Moreover, the resulting Coulomb potential map can provide additional information not available in the electron density map, such as the valence of the ions [1]. Although electron crystallography has successfully resolved three-dimensional structures of proteins from vitrified crystals, its widespread use as a structural biology tool has been limited. One of the reasons is the fragility of protein crystals, which can be easily damaged by mechanical stress and temperature changes, etc. Liquid phase transmission electron microscopy may present an alternative to vitrification and cryo-electron microscopy for electron crystallography [2].

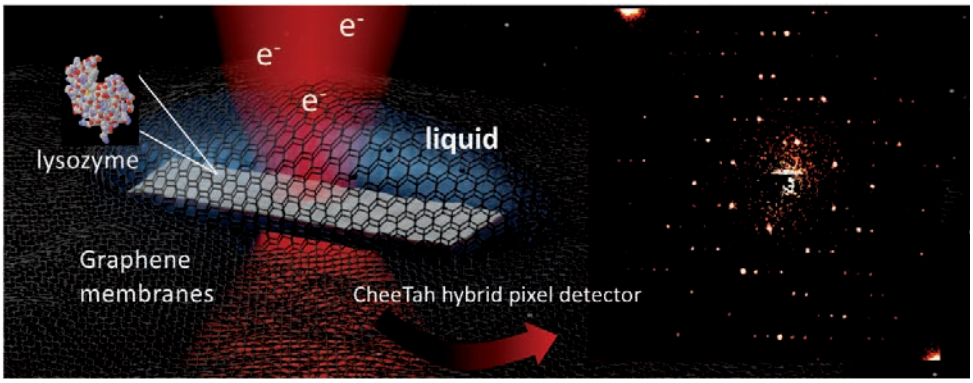

Figure: Lysozyme nanocrystal in crystallization solution is encapsulated in graphene layers for electron diffraction at room temperature. Reflections up to 3 angstroms are obtained.

In this work, nanocrystals of lysozyme with a size range suitable for electron diffraction were grown using the batch technique [3]. These nanocrystals were then encapsulated by graphene membranes in their mother liquor on the electron microscopy grids. Graphene is a two-dimensional material with exceptional mechanical strength and excellent thermal and electrical conductivities. These properties make them very suitable as a substrate for samples in electron microscopy studies. Besides the ability to seal the sample solution hermetically, the graphene layers further protect the sample against radiation damage from the imaging electrons in the microscopy.

Electron diffraction experiments on the encapsulated crystals were carried out on the F20 microscope of the IBS/ISBG electron microscopy platform at room temperature with the standard room temperature sample holder. Using the low-dose technique routine for imaging biological samples and the hybrid pixel detector installed on the F20 microscope, diffraction spots of up to 3 Å resolution were obtained. Indexing of the diffraction patterns is also possible thanks to a pattern matching algorithm.

Nanosized hydrates are important in many fields of science and technology, including energy conversion and storage, and biomedicine [4]. The technique employed here for room temperature electron crystallography can potentially be applied to many other organic or inorganic hydrates in different research areas.

M. Spano, D. Housset and W.L. Ling (IBS)

[1] T.B. Blum, D. Housset, M.T.B. Clabbers, E. van Genderen *et al.* (2021). Acta Cryst. D Struct. Biol., **77**, 75-85.
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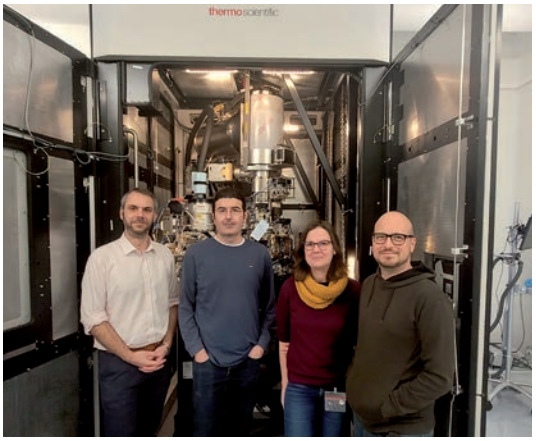
News from the platforms

CM02 is born

After several years of waiting, the France Cryo-EM project is becoming reality. This project will enable France to catch up its lack in term of big instruments for cryo-electron microscopy. France Cryo-EM is part of the “Plan Investissement d'Avenir 3” scheme and has enabled the purchase of three state-of-the-art 300 kV cryo-electron microscopes. The microscopes will be located at Illkirch (IGBMC), Grenoble (ESRF) and Saclay (SOLEIL).

For Grenoble, the microscope was delivered at the end of 2023. Prior to this, since May 2023, ESRF had been the prime contractor for the construction of a new hutch to house the microscope. Most of the construction work was completed in September, and reassembly of the microscope began at the same time. The manufacturer's tests went well (resolution greater than 1.3 Å on apoferritin) and the team that will be in charge of the instrument has now started to take it in hand at the beginning of January with the perspective of opening the instrument to users at the beginning of April 2024.



The CM02 team (from left to right: Félix Weis; Grégory Effantin; Pauline Juyoux; Lefteris Zarkadas) in front of the Titan Krios G4

This microscope, a Thermo Fisher Scientific (TFS) Titan Krios G4, equipped with a cold FEG, a Selectris X energy filter and a Falcon 4i, will operate as an ESRF CRG line. One third of the beam time will be allocated to ESRF users while the rest will be allocated via a curated process for French projects. This microscope, which will be able to carry out single-particle and tomography experiments, will be operated by a team of 5 people from the IBS/ISBG (see photo).

A big thank you to everyone involved in this project, not only at management level at the IBS, ISBG and ESRF, but also at construction level (coordinated by Thierry Marchial) and from the start of the day-to-day construction of the hutch to its completion (Thierry Giraud and Christoph Mueller-Dieckmann) and to the TFS engineers (Thibaut Merle and Pierre-Yves Mille in particular) who reassembled the instrument.

G. Schoehn (IBS)

Automation of complex experiments at MASSIF-1

MASSIF-1 was the first beamline to offer so-called 'unattended data collection' over 10 years ago and has been at the forefront of automation ever since. We have always prided ourselves on collecting the best possible data, from even the most challenging of samples, rather than applying automation only to "standard" or "easy" projects. By carefully extracting as much information as possible from each sample, the beamline centers the best diffraction volume of the crystal and adapts the beam size to the crystal size down to 10µm. After symmetry characterization and calculation of the best strategy, the full data set is collected in the best manner, including multiple position and helical collections [1]. All this without any user or operator present, optimizing the use of beamtime day and night. Building on these developments, we continue to automate the most complex experiments and data collection strategies. One of the most pernicious problems in data collection is the 'missing wedge' of data than can occur with low symmetry space groups. This can be alleviated by collecting multiple orientations and merging the sweeps, but this is a complex and time-consuming process that few users are willing or able to perform. In collaboration with Global Phasing Ltd, we have integrated their workflows for multi-orientation data collection within our own pipeline. If a missing wedge is predicted following characterization, a multi-orientation strategy is calculated. Once data collection in the first orientation is completed, the mini-kappa goniometer fitted on the MD2S diffractometer is opened and a second round of X-ray centering triggered. The second sweep is then collected at the kappa angle that has been predicted by the workflow. The resulting data sets are then automatically scaled and merged together using Global Phasing's autoproc [2] software and a single data set presented to the user through ISPyB. Both the data statistics and the resulting map is significantly improved (Figure 1). In combination with the CrystalDirect harvester [3], that allows fully automatic crystal mounting and data collection at cryogenic and ambient temperatures, MASSIF-1 is a world leader in automating complex experiments and data collection strategies.

Please contact us to discuss how we can get the best data from your samples.

M.W. Bowler (EMBL) and D. Nurizzo (ESRF)

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[3] U. Zander, M. Cianci, N. Foos, C.S. Silva *et al.* (2016) Acta Crystallogr. D Struct. Biol., **72**, 1026-35.

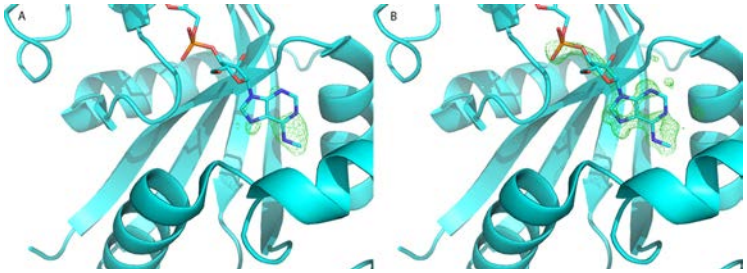


Figure 1: The thin end of the wedge. Difference density observed in the m6A adenosine binding site of the *T. gondii* protein YTH from a single sweep (A) and merged multi-sweep (B) strategies from the same triclinic crystal.

Time-resolved serial oscillation crystallography on MASSIF-3 beamline at the ESRF

MASSIF-3 is a microfocus X-ray beamline at the ESRF dedicated to macromolecular crystallography (MX). A recent development in the domain of time-resolved MX, is the adaptation of the "oscillation" method (Figure 1a) to record diffraction data with time resolution limited to several milliseconds (TR-SOX, [1]). In this setup, a crystalline sample is sandwiched and sealed between two Mylar foil sheets (Figure 1b), then mounted on a goniometer using a standard base. A *MeshAndCollect* [2] protocol is performed: first, a mesh scan is followed by the collection of a small wedge (typically 5°) of diffraction data from each diffracting position inferred from the mesh scan. At the beginning of each wedge collection, a short pulse of light (controlled duration) is focused to illuminate crystals and initiate a reaction. This pulse of light is synchronised with the detector to trigger data acquisition. The fast acquisition rate of an Eiger X 4M detector facilitates the collection of low-dose data sets at ~1.5 ms exposures per image. Subsequent data processing involves merging the data and using cluster analysis to select isomorphous datasets for merging. Finally, within the isomorphous set, the wedges are divided into different time steps, reintegrated and merged to solve the structures. Among the advantages of the method compared to "still"-oriented time-resolved techniques (e.g. jet) is better data accuracy, the possibility to select isomorphous data sets and lesser data required for higher completeness. The method is ideal for studying repeatable light-activated reactions

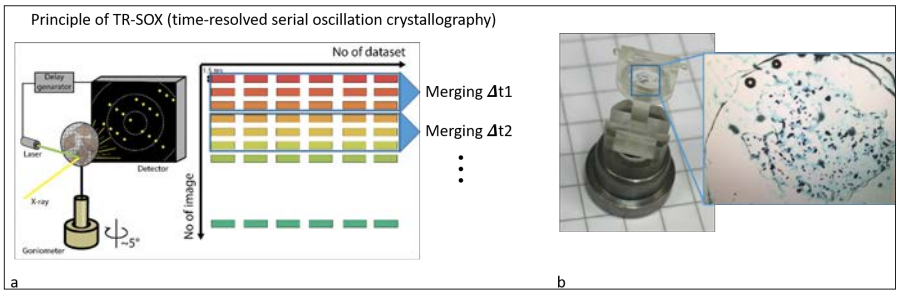


Figure 1: Principle of TR-SOX experiment. (a) The experimental setup and the scheme for merging data into different time steps. (b) The sample holder for room-temperature data collection for the Mylar foil sandwich with bacteriorhodopsin crystals.

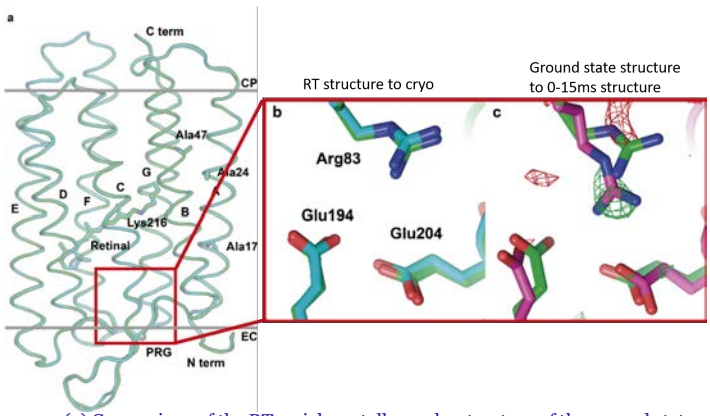


Figure 2:. (a) Comparison of the RT serial crystallography structure of the ground state of bacteriorhodopsin mutant BR_{TM} (green) with the single crystal structure obtained at 100 K (cyan). (b) Comparison of the PRG regions the serial crystallography structure of BR_{TM} solved at RT (green) with the cryogenic structure from the single crystal (cyan). (c) Laser induced changes in the PRG structure. Ground state structure is coloured green, while active state structure (0 - 15 ms structure) coloured pink. $Fo^{0\text{-}15ms} - Fo^{ground}$ isomorphous difference map is countoured at a 3σ-level.

(photocycles) of proteins, however, it has limited applicability to non-repeating reactions (i.e. one hit per sample).

Using TR-SOX [1], we resolved structural changes during the photocycle of a bacteriorhodopsin mutant with a step size of 15 ms using only 119/160 isomorphous partial 5°-wedges (Figure 2), collected from two samples. Each data comprised 50 images, collected at a rate of 1.5 ms/image: 71 ms in total. The reaction was initiated by a 2 ms pulse, produced by laser with shutter, focused on the sample into a 100 um spot, carrying 4 mW of power. The calculated absorbed X-ray dose in each partial data set is 12 kGy, which is extremely low even for ambient temperature experiments. Each data set was then reintegrated into smaller wedges corresponding to five 15 ms time steps and merged with the respective wedges from the isomorphous set. Finally, each structure of the 15 ms steps were obtained using molecular replacement and refined (Figure 2).

I. Melnikov (ESRF), S. Bukhdruker (IBS/ESRF)

[1] S. Aumonier, G. Santoni, G. Gotthard, D. von Stetten *et al.* (2020) IUCrJ, 7, 728-736.
[2] U. Zander, G. Bourenkov, A.N. Popov, D. de Sanctis *et al.* (2015) Acta Crystallogr. D Biol. Crystallogr., **71**, 2328-43.

Novel Agilent instrument installed at the IBS mass spectrometry facility

Last autumn an electrospray quadrupole-time of flight mass spectrometer (ESI-Q-TOF, 6545XT, Agilent) coupled with liquid chromatography (LC) was installed at the IBS. 6545XT is an excellent instrument for studying intact proteins. For instance, it determines the purity of a protein and the presence of truncations (e.g., loss of the first Met). It also allows the characterization of post-translational modifications (PTMs) such as phosphorylation, disulfide bonds and glycosylation. It is possible to study the binding of small molecules to proteins. Indeed, we could characterize the ligand binding corresponding to missing density in a cryo-EM structure. Since 6545XT can reach very high m/z, we investigate antibodies (Abs) and their PTMs with great accuracy and sensitivity [1]. Recently, we have established a collaboration with a Lyon-based company specialized in the development and production of treatments based on polyclonal Abs. Moreover, we intend to support the optimization of crosslinking protocols. Indeed, we can compare crosslinked samples differing in terms of reaction time, types of crosslinkers and concentrations. Indeed, 6545XT is complementary to a MALDI-TOF/TOF (the mass spectrometer used for membrane protein characterization and sequencing) and to a nano-ESI-Q-TOF (used for native MS experiments). Overall, 6545XT is more sensitive and accurate than our previous LC-ESI-TOF. Therefore, it allows us not only to provide better characterization of samples during routine analyses, but also to open new scenarios. Please come to us to discuss about novel questions on your preferred biological systems.

E. Boeri Erba (IBS)

[1] Agilent Technologies, publication number 5991-7813EN, https://www.agilent.com/cs/library/applications/5991-7813EN.pdf

A LC-ESI-Q-TOF mass spectrometer (6545XT, Agilent) has been installed in October 2023 at the IBS mass spectrometry platform.

EVENTS

Grenoble Host-Pathogen Interactions Club

More than digestion: what's in our gut and how does it impact our health?

On December 15, 2023 over 65 scientists gathered at the Institut de Biologie Structurale (IBS) to discuss these questions at the 8th meeting of the Grenoble Host-Pathogen Interactions Club (HPIC), which was centered on the theme "Focus on the microbiome". Despite last-minute circumstances obliging him to present remotely, keynote speaker Michael Zimmermann (EMBL Heidelberg) gave a captivating talk about unraveling the contributions of gut microbiota to carcinogen metabolism and tumorigenesis. During the second keynote talk, Philippe Cinquin (TIMC) wowed the audience with his presentation of an innovative non-invasive gut sampler capsule designed for intestomic studies of the small intestine. This pioneering technology was developed by the Grenoble medtech startup that he co-founded, Pelican Health. The programme also featured insightful short talks by Lama Shamseddine (LCBM – CEA Grenoble), Dalil Hannani (TIMC), Evelyne Jouvin-Marche (IAB), and Guillaume Hoffmann (IAB), offering a glimpse into the diversity and high quality of research projects conducted in the Grenoble area. The organising committee thanks the speakers and audience for their contributions and active participation, and looks forward to reconvening again for the next event, tentatively planned for later this spring. For updates on Club events and to sign up to the mailing list, please visit https://hostpathogen.fr.

C. Petosa (IBS)

CRISPR-Cas & Genome Engineering meeting 2023

After a kick-off edition at IAB in 2022, there were more than eighty registered participants who gathered at the IBS on November 30th 2023 for the second edition of the seminar series dedicated to CRISPR and Genome engineering. This event was jointly organized between the InGeprot and EEF platforms at IAB and EMBL, respectively.

The program of this half day event featured invited lectures from Alexandre Paix, Genome Editing Specialist at EMBL Heidelberg, who presented his work and proposed a bona fide rationale for efficient genome editing across animal models, and from Michael Schmitz, a postdoctoral researcher in Prof. Jinek's laboratory at the University of Zurich, who unraveled by Cryo-EM the molecular mechanisms of new type V CRISPR-associated transposons. In addition to short talks, the meeting also included two presentations from platform managers extensively using CRISPR and genome engineering: Michel Wassef from CRISPR'IT at Curie Institute Paris and Neil Humphreys from the Gene Editing and Embryology Facility at EMBL Rome. The event received sponsorship from Integrated DNA Technologies and ThermoFisher.

The organizers were delighted to see an increasing interest for this field in local research labs and fruitful discussion between participants and speakers. Further communication regarding the next edition will soon be made.

M. Pelosse (EMBL)

AMAX2023 - Advanced Methods for Ambient Crystallography

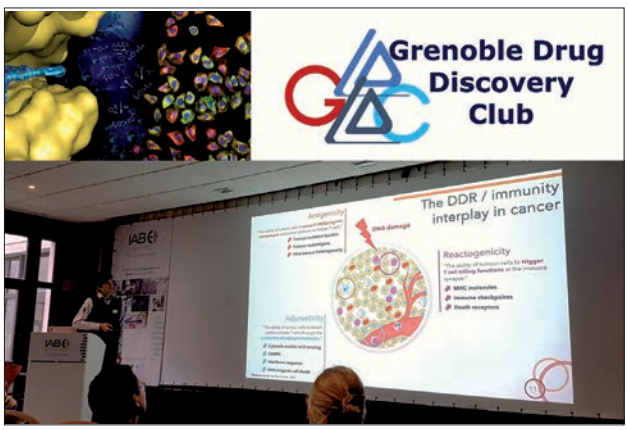
The vast majority of protein structures have been determined over the last few decades using cryocrystallography, an invaluable tool to help understand macromolecular function. Nevertheless, cryogenic temperatures might hinder the interpretation of experimental models, by revealing structural conformations that are less relevant in more physiological conditions. For this reason, interest in room temperature crystallography is increasing again, also thanks to the recent developments in the field. The EMBL-ESRF Joint Structural Biology Group, with the support of STREAMLINE, organized the first edition of the Advanced Methods for Ambient Crystallography workshop (AMAX2023) on 21 to 23 November 2023. Twelve applicants were selected to participate in the practical course, which focused on the latest developments in room temperature macromolecular crystallography carried out at beamlines MASSIF1 and ID29. On the first day, world leading experts from European and US laboratories introduced the scientific case for room temperature crystallography and the latest methods for the study of macromolecules at (close to) physiological conditions. The impact that this resurrected technique can have on the understanding of protein function and its implications in the development of new pharmaceutical molecules was also discussed. On the second day, the participants were divided into two groups and carried out practical sessions on both beamlines and were

able to successfully collect data from their own samples. The last day focused on data processing, where the participants analysed the data they collected using the ESRF newly implemented virtual environment VISA (visa.esrf.fr).

D. de Sanctis, J. Orlans, D. Nurizzo (ESRF) and M. Bowler, N. Foos, S. Basu (EMBL)

Grenoble Drug Discovery Club

The Grenoble Drug Discovery Club (GDDC - https://grenobledrugdiscovery.fr) organised its fifth scientific meeting on 9 November 2023, as a one-day Face-to-face workshop which took place at the IAB in La Tronche. The meeting was well attended with over 80 registered participants who joined from the various Grenoble research institutes: CEA, DPM-UGA, LRB-UGA, EMBL, ESRF, IAB, IBS, IRIG, and the Laboratoire Jean Kuntzmann. For this edition, the organisers gave the stage to several young and promising scientists, and the collection of invited speakers included: Roman Chabanon (Institute Gustave Roussy, FR), Giovanna Lollo (University Claude Bernard Lyon 1, FR), Ilaria Silvestri (Italian National Research Council, IT), and Christopher Swale (Institute for Advanced Biosciences, FR). The programme also included the presentation of the "Plateforme Intégrée de Criblage de Toulouse (PICT)" by Virginie Nahoum (IPBS, FR), short talks by Mathias Eymery (EMBL) and Serena Rocchio (EMBL), and two local startup companies, ERAS labo and Synthelis , were given the opportunity to come and



present their activities and services to the participants. Lively scientific exchanges continued during the poster session. The jury awarded two poster prizes to Morane Beaumet (DPM-UGA) and Mohammad Rida Hayek (IBS).

The organising committee wish to thank the sponsors: CLARA (https://www.canceropole-clara.com), Labex GRAL, Labex Arcane and the PSB, for their support, as well as all the speakers and participants for making this event a success, and look forward to meeting everyone again in November 2024, for a joint workshop that will be co-organised with the Grenoble Host-Pathogen Interactions club.

F. Bernaudat (PSB)

Signalling through chromatin: from molecules to ecosystems

A recent symposium co-organized by EMBL, IBS and IAB, with colleagues from the Ecole Normale Superieure and the College de France in Paris took place from the 2 to 4 October 2023 at Minatec that put Grenoble in the spotlight of epigenetic research!

Over 200 attendees from all over Europe, the US and Asia came together to discuss innovative aspects of chromatin and epigenetics, from the atomic to cellular, organismal, and population scales. The symposium comprised eight sessions, exploring chromatin dynamics and its link to several DNA and RNA-based processes such as transcription, DNA replication, repair and recombination. Dedicated sessions featured the translational implications of epigenetic studies and the development of "epi-drugs".

Speakers of outstanding international caliber presented integrative approaches in epigenetics research, such as quantitative proteomics, metabolomics, structural biology, single-cell epigenomics and population studies in different model organisms, from yeast to plants and mammals, including 3D culture models. During the poster sessions the students had a chance to exchange among each other and with renowned scientists about their progresses, with three of them selected for poster prize awards. The gala dinner at the O2 restaurant on the Grenoble Bastille was a further occasion for all the participants to gather informally and exchange about their scientific interest and career perspectives, creating a unique melting pot that will certainly

spark new collaborations and exciting new lines of interdisciplinary research in the field.

The event, which represents the fourth edition of such an international symposium organized by the "Epigenetics Club of Grenoble", was crucially made possible by the joint effort of academic institutions, including EMBL, IAB, IBS, the UGA, IBENS, CIRB, CLARA Canceropole, AVIESAN, and the Labex GRAL and MEMOLIFE, together with six corporate sponsors that are active in the field of epigenetics, namely Active Motif, Diagenode, Oxford Nanopore, Becton, Dickinson and Company (BD), BGI Group, and Arima Genomics.

M. Marcia (EMBL)

Science in the Mountains: celebrating Stephen Cusack's scientific career

Over 100 participants gathered in Grenoble to celebrate the remarkable lifelong scientific achievements of Stephen Cusack FRS, former head of EMBL Grenoble. Among the diverse group of 32 speakers, were former lab members and collaborators, current and former EMBL staff, ESRF, IBS and EMBL directors, and many distinguished scientists, including Sir David Stuart and the 2009 Nobel laureate Venki Ramakrishnan. Their talks covered not only their latest scientific results but also their interactions with Stephen and the influence he had on them and featured many humorous and moving personal anecdotes as well as highlighting his passion for wildlife photography and the great outdoors.

The talks also explored the many initiatives and local collaborations that Stephen was instrumental in setting up. In particular he contributed to technology development for synchrotron-based structural biology research, carried out in a close and long-standing collaboration with the ESRF, through the creation of the EMBL-ESRF Joint Structural Biology Group (JSBG). He also co-founded, with Sir David Stuart and others, the Europe-wide research infrastructure Instruct, and was one of the initiators of the Partnership for Structural Biology with the ESRF, ILL and IBS. These enduring partnerships have contributed to a highly productive atmosphere of scientific collaborations locally and internationally.

Stephen gave a final inspiring talk, summarizing his career that started with a PhD in theoretical physics from Imperial College London. He then decided to switch to the field of structural biology and joined EMBL in Grenoble as a postdoc in 1977 and never left! In 1989, he was appointed Head of Site, a role he carried out until 2022. He initially determined whole virus structures with neutron small angle scattering, then started using X-ray crystallography, and more recently electron cryo-microscopy. His talk highlighted only some of the many important contributions he and his group have made to the structure and function of protein-RNA complexes, such as aminoacyl-tRNA synthetases, the signal recognition particle and the innate immune receptor RIG- I. A major focus has been, and still is, on understanding how the influenza polymerase works, research that led to the creation of Savira Pharmaceuticals in 2008, a company dedicated to the identification and development of efficacious and selective anti-influenza drugs.

The celebration ended with a dinner on a balmy September evening at the Château de la Commanderie, preceded by a piano recital by former PhD student Maria Lukarska, who played a Chopin Nocturne and Ravel's Alborada del gracioso. "I was very moved by this wonderful event where I was able to reconnect with many people who have been so important to me during my career," said Stephen. "And without the inspiring serenity of Grenoble's majestic and wild mountains, I don't think I would have achieved so much," he reflected.

Congratulations to Stephen Cusack for his remarkable lifelong scientific achievements!

A. McCarthy and M. André (EMBL)

ANNOUNCEMENTS

Stephen Cusack FRS has been appointed a visiting Professor of Structural Biology at the Sir William Dunn School of Pathology of Oxford University. Stephen is the former head of EMBL Grenoble, a role he carried out until 2022, and a symposium 'Science in the Mountains' took place in September 2023 to celebrate his scientific career (see Events section). We're also pleased to announce that Stephen will continue at EMBL with Emeritus status.

Rebekka Wild, team leader in the SAGAG Group of the IBS, has received an Impulscience® fellowship from the Bettencourt-Schueller Foundation to study the molecular machinery responsible for the biosynthesis of glycosaminoglycans, which are long sugar chains playing key roles in many cell processes. To this end, Rebekka will use structural biology approaches, in particular single-particle cryo-electron microscopy and cryo-electron tomography, as well as *in vitro* functional and biophysical assays and *in cellulo* studies. Eventually, her studies will contribute to the development of drugs designed to protect cells against viruses or cancers. (Photo: © Alexandre Darmon/Art in Research for the Bettencourt-Schueller Foundation).

Jérôme Boisbouvier, group leader of the NMRLA group at the IBS, has received his third ERC Grant, an Advanced Grant, to develop new routes to study extra-large biomolecular assemblies using solution-state NMR. The XXL-NMR project aims to set up an approach for greatly simplifying the NMR spectra of very large protein complexes and their analysis at atomic resolution. This project will propel the biological applications of NMR far beyond their current limits, transforming solution NMR spectroscopy into a highly competitive method for the study of large medically relevant biomolecular assemblies and molecular machines hitherto considered inaccessible.

The EMBL Grenoble spin-off ALPX is among the top 10 European Clinical Research Organisations (CRO) for Drug Discovery for the second consecutive year. Founded in 2019, the core technology of ALPX is the remote control and full automation of processes in protein crystallography, used for drug design in the pharmaceutical and biotechnology sectors. Congratulations on this recognition!

PROFILE

On 1 December 2023, **Frank Gabel** has been appointed as the head of the new "Biology, Deuteration, Chemistry and Soft Matter" (BDCS) group at ILL. Prior to joining ILL, Frank was a CEA research director at IBS in the Extremophiles and Large Molecular Assemblies (ELMA) Group. The PSB newsletter met with Frank, to learn more about him and to discuss his vision for the development of the BDCS group and biology at ILL.

Could you tell us a few words about yourself and your scientific background?

My interest in natural sciences, in particular astronomy and physics, awoke relatively early in my childhood: I was wondering about the stars and the universe, and was curious about the strange forces that you feel when walking on a merry-go-round and why spinning tops don't fall over. In my teens, I started reading popular science magazines and during my time at high school I participated in the German national competition for the International Physics Olympiad. It was therefore a natural choice for me to study physics at the Technische Hochschule Karlsruhe (now KIT) after my high school graduation and a civilian service in 1995. While focusing on physics, I was intrigued by ongoing technological developments such as the human genome project and I started reading biology textbooks (e.g. Campbell) in my free time.

What brought you to Grenoble and to the IBS, and today to ILL?

After four years of very theory-oriented physics studies in Karlsruhe, I wanted to broaden my cultural horizon and spend my final university year abroad. English being the everyday language of science, I was rather aiming at a country where I could use (and improve) my second foreign language, French. The specific choice of Grenoble was due to a lucky circumstance: Prof. Dieter Engelhardt was organizing individual exchanges between Karlsruhe and UJF (now UGA) Grenoble, where he himself had spent time as a student in the late 1950s. Along with whole generations of German (and French) students, I benefited from his unique support and connections to the academic community in Grenoble.

When I was looking for an internship at the end of my DEA "Physique de la Matière et du Rayonnement" in late 1999, I was again lucky by meeting Dr. Giuseppe (Joe) Zaccaï at IBS who proposed a project on membrane dynamics by incoherent neutron scattering which led to my first experiments at ILL. Enjoying the exciting scientific topics at the interface between physics and biology, as well as the international atmosphere on the EPN campus, I decided to continue a PhD project with Joe and Dr. Martin Weik at IBS on "protein dynamics by neutron scattering".

After a 2.5-year postdoc interlude at EMBL Heidelberg in Dr. Michael Sattler's NMR lab (combining SAXS/SANS with NMR for the structural study of bio-macromolecular complexes), I was recruited as a

permanent CEA “ingénieur-chercheur” at IBS in 2006 with the task to reinforce the biological small angle scattering expertise at the institute and within the newly founded PSB. After a part-time detachment to the ILL LSS group in 2012-2019, and after so many years of successful experiments and exciting collaborations, it was tempting for me to accept the offer to become a group leader at this prestigious institute.

In the end, what started out as a short stopover ended up in more than 20 years of living and working in Grenoble!

What have been your research projects in the past years, and how has the PSB contributed to your work?

Since my return to IBS in 2006, many of my projects have been centered on the use and development of advanced Bio-SAXS/SANS, often in combination with other techniques. Examples include a study of solvent interactions with proteins as a function of their physicochemical surface properties, as well as time-resolved substrate processing by the proteasome and assembly of large proteolytic macromolecular machines *in vitro*. For these projects I have benefitted a lot from a very favorable local environment in Dr. Bruno Franzetti’s ELMA group at IBS, which brings together biologists, biochemists and physicists for the characterization of challenging and novel extremophilic biomacromolecules and the complexes they form.

The proximity of ESRF and ILL as leading photon and neutron sources, as well as the talented and dedicated beamline and instrument staff turned out to be indispensable for getting the best data out of weakly scattering and often fragile biological samples. In addition, the variety of complementary instruments and platforms operated by the PSB partners (within walking distance!) for sample characterization was a real asset for most of my projects. You often realize the strength of PSB only if you go to other places!

Will you still do research in your new position? If so, will it be a continuation of past projects, or will you develop new ones?

While my new position at ILL requires a lot of management and organisational tasks, I am strongly motivated to continue to do research. Some of it will be a continuation and elaboration of past projects, but I would also like to start some new projects. The joint use of X-rays and neutrons for complex biological systems, and integrating complementary information from Cryo-EM, crystallography, NMR, but also structure predictions with AI will certainly be part of it. Furthermore, I would like to develop novel deuteration protocols with my staff, and enlarge the variety of deuterated molecules that we can produce, including samples containing lipids.

Your first mission will be to set up/implement the new "Biology, deuteration, chemistry and soft matter" (BDCS) group at ILL. How do you envisage the organisation of the group and how it will evolve in the next few years?

The implementation and organization of the new group represents indeed a challenge. It consists of several excellent teams (deuteration, lipid and chemistry labs, as well as the ILL part of the PSCM) that have worked relatively independently in the past.
A first task will be to coordinate the interactions between the different teams and centralize the communication of the whole group with the user community via an update and renovation of the webpages and the proposal systems. It is important that ILL users are aware that a large variety of laboratories at the IIL exist with complementary techniques to neutrons, which can accompany them before, during, and after their experiments so that they can get the best out of their allocated neutron beam times.

In parallel to these user program activities our group will conduct its own research program on neutron-related biology, chemistry and soft matter projects, and interact strongly with the instrument groups at ILL. I will try to promote and encourage research projects which match the qualifications and complementary expertise of the outstanding scientists and research engineers of BDCS to create a synergy within the group. Developing advanced methodological approaches, as well as novel sample preparation and deuteration protocols will ultimately also benefit the user community when made available to them.

According to you, how does the BDCS fit in the PSB environment?

I would say that our new group not only fits in the PSB (and PSCM) environment, but is at the heart of it since we are located both in the CIBB and Science buildings! I believe we can thus act as a hub for interactions between the two large-scale facilities ILL and ESRF, but also promote collaborations with IBS and EMBL, our neighbouring biology partner institutes. In addition to being open for scientific collaborations within PSB, staff from the BDCS group and ILL will contribute to the organization of local teaching and training events. In 2024, we foresee the organization of an EMBO practical course on BioSAXS/SANS from September 16th to 20th and a PSB Spotlight day “Neutrons in Biology” (June 28th).

What is your vision for the future of biology at ILL and/or for neutrons in general?

Over the past years the European neutron community has been under pressure due to the closure of several facilities (e.g. LLB in France, BER-II in Germany), while others have temporarily not been available, and the new European spallation source (ESS) in Lund is not (yet) operational for user service. ILL is therefore playing a more crucial role than ever for keeping the neutron experimental community alive and, together with the other neutron centres, is providing training for the next generation of neutron scientists.

Neutrons are a complementary probe to X-rays and electrons: they are sensitive to light atoms, in particular hydrogen, and radiation damage is negligible. Moreover, like NMR, interactions of neutrons with matter is isotope-dependent, i.e. they can distinguish hydrogen from deuterium, allowing thus for specific labelling. While coherent scattering contains information on structure, incoherent scattering, combined with a measure of the energy exchange, provides information on molecular dynamics in biological samples.

Neutrons will therefore continue to play an important complementary role with respect to other techniques (X-ray and electron scattering, Cryo-EM, NMR…) in the form of integrative structural (and dynamical) biology approaches. I also believe that experimental neutron scattering data from complex biological systems should (and will) be combined more systematically with AI model predictions, and with molecular dynamics (MD) modelling at a multitude of length- and time-scales, from atoms to whole cells and beyond.

F. Bernaudat (PSB) and L. Gajdoš (ILL)

NEWCOMERS

Oleksandr Glushonkov, from the M4D cell imaging platform (ISBG), obtained a CNRS research engineer position in December 2023. Oleksandr completed his PhD in biophysics at the University of Strasbourg and then worked as a postdoc in the team of Dominique Bourgeois at IBS. In June 2021, Oleksandr joined the M4D platform, where he is in charge of two super-resolution microscopes, provides support for other instruments and contributes to future developments such as cryo-SMLM. Oleksandr will be glad to share his knowledge and expertise in the field of single-molecule localization microscopy and to guide platform users in their labeling, acquisition and data analysis strategies.

Pauline Juyoux joined the MEM group at IBS in January 2024 as an ISBG research engineer. She will be part of the operating team for CM02 at ESRF, the new Titan Krios cryo-electron microscope (see News from the platform section). Drawing from her background in cryo-EM and integrative structural biology, acquired through her PhD and postdoc experiences at EMBL Grenoble and IBS, Pauline looks forward to contributing to the cryo-EM community.

Sihyun Sung joined EMBL Grenoble in December 2023 as a staff scientist in the Marquez team and will contribute to the operation of the High Throughput Crystallization Laboratory (HTX Lab). His focus is on technology and method development in macromolecular crystallography, particularly in the area of fragment screening and structure-based drug design. His expertise in using both conventional and time-resolved X-ray crystallographic structural biology as well as the practical skills he acquired during his PhD at POSTECH in Korea and as an EIPOD postdoctoral fellow at EMBL Hamburg in Germany can contribute to the field of fragment screening structure-based drug design.

Apostolos Vagias joined the Large Scale Structures (LSS) group at ILL as a co-responsible for D22 instrument in November 2023. He has a polymer physics background and will support the commissioning of the SAXS device at D22, envisioning simultaneous SAXS/SANS experiments. Apostolos is a research scientist on soft matter with expertise in biophysics of macromolecules, hydrogels, polymer networks and anchored polymer films under pressure. Until October 2023, he worked at the Heinz Maier-Leibnitz Zentrum / TU Munich in Germany. His aim is to assist the soft matter task force at the ILL. Apostolos's collaboration perspectives include the PSB, PSCM, Computing for Science, the Soft Matter Science, the sample environment and theory groups.

DATES FOR YOUR DIARY

9th April 2024 – PSB/GRAL student day

The goal of this "PSB x GRAL student day" is to give young scientists a chance to interact with each other and to present and discuss research projects in a relaxed & informal atmosphere. For further information on the programme and registration: https://psbxgralstudentday.sciences-conf.org/registration

15th to 19th April 2024 – Tutorial in Macromolecular Crystallography

The aim of the tutorial is to introduce the theoretical background of crystallography and related techniques, to give a complete presentation of macromolecular crystallography techniques together with an introduction into its hands-on aspects. For further information on the programme and registration, contact: Wim.Burmeister@ibs.fr

25th April 2024 – PSB Seminar

Professor David Drew (Stockholm University) will give a PSB Seminar entitled "The Wonders of Small Molecule Transport" in the IBS seminar room at 11 am. For more information on the abstract of his talk, please check: https://www.psb-grenoble.eu

28th June 2024 – PSB Spotlight on "Neutrons in Biology"

This event will comprise of half a day of lectures on the different techniques available at ILL and which are useful for biology, including SANS, reflectometry, crystallography, inelastic scattering, deuteration at the D- and L-labs, and the chemistry and PSCM labs. A guided tour of the instruments and laboratories will be organized in the afternoon. For more information: https://workshops.ill.fr/event/428/

1st to 8th June 2024 – EMBO practical course on "Structural Characterisation of Macromolecular Complexes"

Recent developments in cryo-EM/ET, super-resolution microscopy, and protein structure prediction - coupled with increasingly sophisticated methods of sample preparation - have revolutionised structural biology. Course participants will receive a comprehensive overview of state-of-the-art structural methods, with a focus on sample preparation, characterisation, and data integration strategies. For more information: https://www.embl.org/about/info/course-and-conference-office/events/mmo24-01

8th to 12th July 2024 – EMBO practical course on "Time-resolved macromolecular serial crystallography"

The advent of serial crystallography at free electron laser sources and the following adaptation of these methods at 3rd and 4th generation synchrotrons have opened new possibilities to perform room temperature time resolved studies in macromolecular crystallography. This course aims to train the next generation of researchers in sample preparation, crystal delivery methods and data collection, data reduction, and analysis of the electron density map differences. For more information: https://www.embl.org/about/info/course-and-conference-office/events/ser24-01

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The Partnership for Structural Biology (PSB) is a collaboration between a number of prestigious European and French scientific laboratories in Grenoble. The PSB is unique in combining world leading user facilities for synchrotron X-ray and neutron scattering with NMR, electron microscopy, molecular biology and high throughput techniques on a single site together with strong projects in a broad range of structural biology.