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► **To cite this version:**

Rapport d'évaluation d'une entité de recherche. CRMSB - Centre de résonance magnétique des systèmes biologiques. 2010, Université Bordeaux 2. hceres-02033674

HAL Id: hceres-02033674

<https://hal-hceres.archives-ouvertes.fr/hceres-02033674v1>

Submitted on 20 Feb 2019

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agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit
Centre de Résonance Magnétique des Systèmes
Biologiques – UMR 5536
From the
Université Bordeaux 2 Victor Segalen
CNRS

May 2010



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AERES report on the research unit

Centre de Résonance Magnétique des Systèmes

Biologiques – UMR 5536

From the

Université Bordeaux 2 Victor Segalen

CNRS

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010



Research Unit

Name of the unit : Centre de Résonance Magnétique des Systèmes Biologiques

N° in case of renewal : UMR 5536

Unit Director : Mr JM FRANCONI

Members of the review committee

Chairman Committee

Mr Robert MULLER, Univ. Mons, Belgique

Other committee members

Mr Hervé SAINT-JALMES, Université Rennes 1

Mr Ponnada NARAYANA, Univ. Texas, Houston, Etats-Unis

Mr Jean-Philippe RANJEVA, Université de la Méditerranée (Aix-Marseille 2)

Mr Pascal MERLET, CEA Orsay

Mrs Graciela PAVON-DJAVID, Université Paris 13

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD...

Mr Maxime GUYE, CoNRS representative

Mr Jean-Marc CONSTANS, CNU representtaive

Observers

AERES scientific advisor:

Mr Christian BARILLOT,

University representative

Mr Alain BLANCHARD, Vice-Président du Conseil Scientifique, université Bordeaux 2

Research organisation representative

Mrs Florence NOBLE, INSB CNRS

Mr Pascal SOMMER, INSIS CNRS



1 • Introduction

- Date and execution of the visit

The Committee met on November 12th and 13th, 2009. The meeting started at 9 am on the 12th morning. After the introduction, the Committee listened to the presentation by the head of the Unit and his team members about the scientific objectives of UMR 5536, its structure and organization, and some of the projects that are currently in progress. The presentations were followed by series of questions and answers and discussion. Following these presentations, the Evaluation Committee visited the NMR facilities and listened to the presentations by some of the team members. On the afternoon of the 13th, the Evaluation Committee, in a closed door session, discussed their impressions of the center and identified strengths and weaknesses of this research team. This report reflects these deliberations.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The UMR 5536 (Centre of magnetic resonance of biological systems) was created for the first time in 1994. The laboratory has been then renewed regularly up to 2006. Re-created in 2007, the UMR 5536 is a Mixed Research Unit associating the CNRS and the University Victor Segalen Bordeaux 2. Since its creation, the research activities of the laboratory are closely linked with the use of nuclear magnetic resonance techniques (spectrometry and imagery).

The objectives were to use the potentialities and the complementarities of the NMR spectrometry and imagery methods to:

Understand the operation of the living systems in an integrative approach;

Identify and characterise pathological dysfunctions and thus partake of the developments of diagnostic or prognostic strategies

Partake of the developments of new therapeutic strategies;

Propose new concepts, tools and methods in NMR (imagery and spectrometry) and in biology to reach the 3 objectives stated previously.

- Management team:

J-M .FRANCONI (Director) and P. VOISIN (Assistant-Director)

- Staff members (on the basis of the application file submitted to the AERES)

| | In the report | In the project |
|--|---------------|----------------|
| N1: Number of researchers with teaching duties (Form 2.1 of the application file) | 11 | 9 |
| N2: Number of full time researchers from research organizations (Form 2.3 of the application file) | 8 | 7 |
| N3: Number of other researchers (Form 2.2 and 2.4 of the application file) | 7 | 1 |
| N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 13 | 12 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 2 | 1 |
| N6: Number of Ph.D. students (Form 2.7 of the application file) | 4 | 5 |
| N7: Number of staff members with a HDR or a similar grade | 13 | 10 |



2 • Overall appreciation on the research unit

- Summary

This multi-disciplinary research unit has unique strengths and is central to bioimaging. It has expertise in the development and implementation of NMR techniques that very few laboratories can match. For example this group has implemented fast imaging techniques for high resolution anatomy, high resolution magnetic resonance angiography in rodents, and in vivo implementation of dynamic nuclear polarization that substantially improves the sensitivity of conventional NMR for cellular and molecular imaging, including mapping enzyme activities. This group has demonstrated significant expertise in applying NMR techniques to animal studies for investigating cardiac and skeletal muscle metabolism, brain metabolism, hypoxic-ischemic injury in rodent models. They have excellent peer-reviewed publications in reputed international journals. This is in spite of the heavy teaching load carried by the key members of the team. The Director of the team is an outstanding manager and is highly regarded by his team. This research team is well funded. It is involved in large number of biology projects. While application of NMR to biology is the driving force, the Evaluation Committee felt that this group should focus on the development of methodology that is so crucial for all the other groups. In the current set-up, there are concerns that the group has initiated too many biological projects that require huge resources. Another concern is with the aging of the instruments and lack of funds for proper instrument upgrades. This team needs strong support from the University and CNRS to overcome some of these problems.

- Strengths and opportunities

The main expertise of this group is in the development of NMR imaging and spectroscopy methodologies. There are perhaps only one or two groups in France that match this level of expertise. A prime example of this expertise is their undertaking the very risky venture of enhancing the in vivo NMR sensitivity by developing and implementing dynamic polarization transfer technique for imaging enzyme activity. This is a very significant achievement. Similarly this group has developed fast techniques for generating high resolution anatomical imaging, high resolution MR angiography, and flow quantification. They have implemented NMR techniques for investigating skeletal and cardiac muscle integrity, imaging vulnerable plaques, understanding the brain metabolism and brain injury, such as hypoxic ischemic injury and brain tumors. This team has the opportunity to expand these techniques and export them to clinic for human studies. Since 2007, the unit has participated in 6 projects financed by the ANR (National Research Agency) and a large European project. In 2009, 70% of the financing for the research projects is provided by grants and contracts. As a part of the collaborative efforts with UMR 5231, the UMR 5536 is one of the participating units of the Institute of Man and Living Organisms Imagery that is supported by the Victor Segalen Bordeaux 2 University. This project is financed within the framework of the CPER. This team has established both national and international collaboration. This should help increase the visibility for not only this research team but also for the University of Bordeaux. In summary this team has the opportunity to play a central role in Biomedical Imaging Research, in general, and the proposed Institute of Bioimaging, in particular.

- Weakness and threats

Given the heavy teaching load and limited human and instrument resources, the Evaluation Committee felt that this research team is probably involved in too many biological projects for the small number of biologists. This spreads their resources thin. With multiple projects, their efforts would be diluted and it becomes difficult to maintain their leadership role in the development of the methodology which is their main strength.

The second concern is with the lack of necessary instrument time. In order to maintain these instruments, the team has to sell the instrument time to outside users and collaborators which leaves inadequate time for the developmental work. In addition, the instruments are aging and unless there is a fusion of fresh funds, it is difficult to keep them at the forefront.

The office and laboratory space is also limited. For example, the estimated space is 5 sq meters per investigator. This is inadequate and prevents from expanding externally funded projects.

There also appears to be a feeling among the staff that their efforts are not appreciated by the University. The productive and permanent staff has only limited opportunities for career promotion. Therefore, it is quite tempting for the productive staff to seek opportunities elsewhere. Should this happen, it would create a vacuum.

This group has been productive, both in terms of publications and generating funding. Since 2005, this group documents 141 peer reviewed publications, some of them with very high visibility, such as Proceedings of National academy of Sciences, Biochemistry Journal, Radiology, Magnetic Resonance in Medicine, Journal of Cerebral Blood Flow and Metabolism. During this period, the team also presented 127 abstracts at national and international



meetings. They were also awarded a patent (WO 01215826). The number of students that graduated with PhD is 7 and Masters is 21.

- Recommendations

Within the constraints, the Director has been doing an outstanding job in managing this team. The following recommendations are meant to improve it further. 1) Focus on a fewer projects that are consistent with the expertise of the research group. 2) Integrate the projects better for effective use of resources. For example, the trypanosome project that provides insights for better understanding of energy metabolism could have more links with lactate and energy metabolism study in the healthy and pathological brain. 3) Upgrade the instruments by seeking additional funding from within and outside the University. 4) While a merger between UMR5536 and UMR5231 is anticipated in 2015, it is good idea to establish strong collaboration with UMR5231 well before the anticipated merger. The collaboration could start with the identification of a few common projects and holding joint seminars.

- Data on work produced

| | |
|--|----|
| A1: Number of lab members among permanent researchers with or without teaching duties who are active in research (recorded in N1 and N2) | 19 |
| A2: Number of lab members among permanent researchers with or without teaching duties who are active in research (recorded in N3, N4 and N5) | 13 |
| A3: Ratio of members who are active in research among staff members $[A1/(N1+N2)]$ | 1 |
| A4: Number of HDR granted during the past 4 years | 1 |
| A5: Number of PhD granted during the past 4 years | 7 |

3 • Specific Comments

- Appreciation on the results

In order to overcome the sensitivity issues associated with NMR for the application of molecular and cellular imaging, it is necessary to come up with highly innovative schemes. The implementation of dynamic nuclear polarization by this group is one such innovation. While dynamic nuclear polarization is known, this is the first time that this has been applied to biological tissues. This opens up a new area in noninvasive molecular imaging, including mapping enzymatic activity. Similarly this group has implemented fast3D and 4D TrueFISP imaging techniques for acquiring high resolution anatomical in mice. While TrueFISP is a known sequence, the real contribution lies in the application to small structures such as mouse brain or coronary arteries. In addition, their ability to perform angiography on small animals and flow quantification should be of great interest to investigators interested in cardiovascular diseases. This group's work on muscle and cardiac metabolism, antibody imaging for plaque characterization, cellular imaging and gene therapy for gliomas are equally impressive.

This research group has published 141 manuscripts in peer reviewed publications since 2005, some of them with very high visibility, such as Proceedings of National academy of Sciences, Biochemistry Journal, Radiology, Magnetic Resonance in Medicine, Journal of Cerebral Blood Flow and Metabolism. There is room for further improvement in publishing more manuscripts in high impact journals. The team members also presented 127 abstracts at national and international meetings. They were also been awarded a patent (WO 01215826).

The research work by this group in certain areas is at the very cutting edge and is comparable to that of some of the best laboratories in the world.

This team has established excellent research collaboration with both academic institutions and industry. The academic partners include investigators from Helsinki, Lausanne, Glasgow, Munich, Dublin, and Cheque Republic. The



industrial partners include Orion Pharma, Cis Bio International, Siemens, and Guerbet. In addition, this team is a participant in the Nanother European project, a consortium of 18 research groups.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

In 2009, this team recruited a senior scientist from CNRS along with his group of 3 junior researchers.

The number of students that graduated with PhD is 7 and Masters is 33. In 2009, the team has recruited 5 English speaking post-doctoral fellows who are financed by NRA, 3 doctoral students, and three physicians.

This research team has been quite successful in generating funds from various sources as detailed below:

| | | |
|------------------|------------------|--------|
| ANR TECSAN 2006 | Nano-Bio Imaging | 208 K€ |
| ANR PCV 2007 | Imathabio | 270 K€ |
| ANR MIME 2007 | Metabotryp | 263 K€ |
| ANR MIME 2007 | Systryp | 137 K€ |
| ANR TECSAN2007 | Itov | 108 K€ |
| ANR Blanche2009 | Nitro-MRI | 290 K€ |
| European Project | Nnather | 325 K€ |

In addition, 1621 K€ (1080 committed and 541 anticipated) for acquiring 7T/9.4 T MRI scanner as a part of the Bio Imaging Institute. These funds cover significant part of their research enterprise. Given the economic hardships everyone is facing, it is perhaps unrealistic to expect this team to generate more funding. It is therefore important for the University Administration and CNRS to step in and provide the necessary support to ascertain that adequate instrument time is available to the team members and to keep the instruments at their peak.

Considering that this is a primarily a "Methodology Development" group, there are relatively few opportunities in developing socio economic partnership.

- **Appreciation on the strategy, management and life of the research unit**

This group is involved in teaching regular courses as well as training Masters and Doctoral students. Some of the formal courses this group teaches include, General Physics, Biophysics, Specialized NMR, Enzymology, Bioenergetics, Biochemistry and Nutrition etc. Therefore it would certainly help if they could obtain additional university funded positions.

This unit is managed by the Director and is assisted by an assistant Director. These two individuals are assisted by the Scientific Committee (all researchers, teacher-researchers, and research engineer) and the Laboratory Board (4 elected members, 3 appointed members, Director, and the Assistant Director).

The organizational structure is sound and there appears to be good communication between the members of the group.

- **Appreciation on the project**

Currently many of the developed techniques have been tested only on excised tissues. It is necessary to extend these studies to in vivo. For example, in the case of dynamic polarization studies, this perhaps requires design of newer ESR cavities that can accommodate whole animal. This requires long term planning, which appears to be in place.

The team members have done very well in terms of developing and implementing newer technologies that are at the cutting edge. They have excellent publication record. The team members are actively involved in both formal teaching and training graduate students. They have established strong collaboration with various local and international research teams. They have been successful in generating funds to support significant part of their research enterprise. An effective management appears to be in place. The Director is held in high esteem by his team members. The long term viability of the research projects appears good.



There are some concerns that this team is spreading too thin by handling too many biology projects. It would be better if they focus on the development of methodology, which is their major strength, and include a few relevant applications, but develop strong collaboration for developing important biology projects that require NMR technology.

The NMR units, particularly the 4.7 T scanner, require major upgrades for this group to continue the cutting edge research. The instrument time appears to be inadequate since they have to sell the time to outside users for generating funds to keep the facility operating.

Despite the very heavy teaching load (where an additional teaching position could help), this team was able to obtain significant scientific results. This team continues to maintain a very high level of NMR expertise and provide excellent service to the users.

This team needs to retain adequate instrumentation time and skills in order to maintain these high standards. They need to concentrate more on their strong expertise, especially in pre-clinical NMR research. They should not become just a service provider and keep their level of expertise that would be an asset to other research teams and external users.

Finally, this team requires more laboratory and office space. This would enhance their ability to attract more outside funding and more personnel. The university administration and CNRS should provide appropriate support to keep this group that could play a key and central role in the bioimaging program.

The Evaluation Committee encourages strong collaboration between this group and URM5231, well before their anticipated merger in 2015. For example, a collaborative project between UMR 5231 and UMR 5536 team could include in vivo detection of microglial cells by NMR and/or histology or use of nanoparticles. These microglial cells, for example, could also be used as a vector for gene therapy. Identification of a first common project on gene therapy would serve as a good start for collaboration between these two teams.

| Note de l'unité | Qualité scientifique et production | Rayonnement et attractivité, intégration dans l'environnement | Stratégie, gouvernance et vie du laboratoire | Appréciation du projet |
|-----------------|------------------------------------|---|--|------------------------|
| A | A | A | A | A+ |



Monsieur Pierre GLORIEUX
Directeur de la section Unités de recherche
AERES

Bordeaux, le 16 février 2010

Monsieur le Directeur,

Je vous transmets les observations de Monsieur Jean-Michel FRANCONI, Directeur de l'unité « Centre de Résonance Magnétique des Systèmes Biologiques », faisant suite au rapport du Comité de visite de l'AERES.

« Nous avons vivement apprécié la qualité de l'évaluation réalisée par un comité international spécialiste de notre domaines. Nous sommes particulièrement sensibles aux conclusions très positives et encourageantes du comité. Nous utiliserons les précieux conseils délivrés pour poursuivre nos efforts. »

Je vous prie de croire, Monsieur le Directeur, à l'assurance de mes sincères salutations.

Le Vice-Président du Conseil Scientifique,

Alain BLANCHARD



CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE
UNIVERSITE VICTOR SEGALEN BORDEAUX 2

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33076 Bordeaux Cedex
Tel 00 33 5 57 57 12 95
Fax 00 33 5 57 57 45 56

Objet: Courrier contenant les remarques relatives au rapport d'évaluation de l'UMR 5536 par l'AERES.

Cher Collègue,

Nous avons vivement appréciés la qualité de l'évaluation réalisée par un comité international spécialiste de notre domaine: la Résonance Magnétique Nucléaire.

Nous sommes particulièrement sensibles aux conclusions très positives et encourageantes du comité. Nous utiliserons les précieux conseils délivrés pour poursuivre nos efforts et définir nos stratégies.

J-M FRANCONI

Directeur de l'UMR 5536.