CERM

Centro di Risonanze Magnetiche

Università di Firenze

CIRMMP

Consorzio Interuniversitario Risonanze Magnetiche di Metallo Proteine

SCIENTIFIC ANNUAL REPORT

2017

UNIVERSITÀ DEGLI STUDI FIRENZE

Contents

Foreword

The world of NMR is undergoing rapid changes. On the one hand, the emerging new techniques for structural investigation (Cryo-EM, AFM, FEL,…) will resize the relative contribution of NMR to biomolecular structural determination, on the other hand they further highlight the uniqueness and the complementarity of the NMR technique with respect to new and old methods. For example, NMR is the only technique providing both structural and dynamic information *in vitro* and in living systems; at the same time, NMR has also a primary role in material/biomaterial characterization, as well as in metabolomics. These rapid scientific progresses thus offer us a powerful stimulus to continue to develop the methodology, integrating the information coming from NMR with those from other techniques, making it possible to obtain a more and more detailed description of complex biological systems or advanced materials.

The research developed at CERM in 2017 follows this spirit of interdisciplinary and integrated approaches: by browsing through the research section of this report the variety of applications of NMR that move toward the interfaces with other disciplines is clearly apparent: from structural biology to medicine, from material science to information technology. With respect to 2016, we have an increased the number of publications done in collaboration with other laboratories, and a significantly increased average impact factor of our publications. The dialog with other disciplines forces our research to improve its theoretical and methodological bases, in order to be more effective in the applications. For this reason we dedicate a special section of the Research Areas of this report to emerging methods.

In parallel, we progressed in the development of an integrated European Research Infrastructure. CERM/CIRMMP is the Italian node of the INSTRUCT ESFRI Infrastructure, which has now obtained the European Research Infrastructure Consortium (ERIC) status, becoming **INSTRUCT-ERIC**. Since 2016 the **INSTRUCT-ULTRA** project was approved, which aims to accelerate the expanded implementation of INSTRUCT-ERIC by opening up to new members in Europe and partnerships at the global level, with a sharp focus on increasing the effectiveness of user access to key technologies, also working together with manufacturers. Furthermore, we have seen the set-up of the **EuroBioNMR EEIG** consortium, which is being established to create a pan-European organisation to co-ordinate European strategies for investments in biological NMR research infrastructures and to ensure user access to them for all excellent scientific projects. The activity of INSTRUCT-ERIC and other 12 Biological and Medical European Research infrastructures (BMS RIs) is now coordinated by the **CORBEL** initiative, which aim to create a platform for harmonised user access to biological and medical technologies, biological samples and data services required by cutting-edge biomedical research. CORBEL will boost the efficiency, productivity and impact of European biomedical research.

FIGURES

Also for 2017, the Italian Ministry of Research confirmed its support to the Italian node of INSTRUCT-ERIC within the International Action of the FOE funding. CERM/CIRMMP investments and costs in 2017 amounted to € 3.200.000,00: € 260.000,00 towards training and education, € 1.870.000,00 for new equipment and € 860.000,00 towards research activities. An additional € 210.000,00 covered operational costs. The actual replacement value of the instrumentation at CERM is close to € 49.000.000,00.

In 2017, in addition to the faculty staff, the body of researchers included 15 PhD students 9 postdoctoral scientists and 6 undergraduate students.

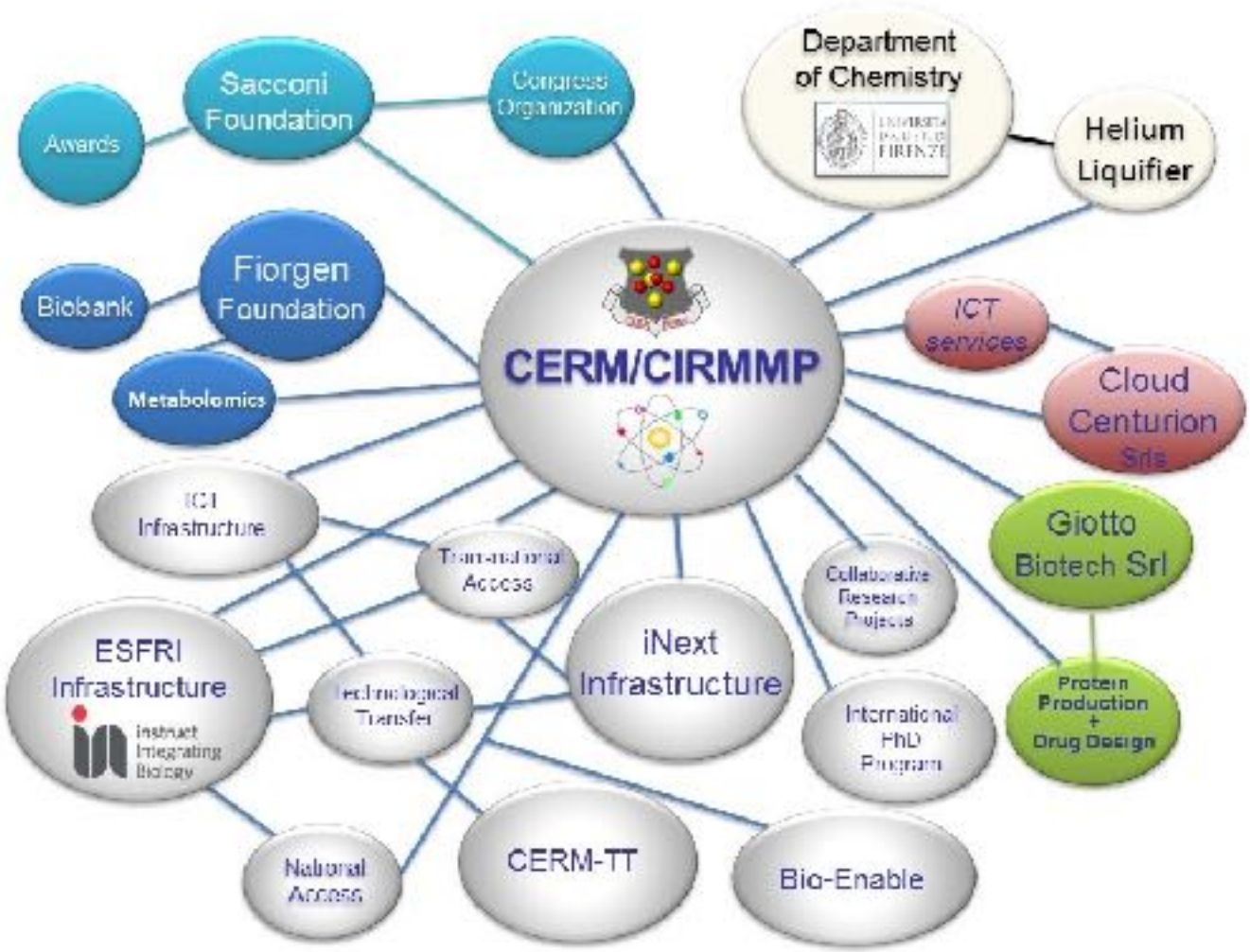
LOOKING AHEAD

The next big achievement for our lab will be the arrival of the new 1.2 GHz Bruker NMR spectrometer which will be ready in 2019. An agreement with Bruker Biospin assures that CERM/CIRMMP will be the first in the world to have that instrument.

We wish to thank all the people that contributed to make CERM what it is today and who continue to drive it forward and all the Institutions that provided their support to CERM.

Prof. Claudio Luchinat

Prof. Lucia Banci


Department of Chemistry
Helium Liquifier
Sacconi Foundation
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Biobank
Metabolomics
CERM/CIRMMP
ICT services
Cloud Centurion Srls
Giotto Biotech Srl
ICT Infrastructure
Trans-national Access
Collaborative Research Projects
ESFRI Infrastructure
Instruct Integrating Biology
Technological Transfer
iNext Infrastructure
International PhD Program
Protein Production + Drug Design
National Access
CERM-TT
Bio-Enable

Who we are

Introduction

CERM, Centre for Magnetic Resonance, is a ***scientific institution for research***, technology transfer and higher education of the University of Florence. It operates in synergy and collaboration with the Inter-University Consortium for Magnetic Resonance of MetalloProteins (CIRMMP) which includes three Italian Universities: Florence, Siena and Bologna. CERM/CIRMMP is an ***infrastructure for Life Sciences*** with a particular focus on structural biology and specialisations in NMR spectroscopy, bioinformatics, molecular and cellular biology, novel drug and vaccine design, and metabolomics. Nevertheless it is open towards interfaces with other research fields, for example new material and biomaterial development, contrast agent and MRI techniques, and ICT technology.

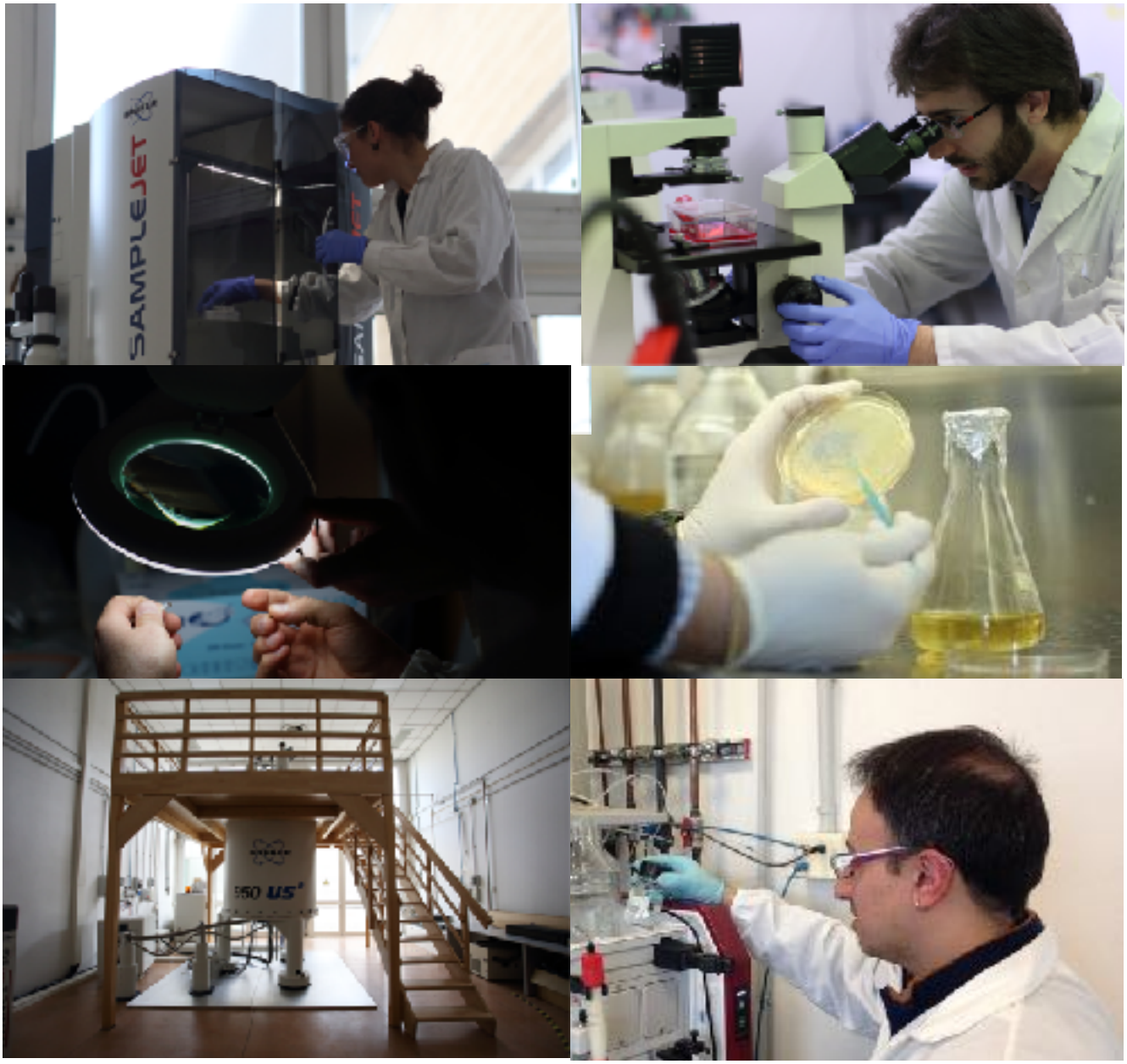
Being a leading laboratory at both national and international level, CERM/CIRMMP receives funding from competitive project calls from the Tuscan Regional Government, the Italian Ministry of Higher Education and Research (MIUR) and the European Commission (EC), as well as from private institutions. Since 1994, CERM/CIRMMP is providing a transnational access to its instrumentation for its expertise and state-of-the-art instrumentation for NMR in Life Sciences.

The core technology at CERM/CIRMMP is NMR spectroscopy, and the onsite instrumentation is among the most advanced in the world. A European transnational access service, funded by EC since 1994 in addition to service provision at national level operating since 1990, places CERM/CIRMMP at the top of the list for experience among the European NMR Research Infrastructures. CERM/CRIMMP actively stimulates interactions between private industry and public research institutions such as Universities, National Research Council (CNR) Institutes and European counterparts, promoting synergistic activities such as collaborations and services to SMEs.

CERM/CIRMMP is a core Centre of Instruct-ERIC, which is the European research infrastructure in integrated structural biology defined in the European Strategy Forum on Research Infrastructures (ESFRI) Roadmap. The Italian centre of INSTRUCT-ERIC, CERM/CIRMMP is also included in the "*Roadmap Italiana delle Infrastrutture di Ricerca di interesse Pan-Europeo*" since 2010. ***CERM/CIRMMP is also an e-infrastructure***, managing a GRID-based platform, together with other laboratories in Europe, for providing access to user friendly platforms and CPU resources for a broad range of computational programs and tools relevant for structural biology. CERM/CIRMMP also promoted the creation of a "*biobank of biological samples and biomolecular resources*", the DA VINCI EUROPEAN BIOBANK. Finally, CERM/CIRMMP has promoted the creation of a centre for research and

technology transfer: CERM-TT, funded by the Tuscany Region, which was inaugurated in July 2015. Since November 2015, CERM/CIRMMP is coordinating BIO-ENABLE, a new distributed Infrastructure funded by the Regional Government of Tuscany in the frame of POR FESR 2014-2020, which is aiming at strengthening and widening the technology transfer to industry.

CERM/CIRMMP is located in the Scientific Campus ("Polo Scientifico") of the University of Florence in Sesto Fiorentino, an area just west of the city of Florence. The campus borders Florence International Airport and yet is a mere 15 minutes from the centre of Florence, world-renowned cradle of renaissance art and culture.



The Infrastructure

CERM/CIRMMP labs

The CERM/CIRMMP building covers an area of 3,000 square meters hosting a number of laboratories, offices and common rooms. The flagship of the Center is the impressive collection of NMR spectrometers which feature the largest magnetic field range in the world (from 950 MHz to the earth field) and ranks it among the best equipped laboratories in the world. The NMR labs are flanked by molecular and cellular biology laboratories where samples for the NMR are produced. A complete list of the instruments available at CERM/CIRMMP is reported at pag. 38. In addition to the main building, further 500 square meters in adjacent buildings are available to CERM scientists and researchers scientifically associated to CERM/CIRMMP: Laboratories at the Department of Chemistry Ugo Schiff and at GENEXPRESS; DA VINCI European Biobank; X-rays facilities; Helium liquifier.

www.cerm.unifi.it

Instruct-ERIC

CERM/CIRMMP is an INSTRUCT-ERIC Core Center. INSTRUCT-ERIC is the European research infrastructure in integrated structural biology, making cutting-edge technologies and high-end methods in a palette of tools for structural characterisation available to users.

Structural biology is one of the key approaches that contribute to the understanding of the molecular and cellular functions. The main experimental technologies are complementary, and increasingly link detailed atomic structure with cellular context. Structural biology is currently in the middle of a revolution enabled by significant advances in various technologies (direct electron detectors in EM, advances in synchrotron sources and detectors, XFELs, ultra-high field NMR, super-resolution cryo-light miscroscopy).

INSTRUCT-ERIC buildup as a number of nodes constituted by Centres featuring the most advanced structural biology instrumentation and top-level expertise in the various methods. INSTRUCT-ERIC offers a **single point of access** to both multiple techniques integrated at one Center or over various Centres, or to some Centers specialised in specific techniques. www.structuralbiology.eu

INSTRUCT-IT is the Italian Instruct National Affiliate Centre. It consists in a core of excellent research institutions and large centers that have a proven track record in structural biology and in service and expertise provision to users. Instruct-IT aims to serve as a national consortium covering all main areas of structural biology research within Italy.

CERM TT

The CERM TT Competence Centre *dedicated to Ivano Bertini*, founder of CERM, was established in response to the request of the Tuscany Region to make available to the industries and production companies in Tuscany centres of technology transfer, innovation clusters with advanced equipment and skills to boost the economic growth of the region.

CERM TT strengthens and optimises the service offered by CERM/CIRMMP to the industry of the area: NMR instrumentation and advanced computing, a molecular biology laboratory for the production of proteins, scientific expertise and excellence, together with maximum protection of industrial IP.

CERM TT performs analytical services and research and development (R&D) for companies. In particular it offers the following services:

- Screening of drug candidates and drug-target interaction studies
- Smart design of drugs
- Analysis of pharmaceutical formulations

Bio-Enable

BIO-ENABLE is a "distributed research infrastructure" led by CERM and including a few of other Centres in Tuscany. Bio-Enable provides access to equipment and expertise to support industrial research and innovation. Tuscan companies operating in fields ranging from pharmaceuticals to biotechnology, from vaccines to biomaterials, from food to nanotechnology, can exploit the services of BIO-ENABLE in the development of their activities to be competitive at international level.

CERM lead the BIO-ENABLE consortium composed by:

- Institute of Neurosciences of the CNR – Pisa;
- BioRobotics Institute of Sant'Anna School of Advanced Studies - Pisa;
- Department of Medical Biotechnologies – University of Siena.

BIO-ENABLE can provide support at various levels and through different types of contracts: from simple access to instrumentation to specific types of advice, help and assistance to industrial research. BIO-ENABLE guarantees total confidentiality of the data collected at the various platforms both during the course of the analysis and in the management and archiving of the data.

www.bio-enable.it

Funded projects

CERM/CIRMMP cooperates at the international level with several universities, research institutions and private industries with which is involved in numerous research projects funded by the European Commission. Projects ongoing during 2017 are:

H2020-INFRADEV INSTRUCT ULTRA - Releasing the full potential of Instruct to expand and consolidate infrastructure services for integrated structural life science research (#731005). https://www.structuralbiology.eu/network/Instruct-Ultra/home

H2020-INFRAIA iNEXT - Infrastructure for NMR, EM and X-ray crystallography for translational research (#653706)
http://www.inext-eu.org/

H2020-INFRADEV CORBEL - Coordinated research infrastructures building enduring life-science services (#654248)
http://www.corbel-project.eu/home.html

H2020-EINFRA Phenomenal - A comprehensive and standardized e-infrastructure for analyzing medical metabolic phenotype data (#654241)http://phenomenal-h2020.eu/home/

H2020-PHC Propag-ageing - The continuum between healthy ageing and idiopathic Parkinson disease within a propagation perspective of inflammation and damage: the search for new diagnostic, prognostic and therapeutic targets (#634821) https://www.propag-ageing.eu/

H2020-EINFRA EGI-Engage - Engaging the EGI community towards an open science commons (#654142)
https://www.egi.eu/about/egi-engage/

H2020-EINFRA Indigo-DataCloud - Integrating distributed data infrastructures for global Exploitation (#653549)
https://www.indigo-datacloud.eu/

THE INFRASTRUCTURE

H2020-EINFRA West-life - World-wide E-infrastructure for structural biology (#675858) https://portal.west-life.eu/

ITFoC Information Technology: The Future of Cancer Treatment https://itfoc.eu/

COST Action 15133 The Biogenesis of Iron-sulfur Proteins: from Cellular Biology to Molecular Aspects (FeSBioNet) www.fesbionet.eu

SPIDIA - Standardisation and improvement of generic pre-analytical tools and procedures for *in-vitro* diagnosis. http://www.spidia.eu/

National Highly Relevance Projects - “Italia - Argentina”

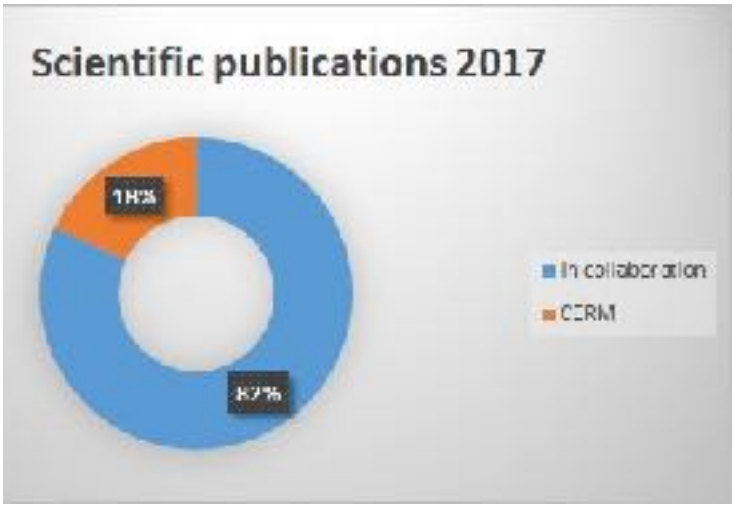
PhosAgro/ UNESCO/ IUPAC Partnership in Green Chemistry for Life

Research Activities

Introduction

During 2017 a number of projects have been carried out, either as an extension of the activities of previous years or as new projects. Most of these projects receive specific funding from national and/or European organisations.

NMR is the core technology of CERM, but year by year CERM research has been oriented more and more toward new applications and toward the integration with other techniques. This is one of the principles of the Integrated Structural Biology that underlays the INSTRUCT-ERIC consortium, where CERM/CIRMMP is the Italian pole. In the following pages it can be appreciated how much the present research in CERM/CIRMMP is spanning a wide range of applications, from the structural biology to the bioinformatics methods and Information Technology, from paramagnetic NMR methods to the development of new contrast agents for MRI, from the metabolomics and biomedicine to the development of new solid-state NMR methods for the characterisation of material surfaces and biomaterials.



In line with our mission to develop NMR as a technique and to integrate NMR with other techniques, we increased the number of publications done in collaboration with other research groups, passing from 75% (in 2016) to 82% (in 2017) of the overall number of publications. With respect to 2016 we keep a good average publication impact factor above 6, that is now 6.05. In 2017 we published 56 papers in international peer-reviewed journals and three books.

A complete list of publications is available at page 46.

CIRMMP has been ranked first among the Italian Interuniversity Consortia in Chemical Science in the last evaluation of the quality of research (VQR 2011-14) by the National Agency for the Evaluation of the University and Research Systems. This excellent level of research of CERM/CIRMMP also contributed to having the Chemistry Department of the University Florence, to which most CERM scientists belong, ranked in the first place in the last Research Evaluation in the Chemical Science Area of the Italian Universities (VQR 2011-14). The Chemistry Department of the University Florence was also winner of the national Project

for Excellent Departments. This witnesses the impact of our research not only in the NMR field, but also in the larger chemical community and in the whole Italian research community.

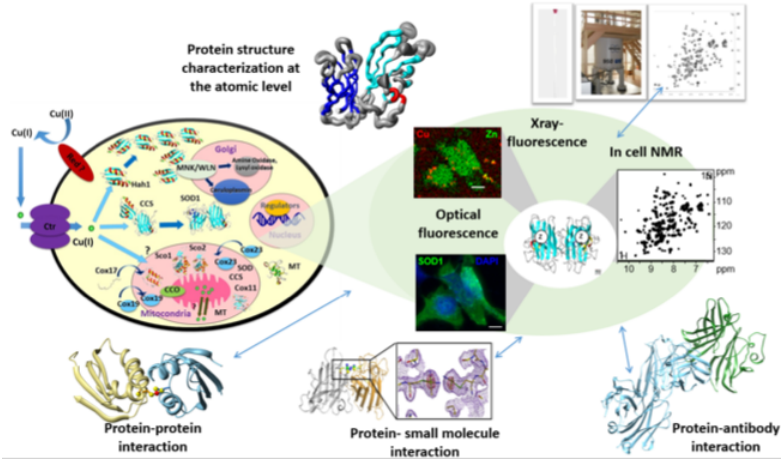
The interdisciplinary character of CERM/CIRMMP research projects, combined with the excellence of its instrumentation, constitutes a point of reference for the scientific community and for the cultural growth in the country, as demonstrated by the significant usage of the infrastructure by national scientists.

Finally, since 2016 CIRMMP has decided to implement a quality system of the NMR lab, and is presently undergoing an ISO9001 certification process. The long-term goal is the obtainment of ISO/IEC 17025 accreditation for a set of key validated NMR analyses.

The Role of Solution NMR in Integrated Structural Biology

Nowadays solution NMR is an indispensable enabling technology for determining not only structures of biomolecules but also their interactions, even weak and transient, as well as for characterising functional processes in solution and also directly in living cells. Through the integration of solution NMR with other structural data derived using different technologies and on different length and time scales, we will be able to understand, on the basis of detailed atomic structure, how proteins, protein complexes or DNA-protein complexes interact dynamically with their functional environment. This fundamental understanding will underpin our ability to provide new therapeutics to meet the grand challenges of an ageing society, public health and global pandemics.

CERM applies solution NMR in an integrated systems biology approach for addressing more and more challenging questions. Such approach is routinely used to understand the role played by a protein in the frame of cellular metabolism, or to rationally engineer an enzyme for a specific industrial process, or to determine how to design novel drugs that target a particular protein, or to understand what changes might improve them.[1,2,3]



The potential of integrated structural biology in unravelling biological processes.

It is no longer sufficient to determine simply the structure and biochemical properties of a protein. In line with the trend towards systems biology, a major challenge now is understanding how that protein functions within a larger macromolecular assembly or in a cellular pathway or even at the organism level.

Understanding dynamic processes that are co-ordinated at a cellular level is not possible using a single technology, but becomes potentially accessible through the integration of a number of approaches, spanning different resolution scales.

Complementary structural biology technologies are required to face such complex systems in dynamic way.

References:

(1) Luchinat, E.; Barbieri, L.; Banci, L. *Sci Rep.* **2017,** *7,* 17433.

(2) Kay, K.L.; Zhou, L.; Tenori, L.; Bradley, J.M.; Singleton, C.; Kihlken, M.A.; Ciofi-Baffoni, S.; Le Brun, N.E. *Chem Commun.* **2017,** *53,* 1397.

(3) Andrałojć, W.; Hiruma, Y.; Liu, W.M.; Ravera, E.; Nojiri, M.; Parigi, G.; Luchinat, C.; Ubbink, M. *Proc Natl Acad Sci U S A.* **2017,** *144,* E1840.

Integrated Structural Techniques

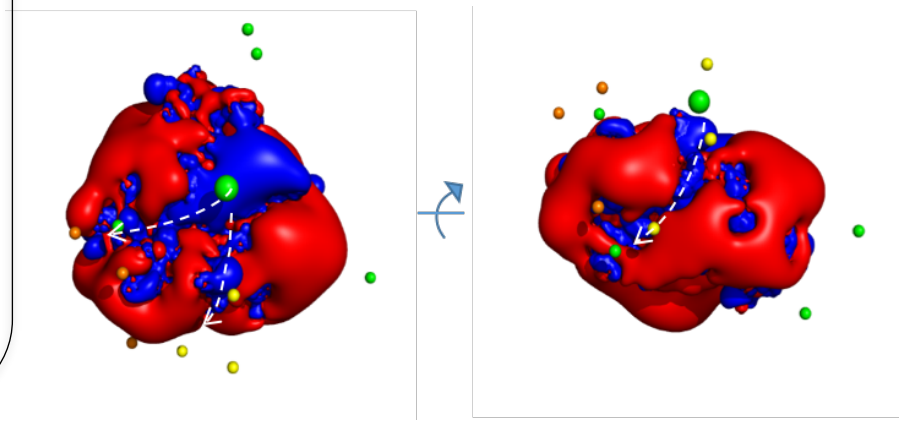
It is more and more often the case that different techniques yield data that are not easily reconciled. NMR data can for instance show the presence of conformational states in solution not detected by X-ray diffraction. Approaches that allow to extract the most of the information from the experimental data without overinterpreting them should thus be implemented.

NMR data can be included as restraints in the widely-used X-ray refinement software REFMAC to assess whether they can be explained by a structural model derived from X-ray crystallography within the accuracy of its diffraction pattern. In this case, the NMR data can be used to provide a structure that complies with both solid-state and solution data and is thus more reliable.
NMR data can also monitor conformational rearrangements in systems comprising of multiple domains. We have developed methods to obtain information on the conformational variability of multi-units systems using the MaxOcc approach, aimed at identifying individual conformations, or groups thereof, that can exist for a large share of time in agreement with the average experimental data. The very good sensitivity of paramagnetic data to minor states allowed the identification of a series of lowly populated states that together populated a small percentage at maximum in the presence of a strongly dominating conformation of cytochrome P450-cam in complex with putidaredoxin.

References:

(1) Andrałojć W., Hiruma Y., Liu W.-M., Ravera E., Nojiri M., Parigi G., Luchinat C., Ubbink M., *Proc. Natl. Acad. Sci. USA* **2017,** *114,* E1840-E1847.

(2) Ravera E., Parigi G., Luchinat C., *J. Magn. Reson.* **2017,** *282,* 154-169

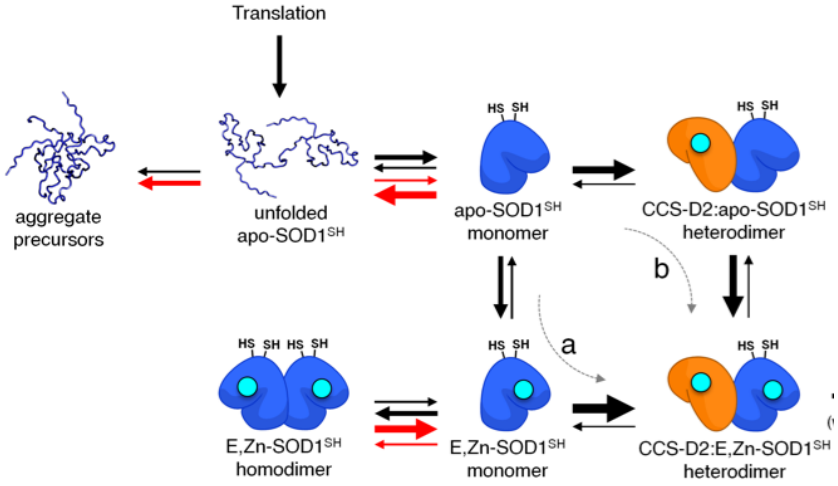


The positive and negative electrostatic potential isosurfaces of cytP450cam shown together with the centre of mass positions of putidaredoxin in a plausible conformational ensemble of the complex. The states are depicted as follows: bigger green sphere – the major state, smaller spheres – the minor states. The white dashed arrows indicate possible paths between the minor states and the main binding site, suggesting that these states could represent productive encounter sites.

In-cell NMR in Human Cells

The in-cell NMR approach developed at CERM is being further extended and applied to human cells. The direct protein expression approach allows monitoring functional processes such as protein folding, metal binding, redox regulation and other post-translational modifications at atomic resolution in human cells.[1] The approach was applied to investigate the role of the copper chaperone for SOD1, CCS, in rescuing the correct folding of SOD1 mutants linked in familial variants of Amyotrophic Lateral Sclerosis (fALS).[2] It was found that the second domain of CCS effectively acts as a molecular chaperone towards the apo state of SOD1 mutants, stabilizing it and allowing zinc binding and correct folding. In another work, NMR in human cells was integrated with NMR data *in vitro* and in other cellular models to investigate the effect of copper(I) on the redox state of the first domain (BIR1) of the human X-linked inhibitor of apoptosis (XIAP).[3] *In vitro*, copper(I) reacts with an exposed cysteine of BIR1 – which is reduced in the cellular environment –causing the formation of a disulfide bond between two BIR1 monomers.

In-cell NMR spectroscopy is a unique tool for characterising biological macromolecules in their physiological environment at atomic resolution. At CERM, we have developed an approach in which proteins are synthesised directly in cultured human cells and observed by NMR. Protein functional processes such as folding, cofactor binding and disulfide formation can be monitored in their physiological environment.



References:

(1) Luchinat, E.; Banci, L. *IUCrJ,* ***2017***, *4* (2), *108.*

(2) Barbieri, L.; Luchinat, E.; Banci, L. *Sci. Rep.* **2017**, *7* (1), 17433.

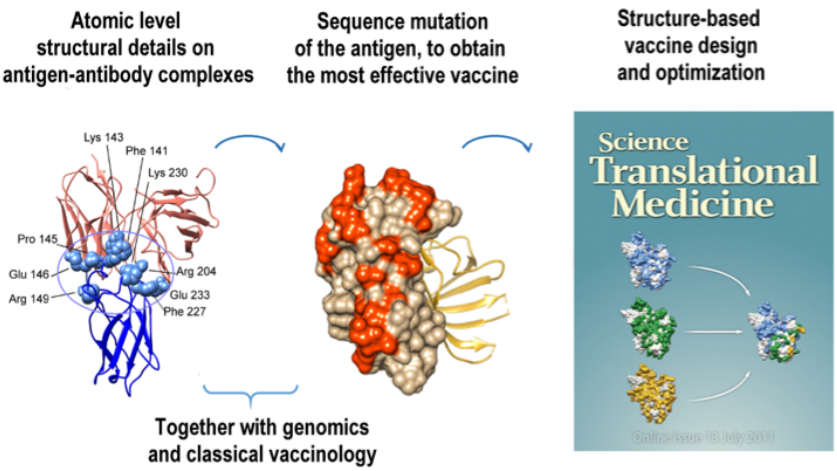
(3) Hou, M. M., Polykretis, P., Luchinat, E., Wang, X., Chen, S. N., Zuo, H. H., Yang, Y., Chen, J. L., Ye, Y., Li, C., Banci, L. & Su, X. C. *Sci. Rep.* **2017**, *7* (1), 16630.

Proposed model for the molecular chaperone activity of intracellular CCS-D2. Red arrows indicate which steps of SOD1 maturation are negatively influenced by mutations. Two possible mechanisms of action for CCS-D2 are shown: (a) SOD1 first binds zinc and then interacts with CCS-D2; (b) apo-SOD1 first interacts with CCS-D2 and then binds zinc. The interaction between SOD1 and copper-bound CCS eventually leads to the fully mature protein.

Structure-Based Vaccine Design

CERM/CIRMMP is a leading centre in the development of an innovative approach in vaccine design. The latter is based on the characterisation of the antigen structure and of its interacting regions with the antibody. With this approach CERM/CIRMMP researchers and GSK Vaccines researchers, were able to create a broadly protective vaccine against more than 500 variants of the bacterial pathogen Neisseria meningitidis *serogroup B (MenB).*

The sequencing of the highly immunogenic antigen from the pathogen *Neisseria meningitides* serogroup B named factor H binding protein (fHBP), showed that there are more than 500 variants classified in three distinct antigenic groups. Bactericidial activity evidenced that there is no cross-protection among the three different groups of variants. To generate an antigen able to induce immunity against all sequence variants, the surface of the C-terminal domain of variant one has been divided into overlapping areas which were mutated to introduce residues of variant two and three. This approach, named "structurally vaccinology", allowed the design of multiple antigenic epitopes on a single protein scaffold with the final aim to engineer biomolecules able to trigger a neutralising effect in various strains of the pathogen MenB. This example demonstrated that the detailed knowledge of the residues recognised by protective antibodies is fundamental for modulating the immunogenicity of the antigen and to improve the bacterial potential vaccine candidate every time that the sequence variability of protective antigens is a major limit to the development of vaccines.[1-5]



Structural vaccinology: a genome-based approach combined with structural biology

References:

(1) Rubino, J.T.; Martinelli, M.; Cantini, F.; Banci, L.; Scarselli, M. et. al *J Biol Inorg Chem*. **2016**, *21*, 185.

(2) Liguori, A.; Malito, E.; Lo Surdo, P.; Fagnocchi, L.; Cantini, F.; Haag, A. F.; Brier, S.; Pizza, M.; Delany, I.; Bottomley, M. J. *PLoS Pathog*. **2016**, *12*, e1005557.

(3) Rippa, V.; Cantini, F.; Veggi, D.; Gentile, M.A.; Banci, L.; Pizza, M.; Scarselli, M. et. al *Clin Vaccine Immunol*. **2015**, *22*, 769.

(4) Cafardi, V.; Martinelli, M.; Rubino, J.T.; Cantini, F.; Scarselli, M.; Unnikrishnan, M.; *PLoS One*. **2013**, 8, e81306.

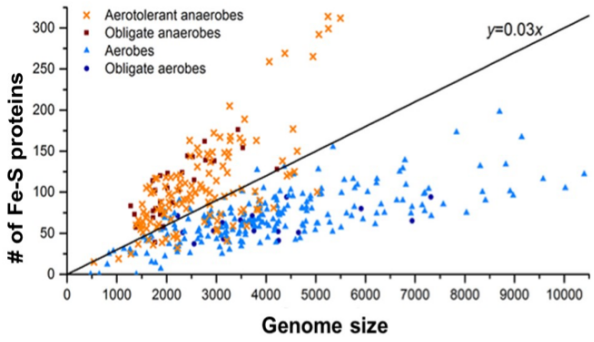
(5) Scarselli, M.; Cantini, F.; Dragonetti, S.; Banci, L.; Pizza, M.; Rappuoli, R. et al *Sci Transl Med*. **2011**, 3, 91ra62.

MetalPDB: a New Version for Novel Studies

In 2017 we published the second version of MetalPDB, which now includes extensive statistical analyses, new query functionalities and manually annotated information on the function of the metal sites. A major extension is also the inclusion in MetalPDB of proteins whose structure do not contain metal ions although their sequence potentially contain a metal site.

We investigated how functional differentiation within metalloenzyme superfamilies relates to structural changes at the catalytic metal site. In general, when the catalytic metal site is unchanged across the enzymes of a superfamily, the functional differentiation within the superfamily tends to be low and the mechanism conserved. Conversely, all types of structural changes in the metal binding site are associated to high functional differentiation. Overall, the catalytic role of the metal ions appears to be one of the most conserved features of the enzyme mechanism within metal-dependent enzyme superfamilies, especially when the metal ion does not play a redox role.

Finally, we applied MetalPredator, a web service that we developed since 2016, to study the entire metalloproteomes of organisms. In particular, the comparative analysis of the iron-sulfur proteomes of prokaryotes showed that aerobic organisms use less Fe-S proteins than the majority of anaerobic organisms with a similar genome size (figure). Furthermore, aerobes have evolved specific Fe-S proteins that bind the less iron-demanding and more chemically stable Fe_2S_2 clusters while reducing the number of Fe_4S_4-binding proteins in their genomes. However, there is a shared core of Fe-S protein families composed mainly by Fe_4S_4-binding proteins.[1,2,3,4,5]



Dependence of the number of Fe-S proteins and Fe-S families on the genome size of the organisms.

In 2017, we published the second version of MetalPDB. By analysing superfamilies of metal-dependent enzymes in MetalPDB, we found that evolution tends to strictly conserve the metal site. When changes occur, they do not modify the catalytic role of non-redox metals whereas they affect the role of redox-active metals. Finally, we compared metalloproteomes of prokaryotic organisms to shed light on the relationship between the environment and metal ions content.

References:

(1) Valasatava, Y., Rosato, A., Furnham N., Thornton J.M., Andreini C.. *J. Inorg. Biochem.*, *in press.*

(2) Putignano V., Rosato, A., Banci L.., Andreini, C., *Nucleic Acids Res.*, **2017**, 46 (D1), D459-D464

(3) Chasapis C.T., Andreini C., Georgiopolou A.K., Stefanidou M.E., *Archives of microbiology*, **2017**, 199, 1141-1149

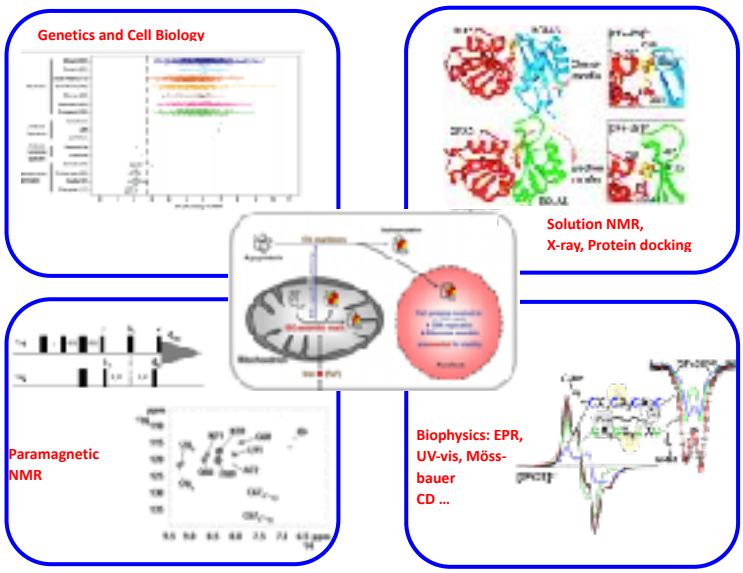
(4) Andreini C, Rosato, A., Banci L.., **2017** *PLoS One* 12, e0171279

(5) Buracco S, Peracino B, Andreini C, Bozzaro S *Front. Cell. Infect. Microbiol.* **2017**; 7, 536

Molecular Mechanisms of Iron-Sulfur Protein Biogenesis in Humans

Iron-sulfur (Fe-S) clusters are ancient protein cofactors involved in fundamental cellular processes. Despite the chemical simplicity of Fe-S cluster, their synthesis and assembly into apoproteins is a highly complex and coordinated process in living cells. Different biogenesis machineries in both bacteria and eukaryotes have been discovered that assist Fe-S protein maturation. An increasing number of human diseases related to misfunction of Fe-S protein biogenesis documents the importance of investigating such process in humans. A picture of the molecular mechanisms that are at the basis of Fe-S protein biogenesis is fundamental to boost the development of treatments on such human diseases.

In the last decade, CERM/CIRMMP focused one of its research activities to the investigation of the molecular mechanisms responsible of iron-sulfur protein biogenesis in humans. In 2017, we investigated how copper toxicity is connected to mitochondrial iron-sulfur cluster proteins and to their assembly processes. The molecular model we proposed indicates that the copper(I) and iron-sulfur protein maturation cellular pathways need to be strictly regulated to avoid copper(I) ion from blocking mitochondrial Fe_4S_4 protein maturation. The molecular function of two mitochondrial proteins, BOLA1 and BOLA3, recently becoming part of the iron-sulfur assembly machinery, was also investigated. The data provided the first indications discriminating the molecular function of the two proteins. Finally, we investigated the function of human mitoNEET protein that has been recently implicated in iron-sulfur cluster repair of cytosolic iron regulatory protein 1, a key regulator of cellular iron homeostasis in mammalian cells. Our data provided novel indications of a possible direct link between the mitoNEET-related iron-sulfur cluster repair pathway and the Ndor1-anamorsin complex, a component of the cytosolic iron-sulfur protein assembly machinery.[1-3]



An integrated approach in Fe-S protein biogenesis

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(1) Nasta, V.; Giachetti, A.; Ciofi-Baffoni, S.; Banci, L. *Biochim Biophys Acta.* **2017,** *1861,* 2119.

(2) Camponeschi, F.; Ciofi-Baffoni, S.; Banci, L. *J Am Chem Soc.* **2017,** *139,* 9479.

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Iron Biomineralization in Ferritin

Mammalian ferritins are generally heteropolymeric nanocages composed by variable amounts of two types of subunits, namely H subunits, with ferroxidase catalytic activity, and L subunits, which lack catalytic activity. The H/L is tissue-dependent. Fast iron metabolism is associated to cages rich in H-subunits. On the contrary, ferritins in iron storage organs are rich in L-subunits, proposed to facilitate iron biomineral formation via nucleation sites.

These sites are here identified as triiron clusters on the inner surface of the cage in homopolymeric recombinant human L-ferritin and natural horse spleen ferritin (1 or 2 H-subunits/cage) (figure).[1] Glutamates E60, E61 and E64 act as bridging ligands between iron pairs, thus driving the cluster assembly. In the fully formed cluster the iron ions are also bridged by peroxide anions, which could originate from ferrous iron oxidation by dioxygen. Substitution of E60, E61 and E64 by Ala significantly reduces the iron biomineralization rates.

As for H-cage, ferrous hexa-aqua ions entering the L-cage via 3-fold channels are observed.[2] MD provides atomic-level evidences that iron(II) release occurs via the same ion channels and the process is facilitated at low pH.

Finally, the overall biomineralization process in L-rich cages appears to be facilitated by some fatty acids.[3]

Iron biomineralization ion L-ferritin occurs via nucleation seeds formed by an unprecedented three iron cluster. Insights on biomineral dissolution were also obtained.

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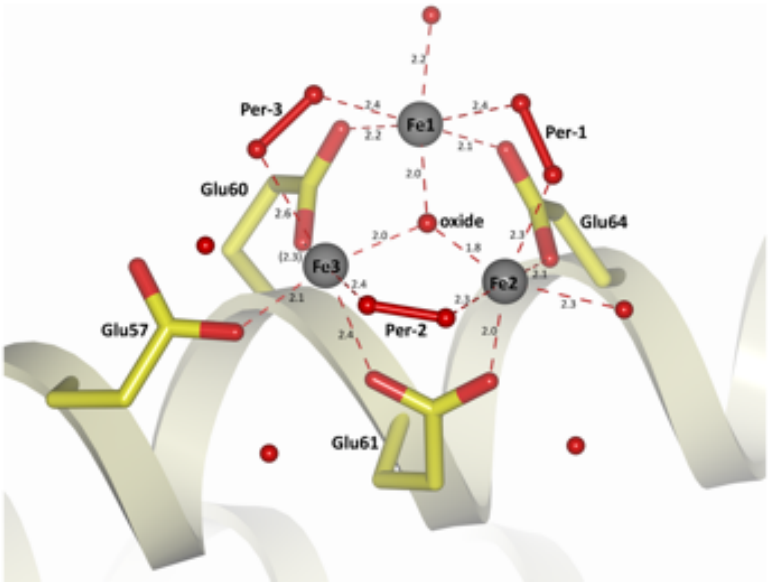
(1) Pozzi C; Ciambellotti S; Bernacchioni C; Di Pisa F; Mangani S; Turano P. *Proc Natl Acad Sci U S A.* **2017**, *114*, 2580-2585.

(2) Sala D, Ciambellotti S, Giachetti A, Turano P, Rosato A. *J Chem Inf Model.* **2017**, *57*, 2112-2118.

(3) Zanzoni S, Pagano K, D'Onofrio M, Assfalg M, Ciambellotti S, Bernacchioni C, Turano P, Aime S, Ragona L, Molinari H. *Chemistry.* **2017**, *23*, 9879-9887.



The (μ^3-oxo)Tris[(μ^2-peroxo)(μ^2-glutamato-κ O:κ O′)](glutamato-κ O)(diaquo) triiron cluster in human L-ferritin.

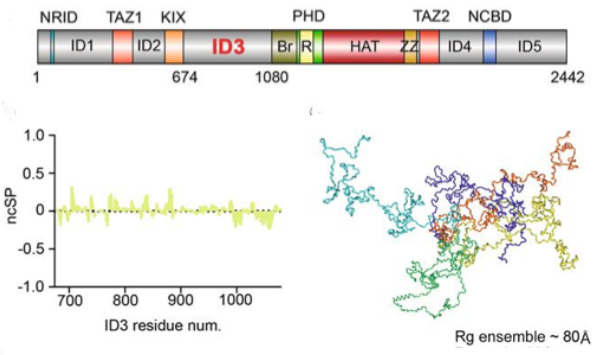
Intrinsically Disordered Proteins

A large number of proteins essential in a large variety of cellular functions are far from being well structured and, actually, structural flexibility represents an advantage in terms of binding plasticity and promiscuity. NMR spectroscopy represents the ideal tool to access atomic resolution structural and dynamic information on these intrinsically disordered proteins (IDPs). The NMR methods developed at CERM enable the study of such polypeptides, including flexible linkers of complex protein machineries, low complexity regions as well as heterogeneous proteins. They allow also to follow the occurrence of post-translational modifications.

Flexible linkers in many cases comprise more than half of the primary sequence of a protein, and their characterisation may be very relevant to elucidate at atomic level molecular functions. An example is provided by the human CREB-binding protein (CBP), a multi-domain transcription factor of about 2500 amino acids, half of which are predicted to be disordered. The characterisation of the third linker of CBP, termed ID3, has been completed by using advanced NMR methods complemented by other biophysical techniques.[1] In an effort to identify new, unexplored functions for this linker we also demonstrated that it transiently interacts with an intrinsically disordered region of the transcriptional regulator ZFP106 in a fashion that disorder of both regions is maintained.

Another transcription factor studied thanks to the NMR methods recently developed was the Achaete-scute homolog 1 (Ascl1) protein, a DNA-binding protein belonging to the basic helix-loop-helix (bHLH) family. The first comprehensive high-resolution characterisation of the structural and dynamic properties was achieved.[2]

Finally, NMR was used to further investigate the structural features of several viral proteins, among which E7 HPV16 is the most medically relevant. For the latter, the occurrence of phosphorylation events were followed in real-time and their impact on the structural stability of the protein was investigated.[3]



The third flexible linker of CBP (ID3 in the schematic representation of tCBP primary sequence) was characterised through NMR (the secondary structural propensities and a few conformers calculated with FLEXIBLE MECCANO [Ozenne *et al, Bioinformatics* **2012** 28: 1463-1470] are shown in the bottom panels).

References:

(1) Contreras-Martos S, Piai A, Kosol S, Varadi M, Bekesi A, Lebrun P, Volkov AN, Gevaert K, Pierattelli R, Felli IC, Tompa P. *Sci Rep.* **2017,** *7,* 4676

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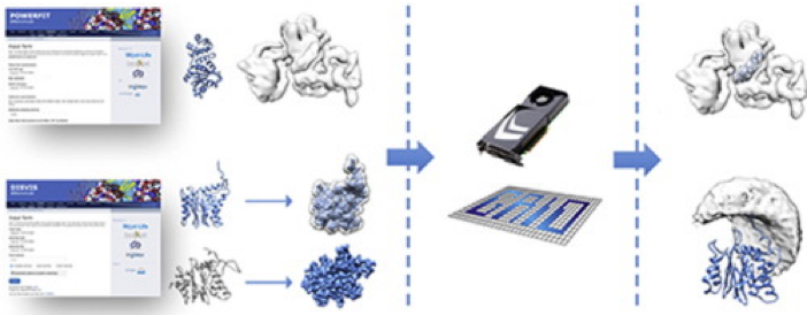
Cloud Computing in Structural Biology

A key computational technique in Structural Biology is Molecular Dynamics (MD), a computer simulation of the physical movements of atoms and molecules as a function of time. MD simulations capture the behaviour of biological macromolecules in full atomic detail. Such simulation may serve as a computational microscope, revealing biomolecular mechanisms at spatial and temporal scales that are difficult to observe experimentally. It has extensive application to biological systems, from protein folding to enzymatic catalysis and the comprehension of signalling cascades. These computational models help to interpret experimental data and make testable predictions. Over the years, we developed methods for free and restrained MD simulations using a grid computational infrastructure, using both traditional CPUs and accelerated computing (GPGPUs), including also paramagnetic restraints.

Further services leveraged GPGPU acceleration to combine high-resolution structures of atomic subunits with lower-resolution structural information, such as density maps from cryo-electron microscopy or distance restraints acquired by chemical cross-linking coupled with mass spectrometry, respectively.



Traditional methods for the calculation of macromolecular structures require the use of various software packages, considerable user expertise and ample computer resources. To facilitate the use of advanced structural biology methods we have developed standardised workflows and made them available through easy-to-use web interfaces.

References:

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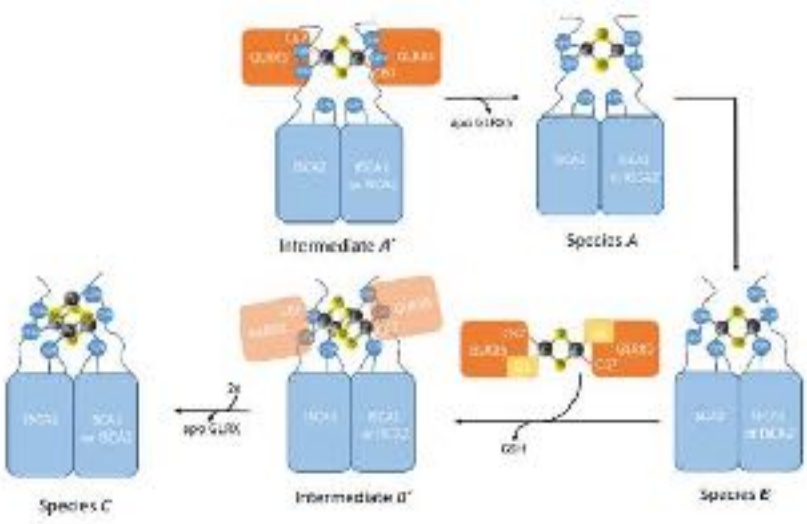
(2) Sala, D., Ciambellotti, S., Giachetti, A., Turano, P., Rosato, A. *J. Chem. Inf. Model.*, **2017**, 57, 2112–2118.

PowerFit combines high-resolution structures of atomic subunits with density maps from cryo-electron microscopy through a rigid-body fitting approach. DisVis aims at quantifying the information content of distance restraints and identifying false-positive restraints. They have been implemented as web portals harvesting both local CPU resources and GPGPU-accelerated EGI grid resources.

NMR of Paramagnetic Systems

Methodological advances in experimental and theoretical approaches continue to extend the range of systems that can be fruitfully investigated and the information content embedded within shifts and relaxation terms arising from the hyperfine interaction.

"Old Fashioned" ^{1}H NMR experiments are still an unravelled tool for the characterisation of metal sites into protein and protein-protein complexes.
In the case of Iron-Sulfur proteins, [Fe_4S_4] clusters give rise to very peculiar ^{1}H NMR spectra, which can therefore be used as a diagnostic tool for the identification of the type of FeS cluster occurring in a given protein as well as of its oxidation state. As an example, snapshots of the mechanism of [Fe_4S_4] cluster formation could be uniquely monitored via paramagnetic ^{1}H NMR spectroscopy.[1]
First principles quantum chemical methods, and a modern-formalism description of the Kurland-McGarvey approach for paramagnetic NMR shifts in the presence of zero-field splitting, provide accurate prediction of all pseudocontact shifts in a metalloprotein. This has been tested in the case of the Co(II)-substituted catalytic domain of Matrix Metalloproteinase-12.[2]



Model of the [4Fe-4S] Cluster Assembly Mechanism by [2Fe-2S]$^{2+}$ $GLRX5_2$, ApoISCA1/ISCA2 interactions

References:

(1) Brancaccio, D.; Gallo, A.; Piccioli, M.; Novellino, E.; Ciofi-Baffoni, S.; Banci, L. *J Am Chem Soc.* **2017,** *139,* 719.

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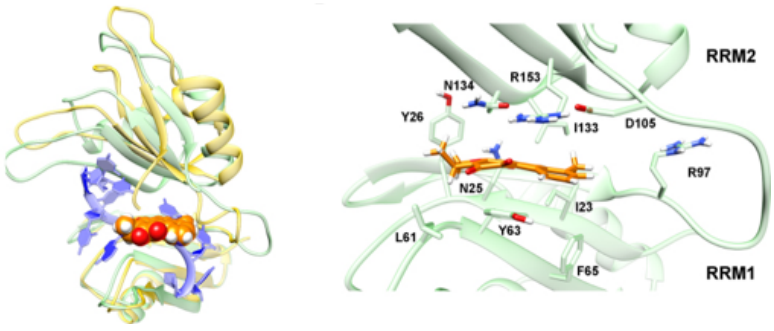
Proteins and mRNAs as Drug Targets

A new PAMAM-based matrix metalloproteinases inhibitor has been developed and tested against MMP-9 which is responsible of ocular surface damages in induced dry eyes syndrome (DES).[1] Following a different line of research we have designed a lipoyl-homotaurine derivative (ADM_12) which reverts in vivo OXA-induced neuropathy, and it is an effective antagonist of the nociceptive sensor channel TRPA1. Unprecedentedly, this safe analgesic showed a synergy with OXA in vitro and proved to inhibit CA IX, a relevant therapeutic target, clearly interfering with pancreatic cancer cell's aggressiveness.[2]

The tumour suppressor protein p53, commonly referred as "guardian of the genome", is one of the most widely studied regulators of cell fate when the integrity of the genome is damaged. In order to restore the p53 activity in some cancer cells, new dual MDM2/MDM4 nano-molar inhibitors have been developed and tested.[3]

The Human antigen R (ELAVL1, HuR) i s highly expressed in many cancer types, and is believed to promote tumorigenesis by interacting with some mRNAs. We have demonstrated that DHTS inhibits the association step of HuR to its target RNAs, and that its cytotoxicity against cancer cells was HuR-dependent.[4]

Structure-based drug design is an approach that can be combined well with solution NMR methods to develop new candidate drugs. This strategy has been pursued here to find new ligands and inhibitors of pharmaceutically relevant biological targets.



Calculated binding mode of DHTS

References:

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(2) Fragai M, Comito G, Di Cesare Mannelli L, Gualdani R, Calderone V, Louka A *et al. J. Med. Chem.* **2017**, *60*, 9003-9011.

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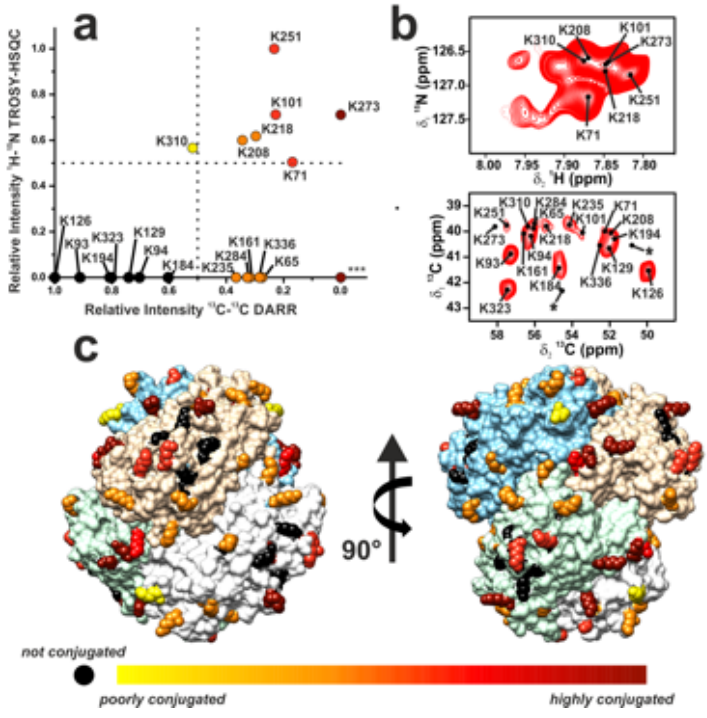
Solid-State NMR for Structural Biology

We are continuously developing new solid-state NMR-based methodologies for providing the structural characterisation at atomic level of proteins have opened new perspectives to study systems in their in-operando *conditions.*

The combined use of very fast (60 kHz) magic-angle spinning and tailored radiofrequency irradiation schemes allows the detection and the assignment of most of the ^{1}H and ^{13}C resonances of a the oxidized Eh-HIPIP I.[1] We have demonstrated that it is possible to probe protein-ligand interactions for protein-based NMR ligand screening when the protein is entrapped in silica.[2]

We have also shown that detailed information on large proteins conjugated with large polysaccharides can be achieved by a combination of solution and solid-state NMR spectroscopy.[3] Finally, we have demonstrated the feasibility of highly-resolved multi-dimensional heteronuclear spectra of a large protein assembly conjugated to PEGylated gold nanoparticles.[4]



A combination of solution and solid state NMR reveals the conjugation degree of the different lysine sites

References:

(1) Bertarello A, Schubeis T, Fuccio C, Ravera E, Fragai M, Parigi G, Emsley L, Pintacuda G, Luchinat C. *Inorg. Chem.* **2017**, *56*, 6624-6629.

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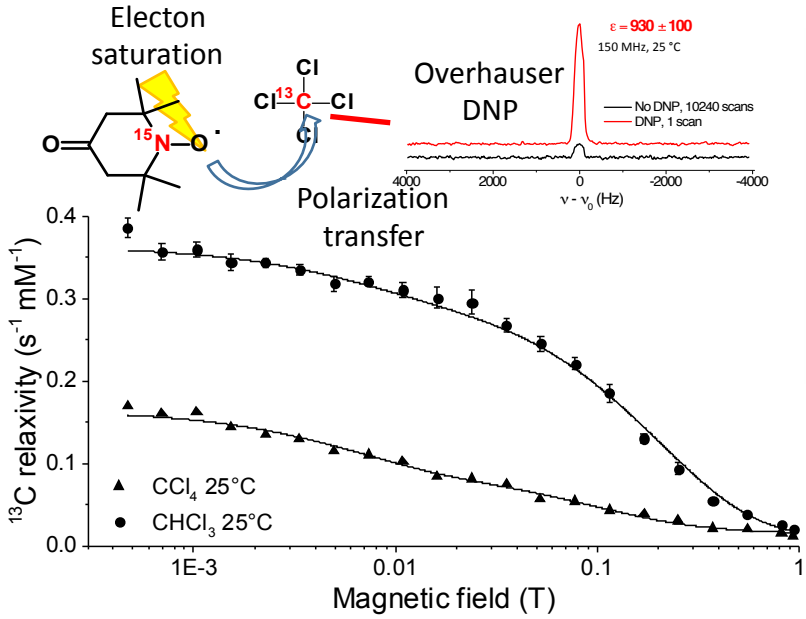
FFC relaxometry and Overhauser DNP

Overhauser DNP is ascribed to the magnetisation transfer occurring in a magnetic field from unpaired electrons to nuclei through stochastic modulation of the hyperfine interaction. Efficient ^{13}C DNP at high magnetic fields (≥3 T) is observable in a variety of liquid organic compounds, in the presence of nitroxide radicals. To shed light onto the ^{13}C-DNP mechanisms responsible for such effect, fast field cycling (FFC) relaxometry measurements were performed. ^{13}C relaxometry showed that ^{13}C relaxation of $CHCl_3$ and CCl_4 is dominated by the contact interaction with the radical occurring through the chlorine atoms, with a 1-ps correlation time. The higher relaxivity measured at low fields for $CHCl_3$ results from the additional contribution arising from the H atom in $CHCl_3$.

Dynamic nuclear polarisation (DNP) in liquid solutions can enhance ^{13}C NMR signals at magnetic fields of 3 T and room temperature up to three orders of magnitude. This increased NMR sensitivity opens new perspectives for detection of organic compounds.



^{13}C relaxivity of CCl_4 and $CHCl_3$ solutions with 200 mM TEMPONE informs on the contact terms responsible for DNP.

References:

(1) Liu, G.; Levien, M.; Karschin, N.; Parigi, G.; Luchinat, C.; Bennati, M. *Nat. Chem.* **2017**, 9, 676-680.

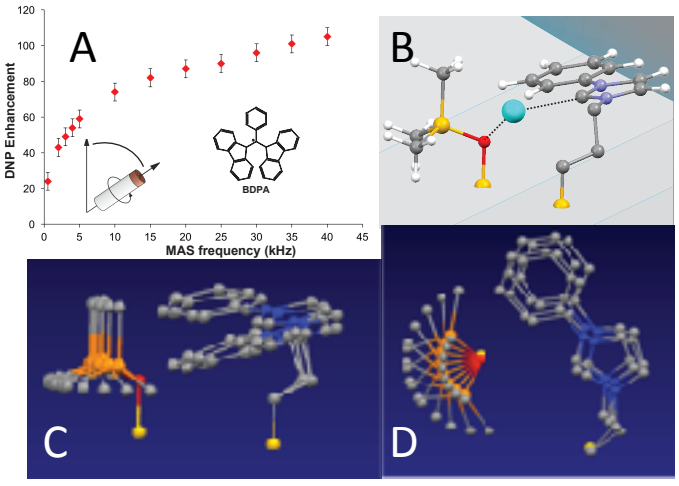
Materials, Solid-state NMR Methods and DNP

Dynamic Nuclear Polarisation (DNP), makes it possible to increase sensitivity in solid-state NMR (ssNMR) by more than two orders of magnitude. This revolutionises the application of ssNMR in the characterisation of materials and biomolecule allowing, for example, the structural determination of very diluted species like surface functionalities.

Solid-state NMR (ssNMR) is the method of choice for the characterisation of many liquid crystals[1], solid chemicals, [2] and materials.[3] The main limitation of ssNMR is due to the intrinsically low sensitivity of NMR. For this reason hyperpolarisation techniques like DNP, able to increase sensitivity of more than two orders of magnitude, are rapidly expanding the application field of ssNMR in the characterisation of solids and in material science. We well demonstrated this potential solving, by ssNMR DNP, a long-standing problem in inorganic chemistry: the structural determination of supported catalysts.

With the sensitivity enhancement of DNP it is possible to achieve a sufficient number of structural restrains to define the 3D structure and the surface of interaction of an inorganic catalyst tethered on the surface of a mesoporous material.[4] This provides an unprecedented level of detail in catalyst design.

Again, in 2017, in two important methodological papers[2,5] we demonstrated how it is possible to increase the DNP enhancements over 100 at high-magnetic field (18.8 T) and fast MAS (40 kHz). This important result was possible with the development of Overhauser effect polarising agents and a detailed comprehension of the spin-diffusion process in DNP. The impact high-field DNP in the investigation of solid biomolecules and material science[6] is enormous.



A) Trend of increasing DNP enhancement at fast MAS B) 3D structural model of the investigated catalytic surface species. C),side view D) top-view of the structural model of the conformational distribution of the investigated surface catalytic system.

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(1) Emsley J. W., M. Lelli, G. R. Luckhurst, H. Zimmermann, *Phys Rev E* **2017,** *96,* 062702

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Metabolomics In Biomedicine

Metabolomics provides a holistic overview of the complex biochemistry underlying life, perfectly fitting with the spirit of systems biology and systems medicine, because of its ability to detect in real time the response of the organisms to pathological stressors. Metabolomics has proved to be useful for the characterization of several pathologies, and offers realistic promises to become in a few years a well-accepted standard clinical tool. For instance, in the context of breast cancer oncology, metabolomics was exploited for risk stratification of early breast cancer patients and for relapse prediction[1].

Chronic Inflammatory diseases is also a class of pathologies that can be studied using metabolomic of urine samples[2].Beside humans, veterinary medicine is also an interesting field for metabolomic applications[3]. Urines, serum, and plasma are the most commonly used bio-fluids in metabolomics. A recent comparison between the latter two shows that they are almost equivalent for metabolomic purposes.[4]

Metabolomics can also be applied for in-vitro testing of the effects of bioactive compounds.[5]

With only one-shot analysis, metabolomics can monitor the health status of an individual with respect to the evolution of multiple diseases.

Metabolomics provides a dynamic portrait of the metabolic status of an individual, permitting a dynamic, simultaneous identification and quantification of metabolites and small intermediate molecules. Metabolomics thus offer a molecular description of the health status of an individual and therefore it has the potential to become the election technique to obtain new insights on the biochemistry of pathologies.

References:

(1) Hart C.D.; Vignoli A.; Tenori L.: Uy G.L.; Van To T.; Adebamowo C.; Hossain S.M.; Biganzoli L.; Risi E.; Love R.R., Luchinat C.; Di Leo A. *Clin Cancer Res*. **2017**, *23*, 1422.

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National and Transnational access

INSTRUCT-ERIC ESFRI Infrastructure – European and National NMR Research Infrastructure

CERM/CIRMMP is the key centre for application and development of NMR spectroscopy within INSTRUCT-ERIC, an ESFRI infrastructure operative since 2012.

INSTRUCT-ERIC provides access to unique instrumentation in a variety of different structural techniques (see pages 9). This innovative approach allows for a description of biological cell at the molecular level, in order to understand how living organisms function in normal and pathological conditions and to design drugs and vaccines. The possibility of access to INSTRUCT-ERIC represents a unique opportunity for researchers, both at the national and European level, to strengthen the innovation capacity of the research performed. The request of access to Instruct-ERIC has exponentially increased since it became operational. The same trend is registered for the CERM/CIRMMP platform.

Since 2016, the access to European users is also provided through the newly funded iNEXT project (http://www.inext-eu.org). iNEXT is a consortium funded by the HORIZON2020 program to offer European researchers access to a wide range of advanced structural biology technologies (including X-ray technologies, NMR spectroscopy, Electron Microscopy and biophysics), to study the structure and function of biological macromolecules and their assemblies, and aspires to promote biomedicine, biotechnology, and biomaterials, involving scientists with or without previous experience in structural biology.

At the end of 2016 has been open also the first call of the CORBEL European access project. CORBEL is an initiative of eleven new biological and medical research infrastructures (BMS RIs), that includes INSTRUCT-ERIC, which together will create a platform for harmonised user access to biological and medical technologies, biological samples and data services required by cutting-edge biomedical research.

In addition CERM/CIRMMP continues to provide access to its instrumentation to all national users whose research is outside the INSTRUCT-ERIC scope, provided their research project matches quality criteria in terms of scientific interest, excellence and feasibility.

In all cases access is granted on the basis of peer-review of the proposals received, and after a feasibility check by the staff scientists of the receiving infrastructure. Technical assistance is provided for the acquisition of the data. Scientific collaborations are welcome but not required. The uniqueness of access provision at CERM/CIRMMP infrastructure lies in the wide number of available NMR instruments, the variety of the NMR equipment (probes, auto-

matic sample changers,…), and the exceptional expertise of the scientific and technical stuff, which represents an ideal environment for research in the field of structural and functional characterisation and of NMR spectroscopy especially applied to biological systems. This allows the optimal use of the instrumentation also in a combined way, when needed. The description of the NMR instrumentation made available under the above mentioned access projects at CERM/CIRMMP is reported in the dedicate paragraph at page 38.

Molecular biology and cellular biology labs are also strategic for the users needs to prepare and/or optimise the large variety of samples for structural characterisation, together with other biophysical equipment for EPR, CD, UV-vis, stopped-flow measurements, manual and automated crystallisation facilities and X-ray diffractometry. Users can also access other university infrastructures available in the campus, such as those of mass spectrometry, Raman resonance, and non-linear spectroscopies.

CERM/CIRMMP also provides access to its computational e-infrastructure which includes a cluster for the more intensive calculations, with 16 blades harbouring a total of 80 CPU cores. Ten servers are used to host services from web pages to databases and to enable access to the European Grid. A number of graphic stations are available for interactive NMR data analysis.

During 2017 CERM/CIRMMP provided overall 437 days of NMR access to external users. A more detailed analysis shows that the access in the frame of INSTRUCT-ERIC, CORBEL and iNEXT, increased from total of 191 days in 2016 up to 254 days in 2017.

Collaborations with Industries

CERM/CIRMMP has a long tradition in collaborations with industries: from simply providing access and service to its instrumentation, to establishing a more collaborative activity in research projects or to the participation as partners in international project calls. In 2017, thanks to the inauguration of the CERM TT center and the BIO-ENABLE project, the pay-for-services access to industries was overall 48 days. This number does not include the access provided industrial partners through collaborative projects.

We warmly thank the following companies for stimulating interactions:

Bracco SpA

Bruker BioSpin

Cloud Centurion Srls

Fiorgen Onlus

Glaxo Smith Kline

Giotto Biotech Srl

Menarini Srl

Valagro S.p.a.

Abiogen S.p.a.

Specialty Fertilizer Products LLC

A special acknowledgment to Gruppo SAPIO Srl,

official supplier of all the cryogenic gases of CERM/CIRMMP

Flanking Institutions

Fondazione FIORGEN ONLUS

The FIORGEN ONLUS Foundation is a non-profit foundation that promotes studies in predictive and personalised medicine. The Foundation conducts research in the application of genomic and molecular data to help finding new drugs or to determine the individual susceptibility to a particular disease or disorder. CERM and FIORGEN work together on the main lines of structural biology and metabolomics.

The study of diseases through the holistic approach of metabolomics can be very useful to obtain new information about their biological mechanisms and their impact on human health. During 2017 FIORGEN Foundation continued its research activity in this field contributing to the publication of a total of 4 papers. At the same time, new emerging applications of metabolomics in the field of food analysis and human nutrition were explored.

As a member of CEN/TC 140 European committee for the standardisation procedures for “in vitro diagnostic and medical devices”, FIORGEN was involved in the production of the Technical Specifications "Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for metabolomics in urine, venous blood serum and plasma ", made available on 2016-05-18.

The FIORGEN Biobank da Vinci European Biobank (daVEB) has been donated to the University of Florence in October 2017. The repository and the IT center of the biobank are hosted by CERM/CIRMMP. Through this biobank CERM has established connections with the ESFRI European Biobank Infrastructure BBMRI, which are reinforced by the metabolomics research activities of CERM and its spin-off FIORGEN foundation.

The interaction between daVEB and CERM is strategic and synergistic. Scientific collaborations in the metabolomic field contribute to the development of SOPs validated by NMR and to the enrichment of the biobank in terms of type and number of samples. daVEB currently houses a collection of unique samples (biofluids, tissues and DNA) of growing importance by number in the following areas: melanoma, rare skin diseases, diseases of the genital-urinary cancer, cardio-circulatory diseases, digestive diseases, breast cancer, non-Hodgkin's lymphoma, diseases associated with the ageing. On the other hand, the biobank acts as a support to the metabolomics research via NMR carried out at CERM by providing a storage service of samples and the associated data, following protocols in accordance with international standards.

The DA VINCI EUROPEAN BIOBANK (daVEB) is a partner of the RISE project (Competence center-RISE Network infrastructure for industrial research and incubation for advanced services to innovative companies), coordinated by CSAVRI; PAR-FAS funding of Regione Toscana It op-

erates as an infrastructure to support experimental development activities and provision of services, with open access to private companies.

http://www.fiorgen.net/

https://www.davincieuropeanbiobank.org

Giotto Biotech Srl

GIOTTO BIOTECH S.r.l. is a SME founded in 2011 as a spin-off of CERM that aims at contributing to the biomedical sciences by providing enabling products and services, with a particular focus on complementary technologies in the field of NMR. GIOTTO BIOTECH provides a full range of compounds and custom manufacturing to supply research needs in the field of biomedical sciences, consulting and services. The company is active in various fields including protein production and isotope labelling, organic synthesis, services for NMR, and information technology. The services include NMR metabolomics and statistical analysis.

GIOTTO BIOTECH is involved in several research projects funded at the European or National level (FLAG-ERA-ITFoC, Information Technology: Future of Cancer Treatment, ITN EC AEGIS, FP7 Pathway-27 "Pivotal assessment of the effects of bioactives on health and wellbeing. From human genome to food industry"; LUS BUBBLE and DICCAPP, both funded by the Tuscany Region).

GIOTTO BIOTECH research activity is carried out in synergy with CERM scientists. As an outcome of this collaboration, in 2017 GIOTTO BIOTECH and CERM researchers co-authored six scientific publications. Among industrial collaborations, GIOTTO BIOTECH is partner with the NMR manufacturer, BRUKER BIOSPIN, in the development of expert systems to assign metabolite signals in biofluids to perform quantitation without human intervention.
http://www.giottobiotech.com/

Fondazione Luigi Sacconi

The Luigi Sacconi Foundation was established in 1996 to honor the memory of *Prof. Luigi Sacconi* who was a prominent figure in Chemistry and founder of the General and Inorganic Chemistry School in Florence where many international scientists have been educated.

Its aim is to promote scientific research in the molecular sciences at the local, national and international levels. Particular attention is addressed to chemistry, in its implications and applications concerning health, quality of life, the environment, energy, and technological and industrial development.

For this purpose the Luigi Sacconi Foundation collects documents and publications, promotes seminars, courses and meetings and other activities supporting the exchange of scien-

tific knowledge, subsidises the activity of Italian and foreign researchers, and establishes awards.

The Sacconi Medal Lecturer 2017 has been awarded to Prof. Guy Bertrand, University of California, San Diego.

http://www.cerm.unifi.it/fondazione

Cloud Centurion Srls

Cloud Centurion is a start-up company that originates from the experience of some researchers at CERM/CIRMMP in the field of Information Technology. It deals with web security and cloud services. Web Security, also known as Cyber Security, involves protecting information by preventing, detecting, and responding to attacks.

The main aspects of Cyber Security are: Confidentiality (keeping your information private); Integrity (knowing that the information has not been changed); Authenticity (knowing who sent the information).

The objective of this Company is to provide a security platform where users can define, visualise, and modify the properties of any uniform resource identifier (URI) element, thereby achieving a full control on how the files hosted on public cloud services are shared. More specifically, the platform allows users to protect their on-line life when exploiting services to share any file type.

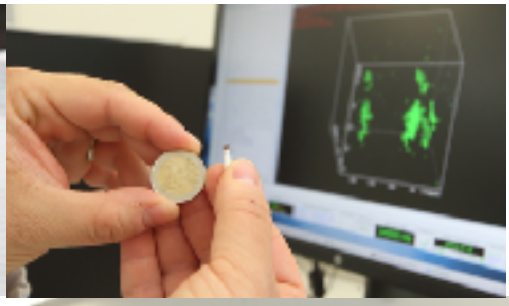
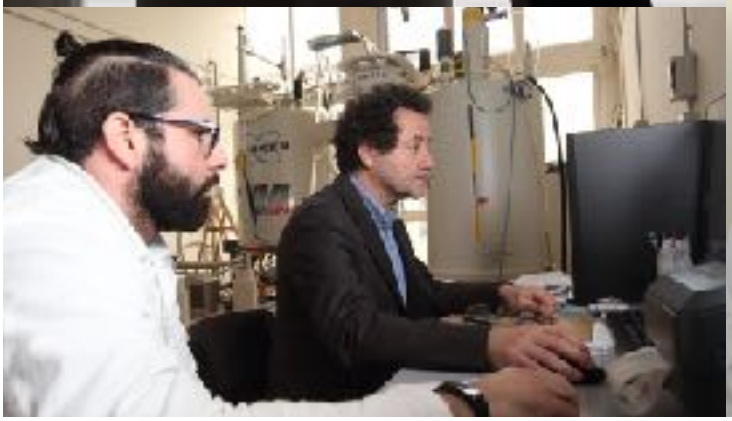
The main goal of the platform is to enable its users to safely exchange files over the internet, in an easy manner that does not involve setting up a sophisticated IT infrastructure.

http://cloudcenturion.eu

Instrumentation

Solution and Solid-State NMR Spectrometers

All NMR instruments are state-of-the-art, digital spectrometers equipped with a variety of cryoprobes as well as of specific probes covering a broad range of frequencies and of observable nuclei. In addition to all the standard pulse sequences for spectroscopic, structural, dynamical, and functional characterisation, tailored pulse sequences for structural determination of high molecular weight proteins and paramagnetic systems are implemented, as well as ^{13}C direct-detection solution protocols for "protonless" NMR experiments and structural characterisation of biomolecules, including unfolded or partially unfolded ones. Pulse sequences and experiment setup have been implemented for the detection and characterisation of paramagnetic systems and in this field CERM has been pioneer since decades. For this reason we have now equipped a 400 MHz instrument with a special 3mm High Power probe designed for the investigation of paramagnetic systems. Solid-state MAS probes cover almost all the presently achievable MAS frequencies, from a few hundred of Hz to ultra-fast MAS regime, and since 2017 we have a new 0.7mm CP MAS probe spinning up to 111 kHz. Special protocols and devices are available for solid state experiments both for biological and inorganic material characterisation. Set-up and pulse sequences for ***in-cell*** NMR experiments are also implemented.


INSTRUMENTATION

B_0 Field (T)	^{1}H Larmor Frequency (Bore)	Probe heads
22.3	950 MHz (NB 54 mm)	TCI Cryo 5 mm solution (^{1}H/^{13}C/^{15}N with ^{2}H decoupling)
21.1	900 MHz (NB 54 mm)	TCI Cryo 5 mm solution (^{1}H/^{13}C/^{15}N with ^{2}H decoupling) TXI RT 5 mm solution (^{1}H/^{13}C/^{15}N with ^{2}H decoupling)
20.0	850 MHz (WB 89 mm)	3.2 mm CP MAS DVT ^{15}N/^{13}C/^{1}H 1.3 mm CP MAS ^{1}H-^{19}F/BB/^{15}N 0.7 mm CP MAS ^{1}H/^{13}C/^{15}N
18.8	800 MHz (NB 54 mm)	TXI RT 5 mm solution(^{1}H/^{13}C/^{15}N with ^{2}H decoupling) QXI RT 5 mm solution(^{1}H/^{13}C/^{15}N/^{31}P with ^{2}H decoupling) ^{1}H-Selective High Power RT (prototype) 3.2 mm CP MAS DVT Low-E ^{15}N/^{13}C/^{1}H 1.3 mm CP MAS ^{1}H-^{19}F/BB-X/BB-Y 1.3 mm CP MAS ^{1}H/^{13}C/^{15}N
16.4	700* MHz (NB 54 mm)	TCI Cryo 5 mm solution(^{1}H/^{13}C/^{15}N with ^{2}H decoupling) TXI RT 5 mm solution(^{1}H/^{13}C/^{15}N with ^{2}H decoupling)
16.4	700 MHz (NB 54 mm)	TXO Cryo 5 mm solution(^{13}C/^{15}N/^{1}H with ^{2}H decoupling) TXO RT 5 mm solution(^{13}C/^{15}N/^{1}H with ^{2}H decoupling) TXI RT 5 mm solution(^{1}H/^{13}C/^{15}N with ^{2}H decoupling)
16.4	700 MHz (WB 89 mm)	3.2 mm CP MAS ^{15}N/^{13}C/^{1}H 4.0 mm CP MAS ^{15}N/^{13}C/^{1}H
14.1	600 MHz (NB 54 mm)	2 x TXI RT 5 mm solution(^{1}H/^{13}C/^{15}N with ^{2}H decoupling) HR-MAS 4.0mm (^{1}H/^{13}C/^{15}N with ^{2}H decoupling) ^{1}H - Selective High Power RT, 5 mm solution ^{1}H - Selective RT, 5 mm solution BBI RT 5 mm solution BBO RT 5 mm solution BBO RT 10 mm solution BB RT -Low-γ -10 mm solution
14.1	600* MHz (NB 54 mm)	TXI RT 5 mm solution (^{1}H/^{13}C/^{15}N with ^{2}H decoupling)
11.7	500 MHz (NB 54 mm)	TCI Cryo 5 mm solution(^{1}H/^{13}C/^{15}N) TXI RT 5 mm solution (^{1}H/^{13}C/^{15}N) TBO RT 5 mm solution (^{1}H/^{31}P/BB) BBI RT 5 mm solution
9.4	400 MHz (NB 54 mm)	BBO RT 5 mm solution BBI RT 5 mm solution (^{1}H/BB) BBI RT 3 mm solution (^{1}H/BB) ^{1}H-Selective High Power 5 mm solution
0.33-1.25	X-band (9.43 GHz), Q-Band (35 GHz)	X and Q Band cavities
0.00024-1	Fast Field Cycling Relaxometer	0.01-45 MHz 10 mm solution tubes

*With sample changer

X-ray Crystallography

CERM/CIRMMP is equipped with standard crystallisation facilities and with an automated nano-dispensing device (Mosquito, TTP Labtech). Furthermore it has full access to the Inter-departmental Crystallography Centre of the University of Florence (CRIST) equipped, among other instruments, with a sealed-tube diffractometer bearing a CCD detector (AgilentTechnologies) for routine in-house data collections. Regular access to synchrotron beam time slots in Europe facilities is also possible.

Biological and Biophysical Facilities and Services

Molecular and Cellular Biology

CERM/CIRMMP is equipped with state-of-the-art facilities for gene cloning and protein expression and purification. Large scale protein expression in prokaryotes and yeast is available through the use of fermenters. Different isotope labelling schemes, including specific labelling schemes oriented to NMR characterisation, can be achieved through the use of auxotrophic strains. Fully equipped facilities for protein purification are available, including last-generation instruments for streamlined purification (ÄKTA pure chromatography system) and equipment for protein purification and reconstitution in anaerobic environment (glove box). A mammalian expression lab for in-cell NMR is also available.

EPR

9.43 GHz (X-Band, continuous wave, Elexsys E 580E) and 35 GHz (Q-Band, pulsed, Elexsys E 580E) instrument.

Multi Angle/Dynamic Light Scattering

Instrument for measurements on batch samples or on in-flow samples (FPLC coupling).

Isothermal Calorimetry (ITC)

ITC device to measure thermodynamical parameters in micro-samples. The instrument is fully equipped for studying protein-ligand and protein-protein thermodynamical parameters.

Optical Spectroscopy

Absorption/Fluorescence Spectrophotometer operating from 1000 to 200 nm, *Circular Dichroism* (CD) spectrometer operating form 1200 to 200 nm (Near-IR, Visible, UV) to derive infor-

mation on the proteins secondary structure or protein-metal interaction, and stopped-flow spectrophotometer are available in the infrastructure.

Biobank

Sample type	Human biospecimens (plasma, serum, urine, tissues, cells), bacterial expression vectors.
Sample storage	Mechanical freezers for storage at -80° C, equipped with auxiliary LN_2 cooling system.
	Tanks for cryopreservation in nitrogen vapor phase (-150° C), with automatic nitrogen supply.
Storage supervision and control system	Sample storage and withdrawal handled by the software Easy Track 2D.
	Continuous monitoring of storage temperature.
Database	Information system based on a set of server clusters equipped with Linux Red Hat Enterprise operating systems and Oracle RAC databases.
	Completely automatized and high speed robotic backup systems.
	Online browsing of daVEB inventory to obtain samples and/or associated data.

Computational Structural Biology Tools

CERM/CIRMMP provides integrated databases and software for genome browsing, metal binding analysis, structure calculation with/without paramagnetic restraints, sequence validation, domain organisation, evolution, protein complex analysis.

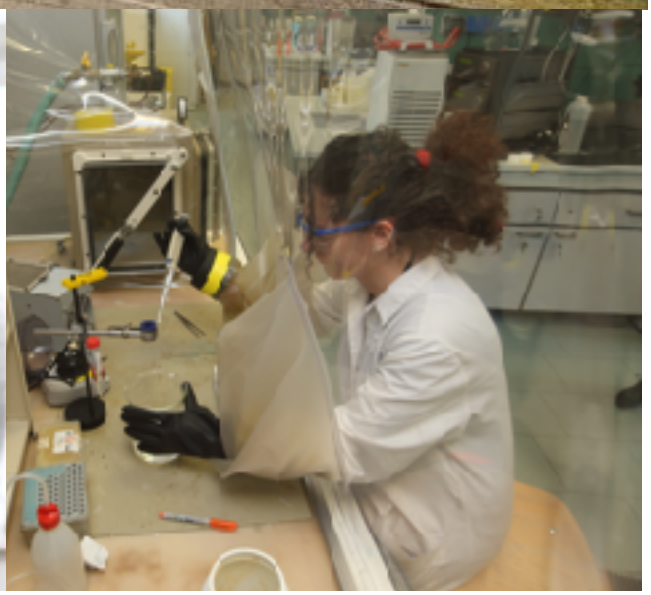
Access to programs for NMR data processing and structural calculations is also provided via web.

Electronic infrastructure (e-infrastructure)

The grid and cloud-based services of CERM/CIRMMP are currently being provided *via* the West-Life Virtual Research Environment (VRE). West-Life (http://about.west-life.eu/) leverages on the success of the WeNMR e-Infrastructure and aims to provide the application-level ser-

vices specific to different cases in Structural Biology. West-Life covers all experimental techniques of Structural biology (X-ray, cryo-EM, NMR, SAXS), enabling researchers in this field to benefit fully of many computational services being provided by collaborative initiatives at the European level, including but not limited to the EGI-ENGAGE and INDIGO-DataCloud projects already mentioned. Some services specific for NMR data included also in the MoBrain competence centre of the EGI-ENGAGE project.

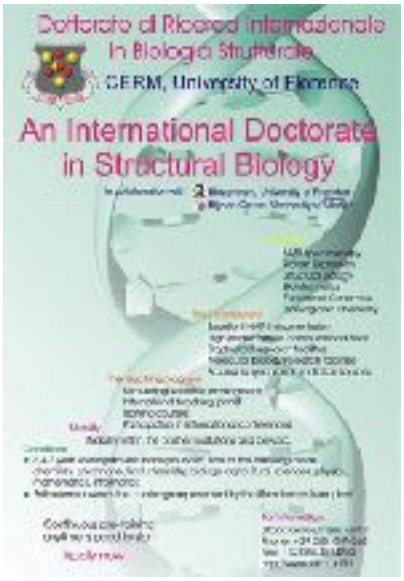
CERM/CIRMMP maintains a node of the European Grid Initiative. The available hardware comprises two clusters with 80 and 1024 CPU-cores respectively, and four TB of shared storage. A cluster with six Nvidia Tesla K20 GPGPU cards is also available.



Training & Education

International Doctorate in Structural Biology

The **International PhD course in Structural Biology** is a research doctorate of the *University of Florence*, hosted at CERM that runs in collaboration with the *Frankfurt and Utrecht Universities*. The scientific fields cover most of the molecular aspects of life sciences.



The main objective of the International PhD course in Structural Biology is the training of research doctors at the forefront of the knowledge in modern methodologies in molecular and structural biology, biotechnology and systems biology. It provides both theoretical and hands-on training in structural techniques applied to biological macromolecules in solution and in the crystalline state, as well as in non-crystalline materials such as fibrils or amyloid, and to biological macromolecules in their cellular environment. It also provides state-of-the-art training in molecular biology for the expression of isotope-enriched recombinant proteins and specifically those for NMR studies. Finally, it offers top level ICT training thanks to the well-established expertise and the exploitation of the e-infrastructure. Bioinformatics, biostatistics and NMR-metabolomics training is offered as well.

The scientific themes covered by the PhD course are:

1. **NMR spectroscopy** (in solution and in the solid state) and X-ray crystallography aimed at studying structure, function and dynamics in biological macromolecules and protein-protein adducts;

2. **Molecular and cellular biology techniques** for the production of proteins, DNA and bacterial and prokaryotic cell growth;

3. **Drug and vaccine development**, through rational design techniques and structural characterisation of biological drugs;

4. **Bioinformatics** to understand the structure-function relationship in biomolecules and in particular in metalloproteins through the large scale analysis of databases
5. ***In cell* NMR** studies, by which molecular pathways and cell import-export mechanisms are investigated;
6. **Metabolomics** studies, in which the individual metabolic fingerprints are related to disease states and fingerprints are utilised to provide early diagnosis or even identification of pre-disease states.

The added value of this PhD course is in the development of a *transnational educational project,* able to form PhDs at the forefront regarding the scientific formation, the knowledge and development of research and technology, capable to consider multi-disciplinarity, transnational cooperation and mobility as primary needs, and to evaluate collaborative projects as a requirement for high quality research. The doctoral program also relies on Faculty members who, in addition to scientists from CERM, include professors from other departments of the University of Florence and from the Universities of Frankfurt, Utrecht, Oxford and Lyon, all top places for Structural Biology.

Full-time attendance is mandatory, as is commitment to research activities. In addition to seminars and courses, students are asked to provide research seminars as a basic tool for their own training. Every PhD student is encouraged to liaise with foreign universities and take part in teaching and research training as well as in internships abroad.

Post-Doctorate

CERM/CIRMMP hosts a number of post doctoral researchers. Some of them are former PhD students who remain at CERM after the end of the PhD, others come from all over the world for performing research projects and being trained in the methodologies in which CERM/CIRMMP excels. There are also several short- or long-term visitors coming from Italian and foreign universities.

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1. P. Turano, *NMR of Paramagnetic Species in Encyclopedia of Spectroscopy and Spectrometry (3rd Edition)*, vol 3, pp. 164-169, Editors JC Lindon, GE Tranter, DW Koppnaal, AP

2. Bertini, C. Luchinat, G. Parigi, E. Ravera, *NMR of Paramagnetic Molecules*, Elsevier, 2017.

3. *Analytical Chemistry: Developments, Applications and Challenges in Food Analysis. Editors: Marcello Locatelli and Christian Celia, Chapter 5. NMR Methodologies in Food Analysis, Chapter 6.* NMR Applications in Food Analysis: Part A; Chapter 7. NMR Applications in Food Analysis: Part B; Nova Science Publishers, 2017:

Events at CERM

Workshop on "*Biomaterial for Catalysis*" 26-27th July 2017

Seminars Held at CERM

Monday, 6th November, 2017 at 6:00 pm, **Dr. Taras V. Pogorelov,** (Department of Chemistry, Biophysics and Quantitative Biology, Beckman Institute for Advanced Science and Technology, National Center for Supercomputing Applications, School of Chemical Sciences and University of Illinois at Urbana-Champaign, IL, USA) - *"Membrane-associated phenomena: capturing dynamic structures in complex environments"*

Thursday, 2nd November, 2017 at 6:00 pm, **Prof. Ray Owens** (University of Oxford, Research Complex at Harwell, Oxford, UK) - *"Structural proteomics: development of an integrated pipeline from genes to crystals"*

Tuesday, 31st October, 2017 at 6:00 pm, **Dr. Petr Rathner** (Johannes Kepler University, Linz, Austria) - *"Investigation of structure and dynamics of STIM1 by NMR"*

Monday, 30th October, 2017 at 6:00 pm, **Prof. Stefano Caldarelli** (Ist. de Sciences Moleculaires de Marseille, Aix Marseille Université, France) - *"Excursions in the NMR analysis of mixtures"*

Friday, 27th October, 2017 at 6:00 pm, **Prof. Pietro Liò** and **Dr. Giovanna Maria Dimitri** (Department of Computer Science, University of Cambridge, UK) - *"Introduction to Deep Learning"*

Monday, 23th October, 2017 at 6:00 pm, **Dr. Kourosh H. Ebrahimi** (Postdoc / EMBO Fellow, Inorganic Chemistry Laboratory, Department of Chemistry, University of Oxford, UK) - *"Mechanistic studies of metalloenzymes"*

Thursday, 7th September, 2017 at 5:00 pm, **Dr. Massimiliano Maletta** (Thermo Fisher Scientific, Eindhoven, The Netherlands) - *"The role of Cryo-electron microscopy in structural biology after the "resolution revolution"*

Monday, 10th July, 2017 at 6:00 pm, **Dr. Shenlin Wang** (Beijing NMR Center, Peking University, Beijing, PRC) - *"Using solid-state NMR spectroscopy to investigate the topology of biomacromolecules"*

Tuesday, 20th June, 2017 at 6:00 pm, **Jean van den Elsen** (Professor of Biochemistry and Structural Biology at the University of Bath, UK) - *"Take the bitter with the sweet"*

Friday, May 19th, 2017 at 12:00 am, **Dr. Alessio Bonucci** (Laboratoire de Bioénergétique et Ingénierie des Protéines CNRS-Marseille, France) - *"In-cell EPR: a new frontier to study protein conformations inside living cells"*

Thursday, 13th April, 2017 at 6:00pm, **Prof. Thomas Vosegaard** (Interdisciplinary Nanoscience Center, Department of Chemistry, Aarhus University, Denmark) - *"Tools to improve understanding and automation of NMR experiments "*

Monday, 10th April, 2017 at 6:00 pm, **Prof. Mag. Dr. Norbert Müller** (Head of the Institute of Organic Chemistry, Johannes Kepler University Lina, Linz, Austria) - *"Nonlinear and dynamic effects in nuclear spin noise spectroscopy"*

Friday, 7th April, 2017 at 12:00 am, **Dr. Helena Kovacs**, (Applications Scientist, Biomolecular NMR) and **Dr. Stefan Jehle,** (Product Manager, Fragment Based Drug Discovery), Bruker BioSpin AG, Fällanden, Switzerland - *"Bruker News: Breakthrough in Multi-Receive NMR Technology / Solutions for Fragment Based Drug Discovery"*

Thursday, 6th April, 2017 at 5:00 pm, **Prof. Stefan Laufer** (Med. Chemistry, Department Pharmacy;Biochemistry, Eberhard Karls University Tuebingen, Germany) - *"Raising the Gold Standard: Design & Development of Highly Selective JAK3 Probes (Janus Kinase 3)"*

Friday, 24th March, 2017 at 6:00 pm, **Prof. Gregg B. Fields** (The Scripps Research Institute, Scripps Florida, Jupiter, USA) - *"Structure-guided Design and Synthesis of Highly Selective Matrix Metalloproteinase 13 Inhibitors for the Treatment of Osteoarthritis"*

Thursday, 16th March, 2017 at 6:00 pm, **Dr. Bruno Rizzuti** (CNR-NANOTEC National Research Council - Institute of Nanotechnology, Rende-Cosenza) - *"Molecular dynamics simulation: from folded to unfolded protein states"*

Tuesday, January 10th, 2017 at 6:00 pm, **Prof. Anders Malmendal** (Department of Cellular and Molecular Medicine, University of Copenhagen, Denmark) - *"NMR on the fly: Drosophila metabolomics in stress and human disease research"*

Group Meetings

13/01 **Sara Bologna** *"Expression and characterisation of human proteins involved in neurological disorders and enzymatic deficiencies"*

25/01 **Maria Grazie Murrali** *"Functional interaction studies of intrinsically disordered proteins"*

01/02 **Davide Sala** *"Application of molecular dynamics to the understanding of metal-binding macromolecules and their adducts"*

PUBLICATIONS

08/02 **Valeria Putignano** *"Bioinformatics tools for metalloprotein analysis"*

15/02 **Maxime Denis** *"Design, Synthesis and Optimisation of Paramagnetic Tags. Hit Optimisation"*

01/03 **Alessia Vignoli** *"Metabolomics: a window on our well-being"*

08/03 **Giovanni Bellomo** *"Aggregation kinetics of prion-like proteins"*

15/013 **Federica Bianchi** *"Characterisation of the human immune response to fHbp after vaccination with 4CMenB through structural and functional studies"*

22/03 **Spyridon Gourdopis** *"Molecular Aspects of Iron-Sulfur protein biogenesis"*

29/03 **Gaia Meoni** *"NMR-based metabolomics: in vitro and in vivo applications"*

05/04 **Eriberto Noel Natali** *"Effects of antigen density on the protective immune response: a structural perspective"*

12/04 **Panagis Polykretis** *"XIAP, taming the beast…"*

26/04 **Stefano Giuntini** *"Characterisation of bioconjugated proteins, L-asparaginase II as model system"*

03/05 **Letizia Barbieri** *"Two new chapters in the SOD1-CCS story"*

10/05 **Francesca Camponeschi** *"MitoNEET-Anamorsin interaction: adding new pieces to the cytosolic Fe-S proteins puzzle"*

17/05 **Linda Cerofolini** *"Assignment and structural characterisation of a large bioconjugated protein assembly integrating solution and solid-state NMR"*

24/05 **Eleonora Mercatelli** *"in cell NMR: towards protein-protein interactions"*

31/05 **Veronica Ghini** *"Cell metabolomics- an innovative tool to investigate cellular processes"*

07/07 **Enrico Luchinat** *"Improve cell viability in the NMR tube (or die trying)"*

14/06 **Vincenzo Maione** *"Maturation of Iron Regulatory Protein 1: a long way to the top"*

21/06 **Riccardo Muzzioli** *"Iron Sulfur cluster proteins; Chapter 4"*

05/07 **Panteleimon Takis** *"Few "clicks" away from more accurate clinical diagnosis and detailed analysis of mineral metabolism: URINE Shift Predictor and complementary tools"*

12/07 **Veronica Nasta** *"From Iron and Cysteine to Iron-Sulfur Clusters and their transfer to recipient proteins"*

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