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01 PRESENTATION: INTRODUCTION

The Spanish Biomolecular Nuclear Magnetic Resonance Laboratory Network or Red de Laboratorios de RMN de Biomoléculas (R-LRB) is a Unique Scientific and Technical Infrastructure (ICTS) in health sciences field. The distributed ICTS consists of a network of high-field NMR instrumentation – including three 800 MHz and three 600 MHz spectrometers- placed in different locations in Spain. This Spanish network offers coordinated open access mechanisms to improve national competitiveness in the biomolecular NMR field, through cutting edge NMR instrumentation and know-how.

The R-LRB assists internal and external users from public and private research centers and is open to both the national and the international scientific communities. The R-LRB is currently composed by three nodes:

http://www.rmn.ub.edu/r-lrb/index.html

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<tr>
<th>LRB</th>
<th>LMR</th>
<th>LRE</th>
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<tbody>
<tr>
<td>Laboratorio de RMN de la Universitat de Barcelona</td>
<td>Laboratorio de RMN &quot;Manuel Rico&quot;</td>
<td>Laboratorio de RMN de Euskadi</td>
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<tr>
<td>Universitat de Barcelona</td>
<td>CSIC</td>
<td>CICbioGUNE</td>
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Words from Prof. Rosa Menéndez, President of CSIC, in the opening of the official inaugural ceremony of R-LRB (7/6/2019).

It's my pleasure to open this inaugural symposium of ICTS Network of Nuclear Magnetic Resonance Laboratories for Biomolecules.

We feel proud of this facility network becoming part of the ICTS national map. This is a significant achievement. In particular, since this is the only new CSIC installation to win entry into the map during this evaluation period. With it, there are 9 ICTS nodes in the CSIC.

But even more important is that this is a story of achievement based on the successful collaboration between three different research institutions; the CSIC, the CIC bioGUNE and the University of Barcelona. Led by the NMR facility of the University of Barcelona, which has been part of the ICTS map since the system was established, the three institutions have succeeded by working together. This "I win / you win" collaborative strategy is the best for building long term, fruitful partnerships. Complementary expertise within the NMR field, and a geographical distribution linking some of the most active regions in Spain, strengthen the network and place Spanish NMR in the right position to face the current challenges in Structural Biology. Our hope is that in coming years this ICTS will continue to grow both geographically as well as in resources and users.

This inauguration is also a recognition of the vitality of the Spanish NMR community, represented here by the president of the NMR group of the Spanish Royal Chemistry Society. Chemistry, in general, and NMR in particular have been
historically strong in our country, and they have gained a deserved international reputation.

Now that NMR is a key player in Biology and Biomedicine, this is a good moment to recognize the importance of Structural Biology in the CSIC. The increasing number of NMR spectroscopists working on biological problems, together with the flourishing community of cryoelectron-microscopists and crystallographers in the CSIC, reinforces the leading position of our institution in Structural Biology in Spain. Aware of its privileged situation, CSIC is carrying out a great financial effort to upgrade its infrastructures, and provide its researchers with the state-of-the-art equipment needed to keep performing outstanding research.

Figure 1.1 Invitation for the inauguration of the R-LRB.

Figure 1.2 Members of The Ministry of Science and Innovation and executive committee of R-LRB.
01 PRESENTATION: TIMELINE

NOV 2018
Updated Map of ICTS

JAN 2019
Open competitive Calls

JUN 2019
R-LRB Meeting

JUN 2019
Official Inaguration

NOV 2019
R-LRB Meeting

NOV 2019
GERMN Workshop

JAN 2020
Open competitive Calls

JAN 2020
New Web & Logo

MAR 2020
R-LRB Meeting

FEB 2020
EPI Meeting

MAY 2020
Installation @ LMR
AVANCE NEO

JUN 2020
Signing the agreement
(UB-CSIC-CIC bioGUNE)

SEPT 2020
R-LRB bylaws approval

NOV 2020
Visit @ LMR
Prime Minister of Spain
Minister of Science
President of CSIC

DEC 2020
R-LRB Meeting

DEC 2020
EUROMAR online Meeting
01 PRESENTATION: LOCATION

The LRB NMR facility belongs to the University of Barcelona and is integrated into the Scientific and Technological Centers of the University of Barcelona (CCiTUB) that includes a wide range of complementary infrastructures; this generates a stimulating environment and synergies for the users. Industrial companies have an important share in the use of the NMR facility and, for some of them, NMR represents an strategic tool.

The “Manuel Rico” NMR spectroscopy Laboratory (LMR) is a scientific-technical service of the CSIC is located on the Central Campus of the CSIC in a historical and privileged location, just a stone’s throw from the “Residencia de Estudiantes” and the Rockefeller building. The LMR is managed by the Rocasolano Institute of Physical Chemistry (IQFR-CSIC).

The LRE is located at the Centre for Cooperative Research in Biosciences (CIC bioGUNE) in the Technological Park of Vizcaya. CIC bioGUNE has modern scientific infrastructures, led by prestigious scientists, which allow it to compete with the main European research institutes.

Figure 1.3 Map of distributed ICTS Red de Laboratorios de RMN de Biomoléculas (R-LRB).
02 GOVERNING, EXECUTIVE AND SUPPORT BODIES

The R-LRB was approved by the “Consejo de Política Científica y Tecnológica y de Innovación” the 6th of November 2018 and formally established by an agreement between the University of Barcelona, the Consejo Superior de Investigaciones Científicas” and CIC bioGUNE, published on 11th September 2020. The management is regulated by the bylaws approved by the Coordination Committee on 23rd September 2020.

Figure 2.1 Organization chart.

The legal representatives of the institutions owning the various nodes, or the people they designate, form the Steering Committee, which oversee the legal and economic aspects of the distributed ICTS. The R-LRB is managed by the Coordination Committee, chaired by a coordinator, who acts as a representative of the R-LRB. The Coordination Committee is formed by the scientific directors and the technical facility managers of each node. The Scientific Advisory Board is formed by six internationally recognized experts and its role is to provide advice to the coordination committee on strategic decisions. The External Access Committee is in charge of evaluating the suitably of competitive access request by users. The access protocol has been approved by the coordination committee and is common to the three nodes.

STEERING COMMITTEE

<table>
<thead>
<tr>
<th>UB</th>
<th>CSIC</th>
<th>CIC bioGUNE</th>
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<tbody>
<tr>
<td>Rector</td>
<td>Vice-President for institutional Affairs and Organization</td>
<td>General Director</td>
</tr>
<tr>
<td>Joan ELÍAS GARCÍA</td>
<td>Rosina LÓPEZ-ALONSO</td>
<td>Jóse Mª MATO DE LA PAZ</td>
</tr>
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</table>
EXECUTIVE COMMITTEE

ICTS COORDINATOR
Miquel Pons
Carlos González (Nov 2020)

LRB
Scientific Director
Miquel PONS
Facility Managers
Margarida GAIRI
Mª Teresa GONZÁLEZ

LMR
Scientific Director
Carlos GONZÁLEZ
Facility Manager
David PANTOJA-UCEDA

LRE
Scientific Director
Oscar MILLET
Facility Manager
Beatriz G. Valle

EXTERNAL ACCESS COMMITTEE

Institut de Química Avançada de Catalunya, CSIC, Barcelona
Ignacio ALFONSO
Centro de Investigaciones Biológicas, CSIC, Madrid
Francisco BLANCO
Centro de Investigaciones Biológicas, CSIC, Madrid
Javier CAÑADA
Facultad de Ciencias y Tecnologías Químicas, UCLM, Ciudad Real
Mª Victoria GÓMEZ
Instituto de Química Física Rocasolano, CSIC, Madrid
Douglas V. LAURENTS
Unidad RMN, RiaDIT, Universidad de Santiago de Compostela
Manuel MARTÍN-PASTOR
Laboratory of Molecular Biophysics, IRBB, Barcelona
Xavier SALVATELLA

Instituto de Química Orgánica General, CSIC, Madrid
Juan Luis ASENSIO
Centro Nacional de Investigaciones Oncológicas, Madrid
Ramón CAMPOS-OLIVAS
Instituto de Investigaciones Químicas, CICCartuja, Sevilla
Irene DÍAZ
Instituto de Química Física Rocasolano, CSIC, Madrid
Mº Ángeles JIMÉNEZ
Structural Characterization of Macromolecular Assemblies, IRBB, Barcelona
María MACÍAS
Instituto de Investigaciones Químicas, CSIC, Sevilla
Pedro NIETO
Departamento de Química Orgánica Universidad de Sevilla
Jesús ÁNGULO
<table>
<thead>
<tr>
<th>Magnetic Resonance Center, University of Florence, Italy</th>
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<tr>
<td>Isabella FELLI</td>
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<tr>
<td>Max F Perutz Laboratories, University of Vienna, Austria</td>
</tr>
<tr>
<td>Robert KONRAT</td>
</tr>
<tr>
<td>Slovenian NMR center, Slovenia</td>
</tr>
<tr>
<td>Janez PLAVEC</td>
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</table>

| Institute for Cancer and Genomic Sciences |
| College of Medical and Dental Sciences     |
| University of Birmingham, UK               |
| Ulrich GÜNTER                              |
| Institute de Sciences Analytiques, University of Lyon, France |
| Anne LESAGE                                |
| Director of the Center for Biomolecular Magnetic Resonance, University of Frankfurt, Germany |
| Harald SCHVALBE                            |
03 RESOURCES

The distributed ICTS consists of a network of the highest field NMR instrumentation currently available in Spain – including three 800 MHz spectrometers– placed in different locations of Spain. Additionally, this ICTS offers access to three 600 MHz spectrometers.
### ESSENTIAL EQUIPMENT

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<th>LRB</th>
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<th>LRE</th>
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<td><strong>LRE-AV600</strong></td>
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<td>Console: Avance III</td>
<td>Console: AVANCE NEO (since May 2020)</td>
<td>Console: AVANCE III</td>
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<tr>
<td>Probe: TCI cryoprobe</td>
<td>Probe: TXI cryoprobe</td>
<td>Probe: PA-TXI, TXI for high salt, QXI (31P), QXI (19F), SEF, TBI, BBO, TXI HR-MAS</td>
</tr>
<tr>
<td>Extras: 6 Preamplifiers: 1H, 2H, 13C, 15N</td>
<td>HR-MAS unit (15,000 rpm)</td>
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<th><strong>LMR-AV800</strong></th>
<th><strong>LRE-AV800</strong></th>
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<tbody>
<tr>
<td>Console: AVANCE NEO (since October 2018)</td>
<td>Console: AVANCE NEO (since May 2021)</td>
<td>Console: AVANCE III</td>
</tr>
<tr>
<td>Probe: TCI cryoprobe</td>
<td>Probe: TCI cryoprobe</td>
<td>Probe: Cryo-TXI, QXI (31P)</td>
</tr>
<tr>
<td>Extras: 4 Preamplifiers: 1H, 2H, 13C, 15N</td>
<td>HR-MAS unit (15,000 rpm)</td>
<td></td>
</tr>
</tbody>
</table>

**Magnet:** 14.1T Ultrashield Bruker
**Console:** Avance III
**Probe:** TCI cryoprobe

**Magnet:** 14.1T Oxford
**Console:** AVANCE NEO (since May 2020)
**Probe:** TXI cryoprobe

**Magnet:** 14.1 T US
**Console:** AVANCE III
**Probe:** PA-TXI, TXI for high salt, QXI (31P), QXI (19F), SEF, TBI, BBO, TXI HR-MAS
**Extras:** 6 Preamplifiers: 1H, 2H, 15N, 19F
**HR-MAS unit:** (15,000 rpm)
04 CATALOGUE OF SERVICES AND ACCESS

The facility is strongly linked to internationally recognized NMR groups that ensure that the facility remains at the leading edge of the technique and is available to offer advice to non-expert users. The dedicated staff of the facility is a team of specialists who take care of the instruments and promoting education in the area of NMR. The facility personnel guide the users according to their need, ranging from experts wishing to implement new experiments to non-expert users requiring help in experimental design and interpretation to take full advantage of the NMR facilities. Typical users come from a wide diversity of areas, including among others:

- Protein 3D structure and dynamics
- Atomic characterization of IDPs and linear peptides
- Structure and dynamics of nucleic acids and their derivatives.
- Biomolecular recognition and interactions (including carbohydrates and lipids).
- Metabolic studies (metabolomics).
- Functional Biology.
- Drug discovery and drug design (ligand screening and optimization).
- Structural elucidation in Organic and Inorganic Chemistry.
- Biologics characterization
- Food Science and Technology.
- New methodologies: NMR applications development.

The R-LRB is open to research groups from public and private centers and offers access to the instrumentation and the know-how of scientific-technical staff responsible for NMR spectrometers. The competitive access corresponds to research projects in which an intensive use of the spectrometers is required. The access is regulated by an open competitive procedure, with an independent and transparent evaluation process. The call for competitive access is permanently open. The potential users must complete the online Access Application Form that will be evaluated by the External Access Committee (see below). A complete description of the access protocol can be found here (http://www.rmn.ub.edu/r-lrb/pages/access.html).

Data management protocols are being implemented to ensure open access and data traceability according to EU directives.
04 CATALOGUE OF SERVICES AND ACCESS: ACESSES

The Network of Laboratories for Nuclear Magnetic Resonance of Biomolecules, R-LRB, as a distributed Singular Scientific and Technical Infrastructure (ICTS, according to its initials in Spanish) of NMR, has granted during the period 2019-2020 a total of 49 Open Accesses to the scientific community for the use of its 6 NMR spectrometers. In all years, the percentage of competitive accesses requested and granted has been higher than 20%. On average, during the 2019-2020 period, the percentage of CAs granted was 25.0%, which represents a value of 5.0% above the committed value. It should be noted that, although in 2020 the demand for access decreased due to the state of alarm due to COVID-19, the percentage of accesses remained slightly above 20%.

Of the Open Access time granted during the 2019-2020 period (a total of 1054 days, 2500% of the total available time), 97% has been executed. The remaining 3% corresponds to ongoing projects, whose fulfillment is being carried out during the current year 2021.

The 49 Open Accesses have been used by a total of 35 different researchers. The number of new users incorporated each year has remained between 44 and 53%. On the other hand, the loyalty of users has been maintained for whom the use of the ICTS NMR spectrometers is absolutely essential for their research projects. Without these instruments, they would have been forced to request these resources in Europe and facilities. Due to COVID-19 lockdown restrictions, travel abroad is severely restricted, so having these instruments in Spain has been indispensable for the progress of many research projects.

Figure 4.2 captures the diversity of the researchers who use the R-LRB; they come from 13 centers located in universities, research institutes and the Spanish National Research Council.
Figure 4.2 Users by type of institute and individual institutes.
05 KNOWLEDGE TRANSFER

R-LRB users published 104 peer reviewed articles - most of them in high-impact factor papers- and 3 book chapters. A total of 147 presentations –both oral and written- and invited lectures in prestigious national and international Congress were given where the research resulting from the use of the R-LRB was presented. Also, 9 PhD students, who used ICTS resources extensively, successfully defended their doctoral thesis during this period.

![Figure 5.1 Statistics of results in R-LRB.](image)

Furthermore, the R-LRB offers to the high-field NMR community both methodological development and application services. New methods are developed on demand. Application services are provided on the fields of IDPs, protein dynamics, biomolecular interactions, structural studies of proteins and peptides, structural studies of DNA, structural studies of carbohydrates, metabolomics, food science and in-cell NMR. In general, each node of the distributed ICTS implements and develops specific NMR methodology, according to their users main interests.

Collaboration between the LRB node from Barcelona and the chemical and pharma industry in Catalonia, previously established, have maintained throughout the 2019-2020 period. In addition, 12 industries have been new users of the NMR facility. The LRB node has an accreditation from FDA and holds ISO quality certificates that have been successfully renewed during the 2019-2020 period. The collaboration with some industries is strategic for their business plan. In addition, the LRE node from Bilbao has been actively involved in supporting several hospitals and health institutes around the country, on the identification of metabolic biomarkers of several diseases. A start-up from CIC bioGUNE is ready to begin the last clinical phases of a new drug for an orphan disease associated to protein instability initially discovered as part of an NMR project.
Side chain to main chain hydrogen bonds stabilize a polyglutamine helix in a transcription factor.  
*Nature Communications* 2019, 10(1), 2034  
https://doi.org/10.1038/s41467-019-09923-2.

The use of the fast-NMR methods implemented at the LRB node of the R-LRB has been key for the research project led by the ICREA Research Professor Xavier Salvatella from the Laboratory of Molecular Biophysics at the Institute for Research in Biomedicine (IRB). Salvatella group has studied by NMR the structural basis of the association between polyglutamine (polyQ) tract length, transcriptional activity and polyQ disorders-based diseases, and addressed how the conformation of polyQ tract of the Androgen Receptor, associated with spinobulbar muscular atrophy (SBMA) depends on its length. Their findings suggest a plausible rationale for the association between polyQ tract length and Androgen Receptor transcriptional activity and have implications for establishing the mechanistic basis of SBMA.

A Myristoyl-Binding Site in the SH3 Domain Modulates c-Src Membrane Anchoring.  
iScience 12, 194–203, 2019,  
https://doi.org/10.1016/j.isci.2019.01.010

NMR spectroscopy has also been crucial for the study of intrinsically disordered proteins (IDPs) and intrinsically disordered regions (IDRs), such as those present in Src family kinases. The Pons’ group has shown that the N-terminal myristoyl group binds to the SH3 domain in the proximity of the RT loop, when Src is not anchored to a lipid membrane. Residues in the so-called Unique Lipid Binding Region modulate this interaction. In the presence of lipids, the myristoyl group is released from the SH3 domain and inserts into the lipid membrane. The fuzzy complex with the SH4 and Unique domains is retained in the membrane-bound form, placing the SH3 domain close to the membrane surface and restricting its orientation. The apparent affinity of myristoylated proteins containing the SH4, Unique, and SH3 domains is modulated by these intramolecular interactions, suggesting a mechanism linking c-Src activation and membrane anchoring.

Metabolic landscape of the mouse liver by quantitative 31P-NMR analysis of the phosphorome.  
Hepatology  
https://doi.org/10.1002/hep.31676

31P-NMR provides an innovative and simple holistic view of the inherent complex metabolism in health, disease and as a response to treatment. In this context, phosphorylated metabolites occupy a prominent position in all anabolic and catabolic pathways. In Millet’s laboratory, they have developed a 31P-NMR-based method to study the “phosphorome” in tissue samples through the simultaneous identification and quantification of multiple hydrophilic and hydrophobic phosphorylated metabolites. The methodology included the standardization and optimization of the protocol to yield a robust and quantitative measurement of the phosphorylated metabolism. They are now adapting this technique to define the metabolic landscape in several organs -including liver, brain, heart, and pancreas- of mouse models and of human tissue samples as well.
The first DNA/ligand complex involving a G-quadruplex/duplex junction.
Chemistry. A European Journal
Cover: doi.org/10.1002/chem.202100456
Paper: doi.org/10.1002/chem.202005026

Researchers of two groups at CSIC used NMR to study a new designed pharmacophore based on cationic aromatic frameworks that selectively binds with high affinity to quadruplex–duplex junctions, while presenting a poorer affinity for G-quadruplex or duplex DNA alone. The structure of the complex between a quadruplex–duplex junction with a ligand of the HIV-1 LTR-III family has been determined. According to these data, the remarkable selectivity of this structural motif for quadruplex–duplex junctions is achieved through an unprecedented interaction mode so far unexploited in medicinal and biological chemistry: the insertion of a benzylic ammonium moiety into the centre of the partially exposed G-tetrad at the interface with the duplex.

SARS-CoV-2 Disordered Protein Targeted for Inhibition.
https://covid19-nmr.de/

The “Manuel Rico” NMR lab, LMR is characterizing SARS-CoV-2 disordered protein and collaborating as part of International Consortium COVID19-NMR in the search of inhibitors as drug leads.
A total of 34 activities have been carried out to disseminate the capabilities of the R-LRB. These actions were oriented to promote cooperation with other institutions and to bring the ICTS closer to the general public. Activities included seminars, conferences, and Open Days to foster the applications of NMR among researchers and/or industry stakeholders. Many activities were disseminated through media and digital tools. When possible, on-site visits to the R-LRB were scheduled in a regular basis from a wide range of visitors: elementary, high schools and vocational training students; high school teachers; science students and future researchers; university or other research institutions management staff; industry stakeholders and policy makers.