# Biomedical Magnetic Resonance Laboratory

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## Institutions

**BIONAND,** Andalusian Centre for Nanomedicine and Biotechnology
**Cost Action** "Applications of MR imaging and spectroscopy techniques in neuromuscular disease" (EU network)
**FPS,** Fundación Pública Andaluza Progreso y Salud (Consejería de Salud, Junta de Andalucía)

## Keywords

Magnetic Resonance, Molecular Imaging, Magnetic Nanoparticles, Diagnostics, Theranostics, Cancer, Neurodegenerative Diseases

## Research Lines

- ✓ Breast cancer metabolomics by HR-MAS
- ✓ Magnetic Nanomaterials for MRI molecular imaging of prostate tumors
- ✓ Metabolomics of neurodegenerative diseases using high resolution liquid NMR

## Scientific Activity

The Biomedical Magnetic Resonance Laboratory (BMRL) Laboratory at BIONAND has a clear translational orientation, focused on the applications of magnetic resonance to biomedical research. In particular, the BMRL has two main research areas: metabolomics applied to early diagnosis and monitoring of disease progression, and MR molecular imaging by using functionalized magnetic nanoparticles.

**NMR-based Metabolomics**: Metabolomics, the youngest of the "omics" sciences, concerns the analysis of the complete set of small-molecule metabolites (such as metabolic intermediates, hormones and other signaling molecules, and secondary metabolites) found in a cell, tissue, organ or organism. NMR-based metabolomics is a growing field that offers the advantage over mass spectrometry techniques of minimal sample preparation and high reproducibility. On the negative side, NMR suffers from intrinsically low sensitivity, however the development of higher magnetic fields together with cryoprobes, has allowed this limitation to be markedly overcome. Another great advantage of NMR is the possibility of studying not only bio-fluids, but also intact tissue, such as tumor biopsies, using magic angles probes. Our research projects are focused on the characterization of the metabolome of both tissue biopsies and bio-fluid for early detection of cancer and neurodegenerative diseases.

**Magnetic Resonance Molecular Imaging**: Molecular Imaging makes reference to in vivo visualization and measurement of biological processes at the molecular and cellular level using endogenous or exogenous biomarkers (contrast agents). Among the different imaging modalities, Magnetic Resonance Imaging (MRI) has attracted a great deal of interest because of its excellent combination of qualities. It is non-ionizing, allows unlimited tissue penetration, and provides very good anatomical information and image resolution. However, to reach the sensitivity needed to image molecular processes, that is, to perform MRI-based Molecular Imaging, both contrast agents and image acquisition sequences need to be improved. Nanotechnology is playing a crucial role in this sense, allowing for development of new magnetic nanoparticles (MNPs), such as iron oxide nanoparticles, with high specificity and sensitivity. On the other hand, MRI data acquisition and processing also need important improvements to allow specific, accurate and artifact-free detection of these MNPs. Our research interests are focused on the development of new nanoparticles and the implementation of new MRI methodologies, for early detection of cancer.

### Research lines:

### ✓ Breast Cancer Metabolomics by 1H HR-MAS NMR

Breast tumors show high variability and their classification based on histological characterization does not reflect the underlying heterogeneity, which is responsible for the different prognosis and response to treatment of tumors with similar diagnosis. This issue has been partially overcome by using a genetic-based tumor classification, which has improved tumor response and outcome 1. However, this classification method is not infallible and there are still some tumors within the same subclass that show different response to treatment. Therefore, there is a need for new biomarkers that might allow a more refined subclassification and could also be used as therapeutic targets.

Metabolomics of intact tissue offers new hopes in cancer diagnosis and classification, as demonstrated by the increased number of publications during the last few years.

Our group in currently working on the development of new classification tools, based on the metabolic profiles of breast tumor biopsies using HR-MAS techniques.

This project is being developed in collaboration with the departments of Radiology, Pathology, and the Andalusian Biobank, at the "Virgen de la Víctoria" Univesitary Hospital, in Málaga.

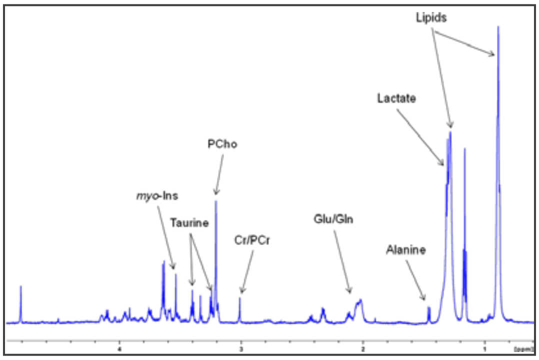


Figure 1. $^1$H HR-MAS NMR spectrum of a breast tumor biopsy.

### ✓ Magnetic Nanomaterials for MRI molecular imaging of prostate tumors

Medical Imaging has evolved enormously over the past two decades to become a fundamental tool for clinical diagnosis. Among the different modalities, MR imaging has attracted a great deal of interest because of its non-invasive and non-ionizing nature. Moreover, MRI offers the advantage of having unlimited tissue-penetration and very good image resolution. However, MRI suffers from inherently low sensitivity, requiring the use of contrast agents to amplify the detectable signal, especially for molecular imaging purposes. Molecular imaging makes reference to in vivo visualization and measurement of biological processes at the molecular and cellular level using endogenous or exogenous biomarkers (contrast agents). In this sense, iron oxide nanoparticles (IONPs) have played a crucial role making it possible to even detect a single cell in vivo by MRI (Shapiro et al. Magn Reson Med 55: 242-9, 2006; Smirnov et al. Contrast Media Mol Imaging 1: 165-74, 2006). The outstanding increase in sensitivity produced by iron oxide nanoparticles is due to their superparamagnetism, which is responsible for the generation of significant local field inhomogeneities. These field inhomogeneities (susceptibility effect) have a strong effect on the spin-spin relaxation process (T2 relaxation) causing a dramatic T2 decay that can be detected as negative contrast using T2-weighted MRI sequences. The susceptibility effects produced by these nanomagnets extend well beyond the size of the nanoparticles, thus producing very large signal amplification and making it possible to perform MR molecular imaging.

In addition, magnetic nanoparticles can be functionalized with different ligands for the specific binding to cell surface receptors that are over-expressed in cancer cells, for instance. This specific binding is the basis of molecular imaging using MRI, for the early detection of cancer.

Our group is interested in the development of new magnetic nanoparticles for the early diagnosis of breast and prostate cancer, as well as new MRI methods that will allow us to image and quantify these nanoparticles in vivo.

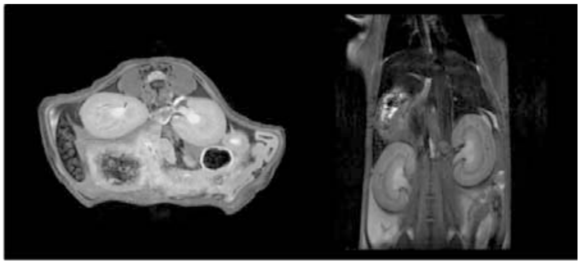

Figure 2. $T_2$-W MRI image of mouse abdomen before (left) and after (right) the injection of IONPs.

### ✓ Metabolomics of neurodegenerative diseases using high resolution liquid NMR

Several in vivo Magnetic Resonance Spectroscopy (MRS) studies have shown metabolite alterations associated with neurodegenerative diseases, particularly changes in the NAA/Cr and NAA/Myo ratios. However, these alterations are nonspecific and show a large overlap with many other pathologies that affect neural integrity, such as ischemia, trauma or brain tumors. The low specificity of in vivo MRS is due to the reduced number of metabolites that can be discriminated in these low resolution spectra.

The situation is completely different in vitro, where a very large number of metabolites can be detected and quantified. Therefore, our goal is to characterize the whole metabolome of CSF from patients with different neurodegenerative pathologies, with special focus on multiple sclerosis.

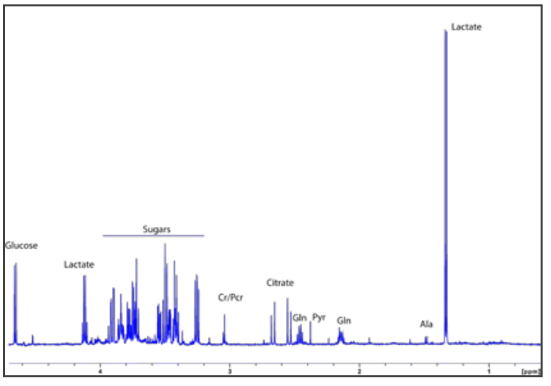


Figure 3. 1D 1H NMR spectroscopy of human CSF

## Collaborations

❖ **Instituto de Ciencias de Materiales de Aragón, ICMA-CSIC/University of Zaragoza** (Spain), Jesus M. de la Fuente, in vivo characterization of magnetic nanoparticles.

❖ **Instituto de Investigaciones Biomédicas Alberto Sols, IIBm-CSIC/Autonomous University of Madrid** (Spain), Pilar López Larrubia, metabolic characterization of brain tumor biopsies

❖ **University of Malaga,** Antonio Jesús Jiménez Lara (Spain), 1H HR-MAS NMR metabolomics of hydrocephalus.

## Research Projects in the last 5 years

- Caracterización preclínica de alternativas para la detección y tratamiento de cáncer de próstata basadas en nanopartículas superparamagnéticas de óxido de hierro funcionalizadas con péptido intestinal vasoactivo (VIP) y doxorrubicina, PI-0559-2013 MS-2, Manuel Pernía Leal; María Luisa García Martín, Consejería de Salud de la Junta de Anadalucía.

- Clasificación Metabolómica de los Tumores de Mama mediante Espectroscopía de 1H de Alta Resolución por Resonancia Magnética de Ángulo Mágico (1H HR-MAS RMN): Valor Diagnóstico y Pronóstico, PI-0780-2012, María Luisa García Martín, Consejería de Salud de la Junta de Andalucía

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