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 biologique et médicale

From the

Université de la Méditerranée

CNRS

March 2011

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

March 2011

Research Unit

Name of the research unit: Centre de Résonance Magnétique Biologique et Médicale

Requested label: UMR CNRS

N° in the case of renewal: UMR 6612

Name of the director: Mr Patrick COZZONE (current), Ms Monique BERNARD (future)

Members of the review committee

Committee chairman

Mr Bernard MAZOYER, University of Caen, Caen, France

Other committee members

Mr Graham KEMP, Liverpool University
Mr Vincent LEBON, CEA, Fontenay-aux-Roses, France
Mr Eike NAGEL, King's College of London, London, UK
Mr Didier REVEL, University of Lyon, Lyon, France
Mr Andreas VOLK, Institut Curie, Orsay, France
Mr Sylvain MIRAUX, University of Bordeaux, Bordeaux, France, CoNRS representative
Mr Gilles KARCHER, University of Nancy, Vandoeuvre, France, CNU representative

Observers

AERES scientific advisor

Mr Pierre LEGRAIN

University, School and Research Organization representatives

Mr Jean Louis MEGE, University of Marseille
Ms Marie-Christine LAFARIE-FRENOT, CNRS
Mr Pascal SOMMER, CNRS

Report

1 • Introduction

• Date and execution of the visit

The visit lasted 1.5 days on March 3-4 with the following agenda:

-Day 1 am (10:00 am – 1:00 pm): committee closed door-meeting, visit of the preclinical MR platform, presentation of the past (P. Cozzone) and future (M. Bernard) team activities, meeting with representatives of supporting bodies (CNRS and University of La Méditerranée)

-Day 1 pm (2:30 pm – 6:30 pm): back-to-back presentations by group leaders: heart (M. Bernard), muscle (D. Bendahan) and Central Nervous System (CNS) (J.P. Ranjeva), followed by a closed-door meeting of the committee

-Day 2 (8:00 am – 2:30 pm): back-to-back presentations by group leaders: rodent models of brain pathologies (A. Viola), methods (F. Kober), followed by 3 parallel meetings with 1) tenure staff researchers, 2) technical staff, and 3) PhD students and post-docs; the committee then proceeded to an exchange with the future director alone, before a 3 hour closed-door meeting.

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

This research unit was founded 25 years ago in Marseille by Professor Patrick Cozzone with the aim of developing biomedical research applications of magnetic resonance. Today, the unit is operating two platforms of MR equipment dedicated to preclinical and clinical research, respectively: 1) the CRMBM, a preclinical (in vitro, ex-vivo, in vivo rodent) Magnetic Resonance (MR) facility founded in 1986 equipped with 4 high-field magnets including 2 for rodent imaging, and 2) the CEMEREM, a clinical MR facility (1.5T and 3T wide bore magnets), founded in 1998 and extended in 2008. The two platforms are located close to each other on the Marseille medical school and university hospital campus. The unit's present scientific activity continues to deal essentially with the development of methods in the field of magnetic resonance spectroscopy and imaging, and with their application to translational research on a variety of heart, muscle and CNS diseases.

The unit is currently composed of 5 scientific teams working on 1) MR investigations of heart pathologies with microvascular alterations (team 1 "Heart", head: M. Bernard), 2) MR of healthy, trained and diseased muscle (team 2 "Muscle", head: D. Bendahan), 3) multimodal MR imaging in humans of CNS disorders including multiple sclerosis, epilepsy, tumors, Alzheimer disease (team 3 "CNS", head: J.P. Ranjeva), 4) the development, characterization with MRI/MRS and validation of CNS rodent models for multiple sclerosis, alcoholism and malaria (team 4 "Rodent models of CNS pathologies", head: A. Viola), and 5) the development of advanced MR methods for tissue perfusion imaging and for chemical shift imaging (team 5 "Methods", head: F. Kober). The unit has also developed a strong partnership with La Timone university hospital, the CRMBM in vitro spectrometers being used to perform routine analyses of biological fluids and cell extracts for the benefit of the hospital clinical departments.

• Management team

From its very early days and up to now, the unit has been directed by Professor Cozzone, an internationally recognized leader in the field of biomedical MR. Over the past four years, Mrs M. Bernard has been the unit deputy-director and will take over the directorship for the following next five years. Meanwhile, Mrs S. Confort-Gouny, who is currently the unit technical director, will become deputy-director while Mr M. Guye will remain the medical director of the unit. In this unit, major decisions are discussed within a strategic council, a body composed of the director, the deputy-director, the technical director, the medical director and the team leaders.

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

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

2 • Overall appreciation on the research unit

- Summary

The unit has established itself over the past 25 years as one of the national leaders in the field of biomedical NMR. Its charismatic director has gathered a team that is very productive, well-recognized, and highly successful in finding financial support. Its MR platforms have been rapidly growing over the past years, resulting in some loss in the global coherence of the unit's research project because of the large number of clinical and preclinical research projects that have been started. Considering the fundamental restructuring of the research system which is happening at both the national and the local levels, the new director should adopt a high profile and proceed to implement the changes recommended below for optimizing the unit's organization and activities and maintaining its leading position.

- Strengths and opportunities

This is a team with a longstanding and rare expertise at the national level in the area of high field MR methods and applications to pathologies. The unit benefits from two state-of-the-art MR platforms for preclinical and clinical research, respectively. Both platforms are located within the vicinity of the university hospital, which provides an optimal setting for conducting translational research. The current director is a highly recognized expert in the MR community who has very successfully gathered over the years an expert multidisciplinary team, particularly in the MR methodology domain, which is well-balanced between senior and junior scientists. In addition, the committee was impressed by the friendly atmosphere and the solidarity that characterize the relationships between the different personnel belonging to this team. The unit appears to be highly supported by both the CNRS and the Université de la Méditerranée and has established a strong partnership with the university hospital that is further reinforced by the services that the two platforms provide to the La Timone hospital clinical departments.

- Weaknesses and threats

Over the years, both MR platforms have been upgraded and expanded with no less than 6 magnets currently under operation, including two machines dedicated to clinical research activities. This has led to a considerable development of service-like activities and puts a heavy routine workload on both the technical and research staff, while making the MR platforms accessible to other teams only through collaboration with and selected by the CRMBM scientists. As a consequence, a multiplication and diversification of research topics has occurred, especially in the clinical neuroscience domain, making it sometimes difficult to clearly identify core research from service activities. A potential threat of this diversification is a progressive lack of coherence between team research activities, such as for example the noticeable discrepancy between pathologies for which rodent models are currently developed and pathologies investigated in humans, which works against the unit's ambitions in genuinely translational research. This diversification also weakens the team's scientific visibility, as it is in danger of appearing progressively more as a provider of imaging expertise and facilities rather than a research centre pursuing its own strategic program of research. In particular, it would be very damaging to let the team's methodologists get too heavily involved in multiple clinical applications, rather than spending most of their time in original method development. A related threat for this unit is the risk of becoming progressively isolated from ongoing local federating initiatives; this is particularly pertinent because the team strongly expressed their desire to remain almost completely focused on MR, keeping the same organization and management style in the years to come. This focus and ethos has served them well in the past, but the world is changing. In particular, the committee was somewhat surprised by the lack of strategic plans on how to interact in the future with major local players such as the Neuroscience Institute or the future nearby CERIMED imaging platform.

- Recommendations

The committee first suggests a clearer delineation between the platform/service activities and the unit core research projects. Such clarification would definitely help some teams to focus their research on a limited number of topics in which they could expect to become international leaders. This would certainly lead the two CNS teams to establish a common scientific strategy, and allow methodologists to work as a team rather than as a group of individuals dealing with separate projects. The committee also encourages the future director to work on establishing strategic plans for future collaborations and participation of the team in local initiatives, particularly in the domains of imaging and neuroscience where this unit should adopt a high profile and lead the move.

The committee's second main recommendation is for each team, and the unit itself, to choose, explicitly and strategically, between the range of projects which are proposed in the report, and which were discussed during the visit. Internationally there are many large research centers of excellence devoted to particular programs of heart, muscle and brain research, often integrating many techniques to answer scientific questions. To compete in this landscape the unit must focus on a relatively limited number of things it does better than almost anyone else, and exploit these hard. This will no doubt include special MR techniques, but may also include collaborative mechanisms for genuinely translational work using mouse models and clinical populations. Thus technical development and strategic collaboration are equally important.

The committee's third recommendation is for the unit itself to decide on how they want to structure their collaborations: setting up clinical multicenter trials? Providing prototype software to other partners? Providing methods as well as normal values and standards to on-site collaborators? Providing animal models? Each of these options requires to put an infrastructure into place, not all of them can be pursued at the same time given the size of the unit.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	7
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	8
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD granted during the past 4 years	8

3 • Specific comments

- ## Appreciation on the results

Over the past 5 years, a number of original findings have been obtained by the unit researchers, including:

- demonstration of the UCP3 gene role in aerobic ATP production and muscle fat content
- quantification of gray matter injury in early multiple sclerosis (MS) patients
- demonstration of functional connectivity alteration in drug-resistant epilepsy using rs-fMRI
- production of first human brain sodium MR images in France
- demonstration of liver dysfunction as a contribution to brain damage using a specific murine model of malaria
- development and validation of quantitative perfusion MRI methods for animal brain and heart

Overall, the unit as a whole has a very good productivity since over the past 5 years its 15 researchers have published 120 articles on its core research topics, and 58 through various collaborations (average of 2.4 articles/year/researcher). 59 other articles have been published by the unit members but are not directly related to the unit scientific activity. Many of these articles are published in reference journals of the domains of MRI/MRS (Magnetic Resonance in Medicine, NMR in Biomedicine), neuroimaging/ neuroscience (Neuroimage, Human Brain mapping, Brain, Neurology, Epilepsia), cardiology (Circulation), and physiology (American Journal of Physiology, Journal of Cerebral Blood Flow and Metabolism), although a somewhat large fraction of the articles published by the unit are found in journals of medium to low impact. Actually, publications in high impact journals of general interest such as New England Journal of Medicine, Lancet, Nature are found in the list of those not directly related to the unit scientific activities. The researchers of this unit have also presented 35 oral communications and 132 posters in scientific meetings and obtained 1 patent for one of their software. Eight theses have come out of this unit in 5 years for a total number of 13 researchers having the habilitation thesis.

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

The unit has established itself as a widely recognized MR platform, nationally and internationally, being both a member of the IBISA and EIBIR consortia. The unit is the home of the editorial office of MAGMA, the official journal of the ESMRMB, and has organized two courses in 2008 and 2009 for this society. The unit has also been deeply involved in the organization of the ISMRM "MR in cancer" study group meeting in 2009. Its director is a member of steering/executive and scientific committee of several international/national institutions and has been made a fellow of ISMRM in 2007. Other members of the unit regularly sit on national (AERES, CoNRS) and international (ISMRM) boards. It is also worth mentioning that Mrs Confort-Gouny, technical director of the unit, has received the 2006 Excellentia award for best woman research engineer.

The unit has been very efficient in raising funds for its research, since it has raised each year 600 K€ on average, which represents 77% of its annual operating budget. Some of these resources came from highly competitive calls, including 9 ANR grants, and some others from participation in national or European collaborative efforts. Locally, the unit has established strong and durable partnerships with various la Timone hospital departments including imaging, neurology and neurosurgery, cardiology and rheumatology. The unit has indeed built over the years a very original and strong partnership with the hospital, providing services not only for clinical research activities, but also for routine testing of biological fluids and tissues using its platforms. The unit has also several national collaborations within the framework of Clinical Research Hospital Programs, European academic collaborations, and a few other collaborations in the US (Ann Harbor, New York) and Australia (Sydney). On the industrial side, it is worth mentioning that this unit has signed a 5-year collaboration agreement with SIEMENS.

Over the past 5 years, the unit has been allocated 6 additional tenure positions, 3 by the CNRS (1 junior scientist and 2 research engineers) and 3 by the university (1 associate professor and 2 assistant professor), which demonstrates its ability to recruit young scientists. It also received 2 post-doc grants from the CNRS that were used to attract two foreign scientists from England and Japan.

- Appreciation on the management and life of the research unit

The unit appears to be very efficiently managed by the director, with the help of a deputy director, a technical director (who coordinates the technical staff), and a medical director (who coordinates interactions with the hospital). A strategic committee meets every 6 weeks to discuss all decision matters, while general assemblies of the unit happen at least three times a year. A regular unit seminar is also a place for information diffusion and scientific exchanges between unit members, while an annual lab retreat is organized outside Marseille which certainly contributes to the very good working atmosphere in this unit.

Sharing of resources (both technical and financial) is a general rule endorsed by all team leaders, although it was clear that methodologists, among whom are several engineers, would very much like to be able to work as a team rather than being dispersed among the different application teams. As for the technical staff, they indicated that they were very much involved in specific research projects, while at the same time being very comfortable and even enthusiastic in participating in common duties. Their careers appear to be properly managed and they have access to any information they might find useful. Regarding PhD students and post-docs, they appear to appreciate very much their working conditions in the unit, their interaction with their supervisors, and the unit authorship policy which allows all of them to publish as first author; indeed, several of them indicated that they would be willing to pursue their career within this research team.

The unit members are deeply involved in teaching in all domains of its scientific activities at both the graduate and PhD levels. The unit itself has the full responsibility of an Inter-university course in "Biomedical NMR". Staff members also deliver lectures in continuing education programs organized by national and international scientific societies. By means of extensive collaborations with clinical departments of La Timone Hospital, this unit plays an important role in the development of MR based clinical research. However, the committee was surprised to find that the unit seems to be less interested in getting involved in other imaging/neuroscience initiatives on La Timone campus.

- Appreciation on the scientific strategy and the project

In almost all aspects, the 5-year proposed project is a continuation of the on-going one. Most of the projects are in the direct line of on-going research activities dealing with multimodal translational MRI/MRS imaging of brain, heart and muscle pathologies. The projects that were judged most original were that of the use of Na-MR for the investigation of multiple sclerosis (team 3) and that of developing a human myocardium perfusion MRI technique (team 5). Actually, it was judged that the number of new and cutting-edge projects was quite modest considering the unit size (15 researchers) and the numerous opportunities offered by the la Timone site both in terms of other complementary imaging technologies and other competitive scientific projects.

Continuity will also apply to the unit management, the difference between the current and future organization being largely limited to the replacement of the current director by the current deputy-director. In terms of resource allocation, the new director has clearly indicated that she will apply the same policy as the one applied in previous years under the directorship of Prof Cozzone, namely the sharing of all resources obtained by all teams, their allocation being decided by the strategic committee. Such a policy has pros and cons, since it truly provides a strategic tool to start cutting-edge and not yet funded projects, but may also create in the long run tensions between teams that are more and less efficient in fund raising.

4 • Appreciation team by team

- Team 1 Heart

Team Leader Ms Monique BERNARD

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2,3	2,3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0,5	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

Considering the human potential of this team, it represents 2.8 full time equivalent researchers. The scientific production of team #1 is concentrated on 14 peer-reviewed papers in good level scientific journals: 2 papers are published in journal ranking IF above 5, and 12 papers with ranking IF below 5 (from 1.33 to 4.6). However they did not include in their specific production, several papers published by the clinical researcher who has joined this team in 2008. The personal production of this clinician would have increased significantly the scientific production of the team (2 Radiology of 2007 and 1 Radiology 2008 + 1 Invest Radiol 2008 at least) focused on the scientific topic of the team. This particular production corresponded to the one year sabbatical period by this person at UCSF.

The heart group has a wide range of projects with a general focus on diffuse or localized ischemia. Specifically novel approaches are developed for:

- Measuring flow reserve in small animals using spin labeling techniques developed by one researcher of the group (excellent)
- Measuring coronary sinus flow in humans (good, not completely novel, technically challenging)
- Quantify diffuse myocardial fibrosis in small animals (excellent)
- Quantify early changes of 31P and NO in rat hearts
- Quantifying 23Na changes in mouse hearts
- Detecting early CV disease (epidemiologic study in patients with fetal growth restriction) – started in 2009, it is an excellent study but with very little MR
- Quantifying "metabolic and contractile parameters as well as indexes of endothelial injury" in transplanted rat hearts with different cardioplegic solutions (lack of methodological detail)
- NO pathway in rat heart cardioprotection
- Aortic measurements in an aneurysmatic mouse model
- High temporal and spatial cine-MRI in mice with valve disease
- Connexin expression in mice

The research in most areas is novel and has high quality. However, there seems to be a lack of consistency between the different projects as well as lack of continuous follow-up and investment in specific areas.

The number and quality of papers is acceptable with approximately 2 papers in the core research projects per year. There is no really outstanding paper in a very high impact journal. The large number of scientific questions addressed by this group (metabolic syndrome, transplantation protection, methodological developments for myocardial blood flow assessment,) is probably one reason for the non-optimal scientific production taken, despite the high quality expertise of this team in Cardiac MRS and MRI.

There is a good track record of PhD and HDR supervisions. The number of papers relative to the number of students is relatively small.

There are good (and seemingly stable) collaborations; however, again, they do not seem to form an overarching strategic framework.

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

There was approximately 750 k€ grant income over the last 4 years.

As mentioned above, the main problem seems to be the lack of an overarching strategy. This also weakens the attractiveness of the group for national and international collaborations, recruitment, or grant success.

The team has worked out structures to agree on which projects to pursue and when to support clinical questions with methodological developments or when to move from method developments to clinical applications. However, there is no defined structure in place to moderate or streamline this process. It is highly dependent on the people working in the team.

- Appreciation on the scientific strategy and the project

This has been discussed above. In principle the team will continue the work already started and expand their activity into more human studies (i.e. obesity, diabetes, and fetal growth restriction).

There are some really novel and interesting projects e.g. spin labeling in animals, detection of CV risk and assessment of cardiac transplant. In addition there is a strong focus on spectroscopy.

- Conclusion

— Summary

This “historical team” in the laboratory has accumulated over the past years a remarkable and important expertise in small animal MRS and MRI. More recently they came into the clinical research field in particular since the acquisition by the laboratory of two whole body MR magnets (1.5 and 3T).

The merge between these two research domains is not fully complete; however they have already obtained several promising results. The suggestion of the committee to this group would be to amplify as much as science is concerned the translational aspect of their research from preclinical development to more human oriented research. This would certainly drive this group to consolidate its position among the leader teams in the field.

— Strengths and opportunities

This is a strong and viable group combining expertise in method development, pathophysiology, animal experiments and clinical applications. The recent presence of a clinical researcher in this group should help to clearly define the clinical questions, which could benefit of some translational research from the animal experiment part of the research program. This opportunity should also amplify in the future the attraction for young clinical scientist such as cardiologists, cardiovascular radiologists.

However this group will have to decide if they want to move to large clinical study validation of their methodological developments or to a more focused proof-of-concept research on limited numbers of patients. Our impression is that they are probably up to now better prepared for the second.

— Weaknesses and threats

The main weakness is the combination of a wide area of topics covered (which seem to be loosely related – if at all), the relatively small size of the group and the difficulty in prioritizing between the many options.

In addition, there are no convincing examples of method translation from animals to humans or even into clinical practice, decision-making or therapy. There is also no concept for re-validation of novel sequences in humans (or large animals), e.g. versus PET, invasive parameters or outcome. The example of coronary sinus flow as a validation tool for arterial spin labeling is not convincing as coronary sinus flow by itself cannot be regarded as a reference standard. A procedure to define reproducibility, validate in humans and then move to clinical projects would be appreciated.

The projects described for the next years to come do not strive sufficiently toward truly international excellence. There is no pathway described to obtain a number of really high-impact manuscripts within the next years.

A non-scientific threat is the new position of the team leader as the director of the whole research unit; the consequent demands on her time will have to be taken into account in deciding how many different scientific questions are to be addressed.

— Recommendations

Scientific suggestions

- Are animal models good models for age and sex differences?
- Could the synergy with other teams be strengthened? E.g. common animal models ? Common systematic method development?
- Would you profit from collaboration with other imaging modalities (e.g. echocardiography, PET, invasive methods)?

Scientific strategy

- How is the relation to Siemens for novel sequences?
- Is there a central image database?
- Are there strong collaborations with postprocessing groups?
- Think about a unifying strategy
- Define the top priorities
- Plan towards the top papers
- Define the top areas where a translation from method development to clinical application can be performed

Organization

- How will the double obligation (director and team leader clinical and basic) of Monique Bernard impact the program

- Team Muscle

Team Leader Mr David BENDAHAN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1,5	1,5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,5	1,5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	2	3

- Appreciation on the results

The team has published original research in four main areas, which we consider briefly in turn.

Technical & methodological development. Even after nearly 3 decades of 31P MRS research on muscle there is little consensus on standard exercise/recovery protocols, and individual groups must establish consistent, technically sound methods and equipment capable of enforcing standard exercise conditions and recording the required data. Over the period of this review, the team has done this to a high standard for human quadriceps, rat gastrocnemius and more recently mouse gastrocnemius. These are an important technical foundation for future work. Another useful development was of an automated segmentation method for quantifying limb composition.

Normal physiology. These include studies of human maturation, and of related subjects such as training: this is of interest in itself, and also in defining the background to current and planned studies on pathophysiology.

Clinical pathophysiology. Probably because the emphasis has been on methodological development there has no original research published in this area since 2006. However, it is a significant part of the future plans (see below).

Translational research. Under this heading there have been a series of studies in animal models on modulators of UCP3 expression (relevant to e.g. human obesity and its treatment) and on endotoxaemia; also a human study on the potential protective effects of repeated eccentric exercise (of clinical and sports physiology relevance); and finally, work on a triadin knockout mouse has not been presented yet.

The team has published 20-25 (depending on definitions) primary research papers, all in journals of a standard which marks the work as at least internationally recognized and in some cases internationally excellent. The group has developed a solid base of equipment and expertise for human and rat/mouse muscle exercise studies, which will underpin their future plans.

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

The group has longstanding internationally recognized expertise in noninvasive approaches to muscle function and metabolism. There have been a number of external research awards, including industrial support, charitable funding, and PhD training grants. There are currently two post-docs, which seems a reasonable complement, and one PhD student (one having just been awarded her degree). The team contains two part-time rheumatologists, and no doubt other clinical collaborations are negotiated in accordance with strategy and practical considerations. There are appropriate and potentially productive collaborations with sports scientists. Collaborations with mouse biologists and industry are clearly important to the research strategy; the team has been pro-active in collaboration with developers of mouse models, in particular.

- Appreciation on the scientific strategy and the project

The muscle plans divide into several areas, which we consider briefly in turn.

Technical development. These include plans to integrate NIRS & VO2 kinetics, and a systematic comparison of different muscles. As noted above this is in general a good strategy in MRS-based muscle research. It would be useful to know more about the NIRS/VO2 plans, and how, specifically, the different modalities will be combined to investigate in vivo physiology (for example in combination with modeling approaches?)

Studies of maturation. The work proposed continues existing studies, and adds some technical refinements. It would be interesting to know whether there are plans to use additional methods (e.g. NIRS) to probe other aspects of the relevant physiology.

Studies of disease. Planned studies include FSH dystrophy and acid maltase deficiency and its therapy. These are certainly topics of clinical and theoretical interest. What is proposed in FSHD is essentially a detailed characterization of the anatomical and functional heterogeneity of the disease, and the extent to which this correlates with genotype. This is interesting and of potential clinical relevance, although it needs to be clearer how this will go beyond the work of the Nijmegen group.

Studies of mouse models. These include studies of myostatin knockouts and myostatin blockade, and of a nemaline myopathy model. These exploit the team's expertise in mouse exercise in the MR scanner. The proposed work on the myostatin knockout mouse may have been overtaken, at least in part, by another group, but interesting results may well be obtained from the proposed experiments using chronic administration of a myostatin blocker. The nemaline myopathy work is also clinically relevant, translational, and interesting. It would not be surprising if the opportunity for more of this kind of work arose, and this should be encouraged and emphasized. In all this work we suggest that it will be important to exploit the team's capacity for repeated multiple non-destructive studies of mouse muscle, to explore the development of normal function and pathophysiological defects, and the time-course of possible therapeutic effects. The combination of MRS with ex vivo mitochondrial measurements will also be valuable, and we suggest this should be expanded.

Each of these sub-projects is well justified and presented in terms of context, objectives and methods. But taken together it is not clear that they fit together as a fully consistent research strategy. In particular, it should be made clearer how studies of normal muscle will help characterizing the human pathologies to be studied, and how animal work will inform studies of the human disease. Relatively little information is given on available or potential funding for these proposed project.

A non-muscle proposal is a study using high resolution MRI of cartilage in Rheumatoid arthritis before and after a biological treatment: this makes sense in terms of the clinical interests of the group, and is a clinically relevant treatment trial, but it needs to be made clear how this relates to the other projects, the specifically muscle work. Finally a possible collaboration with a US group using hyperpolarized 13C MRS to study muscle energetics with high time resolution is potentially very interesting and innovative, but only sketched out in the plan.

- Conclusion

— Summary

In summary the muscle team has published a substantial amount in the areas of technical and methodological development, normal muscle physiology and some clinically relevant animal models. A series of proposals have been made to apply both human and animal methods to new clinical situations and animal models.

— Strengths and opportunities

This team has internationally recognized expertise and reputation in 31P MRS studies of muscle. It has technical strengths in human, rat and mouse muscle MRS, and plans to integrate other modalities (NIRS, VO2 kinetics). It has some strong collaboration, although we suggest that there is greater potential for these than currently exploited. The unit is situated in a clinical setting potentially rich in clinical collaborations.

— Weaknesses and threats

Some of the technical potential has yet to be demonstrated (e.g. the integration of other modalities). Other groups have mouse exercise protocols, although perhaps not as suited to multiple measurements. There are dangers, common to all MR-based muscle research units, of doing simply incremental work, or letting methodology rather than physiological or clinical problems drive the work. Collaboration clinical and experimental, are a way to avoid this. As we suggested above, the committee feels that greater and more evident integration is needed between animal studies and human work.

— Recommendations

This group should play to its strengths, and focus on developing a connected series of animal and human studies, ideally using mouse models to develop pathophysiological hypotheses or proofs of principle of treatment or assessment which can be translated through to the clinic, both as experimental small-scale clinical research on pathophysiology or the development of MR-based surrogate outcome measures, and if possible integrated into large scale treatment trials. This will mean expanding the existing range of collaborations with developers of mouse models, and engaging more with the considerable clinical potential of the unit's location at the heart of La Timone hospital. Large-scale success in this enterprise may require, and also justify, expansion of the clinical MR facilities.

It is well known to be difficult to publish work which uses principally 31P MRS in really high impact-factor journals – this appears only to be possible for highly collaborative and/or innovative studies combining a variety of methods and addressing what are deemed to be key problems. The team has the potential to do this.

The committee's general feeling is that to develop a sustainable program of truly world-leading research the unit has to choose, among a substantial range of things it is good at, a few things it can be the best at. This applies to all the teams to some extent. For the muscle team, this will mean heavily exploiting the translational possibilities of their animal and clinical techniques and collaborative possibilities.

- Team 3 Human CNS

  Team Leader Mr Jean Philippe RANJEVA

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0,75	
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2,25	2,25
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0,1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	5	5

- Appreciation on the results

The goal of the "Human CNS" team is the development of new advanced noninvasive MR methods and their applications for a better understanding of the normal CNS organization and the identification of markers of CNS disorders that can be used in clinical practice. The team is using the full spectrum of available MRI methods (anatomy, perfusion, fMRI, DTI, MTR, MRS), and covers an extremely large panel of cognitive/clinical neuroscience themes including MS, epilepsy, spinal cord trauma, metabolic disorders, schizophrenia, development and maturation, Alzheimer disease, tumors, vegetative state, ALS, and depression. Within this vast research program, it is sometimes difficult to clearly identify what constitutes the team's core research from what is in fact a service provided to other research units or clinical departments.

Nevertheless, over the past 5 years, the team's original contributions appear to be more in the clinical application domains than in the development of new methods, and more specifically in MS and epilepsy where they have reported several original findings. In early MS for example, they have used MTR SPM to quantify both gray matter and white matter injury, and described using combined DTI-FMRI structural disconnection inside the efficient working memory network. Besides this core research on MR characterization of early MS, the team is involved in numerous multicenter clinical trials on MS. In epilepsy, they have used resting-state fMRI to show a decreased baseline functional connectivity in the epileptic zone with increased connectivity on the contralateral side. The team has also made original contributions in the domains of tumor characterization, and transitions in white matter maturation.

The team had 5 very prolific years, with 47 published articles on their core research and 55 through collaborations or participations to other projects, which gives a remarkable average of 3 articles per year and per researcher. In their core research domains, this team mainly published in good-to-medium impact imaging/neuroscience journals (JMRI, AJNR, JNNP, JAD, Magma, J Neurol, …) and sometimes in the best MR and neuroimaging journals (MRM (2), Neuroimage (3), Human Brain Mapping (1)). However, team 3 staff reaches the highest impact journals in cognitive/clinical neurosciences (Brain, Lancet Neurol, NEJM) only as co-authors of other research group publications. The team has also produced 34 articles in French journals, 32 communications in conferences, 30 chapters in books and 4 PhD theses.

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

Team 3 has become very attractive over the past years both because of the recent upgrade and extension of the clinical MR facility, but also because of the importance of clinical neuroscience research domain. Accordingly, this team has expanded and benefitted from the recruitment of 3 permanent staff on university tenure positions. The team has also attracted neurologists, psychiatrists, 3 post-docs and 7 PhD students, which makes it the largest of the 5 teams that constitute the CMRBM.

Team 3 has been extremely successful in raising funds, exhibiting 27 grants for a total of 3.25 M€. 75% of these resources are public funds obtained through competitive calls (ANR (5), PHRC (6)), while the remaining 25% are unconditional grants with pharmaceutical companies. The team exhibits a large list of partnerships, both local (with other research units and neurological departments involved in epilepsy and MS research), national (9 in methods and image processing mostly) and international (4 in London, Manheim, New York and Sousse) that cover and support the large spectrum of themes that are investigated.

Its national and international visibilities are good: in the past 5 years, team 3 staff members have received 51 invitations to give a conference including 25 in foreign countries. Several of them have been elected on boards of scientific societies (GRAMM, ISMRM, special interest groups of ESNR, MS consortia, …) or expert panels (ANR, CoNRS).

- Appreciation on the scientific strategy and the project

The global framework of the team project for the next five years remains the same, namely develop and apply MR tools to better understand/diagnose CNS pathologies in humans. Team 3 strategy clearly differs from that of other teams since all its projects will be conducted in humans, with no attempt to build a common translational research program with the other CNS team of the CRMBM (team 4, rodent models of CNS pathologies).

The spectrum of pathologies under consideration by team 3 remains very wide and is even expanded to include cataract and spinal cord injury. As a consequence, one cannot clearly capture the theoretical framework and specific hypotheses to be tested by team 3 projects, most of them being strongly data oriented.

The proposed research is a mixture of a continuation of on-going and previously funded projects, and of new and maybe more original ones. In particular, a number of new methodological tools will be tentatively developed. The team has recently produced the first human brain sodium-MR images at 3T in France. Using sodium-MRI in human neuroscience research is not an original idea per se, but it is only recently that images with sufficient SNR have been obtained. Mastering this technology is an important step that will give this team an opportunity to look at sodium accumulation in brain tissues in MS, but also in other disorders such as epilepsy, AD and tumors. Another interesting methodological development is that of diffusion tensor MR spectroscopic imaging of N-acetyl-aspartate, which if successful, could open up cutting edge research in the pathophysiology of MS. The development of human spinal cord perfusion imaging and spectroscopy is a third interesting project of the proposed methodological research, and constitutes one example of the kind of translational methodological research that this laboratory can achieve. The other proposed methodological developments (integration of EEG and fMRI, graph analysis, DTI and computational models, spinal cord MRI and finite element analysis) are certainly of potential interest, but seem to be more applications of methods developed by other research units than genuine methodological contributions by team 3 members.

As for clinical research applications of MR, the project is segmented according to pathologies, the most interesting and original being:

- the early prediction of patient deficit (using voxel-based MTR), and identification of their cognitive impairment (rs-FMRI) in MS,
- the study of altered brain connectivity in partial epilepsy (combined FMRI-EEG, DTI, graph analysis)
- the exhaustive exploration of human spinal cord: using perfusion imaging and spectroscopy

- Conclusion :

— Summary

The Human CNS team gathers several researchers having highly recognized expertise in human brain MRI. Its scientific strategy is to implement and apply state-of-the-art MR technologies to study a variety of human brain disorders, searching for potential diagnostic and or therapeutic markers. This team is highly productive, efficient at fund raising but needs to focus its research to reach the excellence level.

— Strengths and opportunities

This team has full and free access to an up-to-date clinical MR facility, including a 3T magnet on which methodological developments down to the hardware level are possible. Through its multiple partnerships with local clinical neuroscience research units and departments, the team has access to patients who can be extremely well characterized and followed over time. Within the CMRBM, the presence of another team with recognized expertise and skills in animal models of brain pathologies is an opportunity for building true translational research in the domain of expertise of team 3. Locally, the existence of a very rich fundamental, experimental, clinical and computational neuroscience community located in the Marseille area is a rare opportunity for a team that has the ambition to be a leader in this domain. Another local opportunity to be seized is the opening of the CEREDIM, a research imaging centre that will give access to complementary imaging technologies.

— Weaknesses and threats

Team 3 is deeply involved in the operation of the clinical MR platform (CEMEREM), providing numerous imaging services to clinical/industrial researchers at the price of co-authorship or funds. This fee-for-service strategy may pay off in terms of number of publications and/or funding, but it considerably blurs the team scientific identification, may inhibit large-scale development of cutting edge scientific projects and/or collaborations, and will likely prevent the team performing to its full potential. In a somewhat related manner, the team seems not to be interested in establishing strong partnerships with the other local imaging and neuroscience institutions, at the risk of being left aside in the future in a domain where it should on the contrary adopt a high profile considering their expertise.

— Recommendations

Team 3 should clearly identify what are the very few topics of their core research in which they want to publish at the highest level, and organize the clinical MR platform activity in such a way that they can save time for their core research rather than being involved in a multitude of research areas.

The team should also open scientific discussions with the head of the other CNS team (team 4) with the goal of building a common line of translational research projects in a domain of common expertise such as for example MS. In the medium term, it seems highly desirable that the two CNS teams fuse together as a single one.

This team should also consider including other imaging technologies as potential tools of interest for solving scientific clinical or fundamental neuroscience issues. In particular, the proximity of the CEREDIM should be the opportunity to access to molecular methods complementary to MR approaches.

Finally, this team of great potential should also be careful at not being left out of the major neuroscience federation under construction in Marseille, as it has much to share with other neuroscientists without losing its strong links with the MR community.

- Team 4 Magnetic Resonance of rodent models of brain pathologies

  Team Leader Ms Angela VIOLA

  - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1,5	1,5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	?
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,5	1,5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	2	2

  - Appreciation on the results

This rather small team headed by a biochemist with important expertise in animal pathophysiology uses high quality multiparametric MRI/MRS approaches to investigate a number of selected brain pathologies on specific murine models comprising genetically modified mice. The association of complementary (structural, functional, metabolic) parameters measured by optimized MRI/MRS methods to characterize non-invasively and longitudinally brain pathologies with high public health impact (multiple sclerosis, malaria, stroke, alcoholism,…) makes these studies original. They are of interest for the MRI/MRS community (demonstration of combined approaches and of the potential of multiparametric imaging biomarkers for pathology characterization) as well as for researchers working on the different brain pathologies (new information and description of early non-invasively assessed markers of pathology). In addition MRI/MRS markers are used for longitudinal therapy follow-up of new drug candidates which is one of the important recognized roles for preclinical MRI/MRS tools increasingly integrated into drug development protocols.

So far, results have been published during 2006-2007 (5 papers as major contribution) in journals with average to high impact factors, including a therapeutic study on a classical multiple sclerosis model (EAE) described in Ann. Neurol 2006, and an original metabolic profiling of a specific malaria model resistant to cerebral malaria described in J. Biol. Chem. 2007. Among presentations at other mainly national meetings, the results of the team were presented extensively at the annual meeting of the ISMRM (International Society for Magnetic Resonance in Medicine, the reference MRI/MRS meeting) in Berlin 2007 (5 contributions) and at a quadrennial national meeting of CNRS section 30 in Nice 2008 (7 contributions). The team leader has also co-authored, again during 2006-2007, 6 papers, plus 1 paper in 2010 (first author) concerning MRI/MRS descriptions of brain maturation and fetal brain pathology in journals with IF<3.5 (as a part-time member of Team 3). Nevertheless it has to be noted that, at the time of writing this report, no other major contribution paper has been published after 2007, with 3 papers being currently submitted (without information available on the review process) on MS, cerebral ischemia), and cerebral malaria. This lack of scientific output over a couple of years, which necessarily has negative impact on the visibility of the team, was explained by problems with animal housing in the central animal housing facility (now solved), interfering with establishment of specific animal models (e.g. malaria model). As a consequence a dedicated animal housing facility had to be set up for the research unit. This task was carried out by the team leader herself.

During the time period covered by the report (2006-2010), 1 PhD thesis was defended in 2008, 1 thesis is currently under way (start 10/2008).

It has to be noted that this team is the only preclinical team individualized in the unit, whereas for heart and muscle research animal and human studies are carried out within the same team streamlining translational research. Research work is carried out in tight partnership with Team 5 (methods research) ensuring high quality and evolution of the used MRI/MRS methodology. Collaborative work with external partners is essentially project-oriented and partnerships seem to be active over a limited time.

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

Invited lectures (about 8) were given essentially at national conferences during 2006-2008 with 2 invited teaching lectures at a European ESMRMB workshop organized by the unit in Marseille (2008). One post-doc from abroad is currently in the team working on cerebral malaria since 12/2008 (CNRS fellow-ship). The most significant competitive funding is an ANR BiotecS grant (204k€, 2009-2011) obtained for a collaborative project with a Marseille-based industrial partner (Trophos SA) and concerning evaluation of a new drug candidate for MS. This work has recently (11/2010) resulted in an official press release by Trophos SA concerning novel compounds to promote axon repair and remyelination in multiple sclerosis. Academic collaborations are mainly national and local; one collaboration has been established with the University of Sydney concerning cerebral malaria (J. Biol. Chem. paper in 2007), but this collaboration is no longer mentioned in the project description.

Overall, the impact and attractiveness of the team are currently mostly national with efficient and stable links to local partners.

- Appreciation on the scientific strategy and the project

The project of team 4 builds upon the results and expertise acquired during the past years concerning the different brain pathologies studied in various murine models. Research is planned to be continued on its core topics (multiple sclerosis, alcoholism, experimental cerebral malaria) questioning pathology mechanisms and therapeutic aspects via multiparametric approaches combining in vivo MRI/MRS, anatomopathology and, more recently, molecular biology. This multimodal strategy investigating pathology mechanisms at the cellular level and in vivo is very pertinent and promising, and should lead to original results and new information.

More precisely the team plans to continue work in three main fields: 1. Evaluation of new therapeutic approaches in different murine models of multiple sclerosis; 2. Cerebral effects of alcohol: role of scyllo-inositol; effect of antenatal exposure to alcohol 3. Experimental cerebral malaria (ECM): early markers, mechanisms, new therapeutic approaches.

The different projects are well motivated with respect to current literature and can be expected to generate original results extending current knowledge. Except the ECM project, scientific programs are to be carried out in tight collaboration with members of Team 5 (MR methods) and the technical support staff. It has to be noted that these unit members are also largely involved in clinical and preclinical developments for the other teams. Absence of details on FTE percentage gives little visibility on effectively available manpower for the projects. Several methodological developments are indeed related to part of the projects (implementations of the MEMRI approach, high speed CSI, optimization of MRI/MRS techniques for mouse neonates). Taking into account the current team members including temporal staff, human resources are evenly attributed to the projects already under way. However there is little visibility for future resources, human and financial, beyond 2011 (currently one grant application submitted to ANR "Blanc" concerning MS). The "alcoholism" program involves mostly permanent staff (Teams 4 and 5) and should therefore have a good chance of advancing at a good pace, but it is currently only modestly funded by the IREB.

Nevertheless, according to the unit director, consolidated global funding for the unit currently covers all expenses till 2013, given the sharing of all financial resources.

In this context, one may argue that with the currently submitted scientific papers being accepted the team will improve its position to raise new funds specific to its projects.

Whereas the described projects have potential for clinical translation, there is surprisingly little explicit relationship with the projects of team 3 "Human CNS". The team leader has contributed to a clinical project on brain maturation but this project does not seem to be a priority any more. It would probably be useful to prioritize and/or set up projects in view of translational collaborative research involving Teams 3 and 4. This would also better fit within the general strategy of the research unit.

- Conclusion :

— Summary

Team 4 is a single tenured researcher group dedicated to preclinical multiparametric MRI/MRS studies, combined with histology and molecular biology analysis. The team is individualized with respect to the "Human CNS" team 3 of the research unit. The team develops (or sets up) and investigates murine models of brain pathologies with high public health impact (e.g. MS, malaria, alcoholism). High quality and evolution of MRI/MRS methodology is ensured by tight collaboration with team 5.

— Strengths and opportunities

- Team 4 has important expertise in using modern non-invasive multiparametric preclinical MRI/MRS strategies (anatomical, functional, metabolic) and their association with histology and molecular biology analytical tools. This expertise is intended to be extended (additional MRI methods, optimization of information/time ratio of current protocols) and should open up opportunities for new partnerships with research groups in the fields of brain pathologies.
- Team 4 has important expertise in generating and handling murine animal models for brain pathologies.

— Weaknesses and threats

- Permanent staff of team 4 dedicated to core projects (1 researcher (team leader), 1 engineer (molecular biology)) is small with respect to the number of projects, and visibility for future evolution of permanent and non-permanent staff is currently poor.
- There is currently little visibility for team-specific funding beyond 2011
- Attractiveness of the team is currently essentially local and national
- There has been a decrease of scientific output between 2008-2010, which can be explained by infrastructure issues, and which should be temporary, but which should also negatively impact the teams' chances to successfully apply for grants in the near future.
- There are only few direct connections between projects of team 4 and team 3 (Human CNS).

— Recommendations

It may be anticipated that, given the small size of the group, there will be need to prioritize the described projects, based on criteria ensuring (i) increase of international visibility (by definition of a main scientific niche), and (ii) focus on preclinical-clinical translation within the research unit. This would probably ensure more continuous scientific output (even though it is known that work with complex animal models is particularly prone to a number of unpredictable setbacks which may slow down progress of research).

Due to the planned evolution of preclinical MRI methodology specific to the teams' projects, it should be useful to hire an engineer exclusively dedicated to these developments, nevertheless being under direction of team 5 members (e.g. integration into future grant applications of team 4).

- Team 5 MR Methods Research

Team leader Mr Frank KOBER

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	0	1

- Appreciation on the results

The main methodological developments achieved from 2006 to 2010 have consisted in developing/optimizing acquisition procedures for perfusion and diffusion MRI of the CNS. The originality of this work is evidenced by its excellent scientific visibility. Six articles have been published by team 5 on this topic, presenting the original results achieved by the team. These developments and results - especially acquisition time reduction with EPI encoding - open new perspectives for non-invasive longitudinal in vivo small animal studies. Appropriate partnership with physicians will allow translation to human studies.

The team has made two other notable developments in the field of data processing:

- in the field of spectroscopic imaging processing, an algorithm for CSI post-processing (CSIAPO) has been patented by team 5;
- In the field of "conventional" image processing, numerous contributions have been brought by team 5 to the analysis of MRI data collected by the other teams. However these contributions have not leaded to significant scientific output: team 5 reports only one published article in the field of image processing. This may be partly explained by the fact that a key recruitment was only recently made (2007).

The number of publication by team 5 on its core expertise is rather low in 2007 but the last 3 years have been extremely productive, which demonstrates a positive and encouraging trend.

The research activity relies on appropriate local partnerships complementing the imaging expertise of the team (Institut des sciences du movement, service d'anatomo-pathologie).

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

Up to now the scientific visibility of team 5 mostly relies on the high visibility of the team leader (conference chair activities, editorial activity, invited lectures and teaching).

A striking feature of team 5 is the lack of PhD students and the limited number of postdocs (just 1) from 2006 to 2010. This questions the team position in the delicate research/support balance. However 2 PhD students have been recruited recently, showing a positive evolution.

The ability to raise funds by the 2 permanent researchers must be noted: they are PI of significant ANR grants obtained in 2008 and 2009. These 2 grants have been driving the research activity of the team as shown by the fact that most articles published by the team report results related to these research programs (QASAREM and TRAUMATISM).

Industrial partnership of the team includes a research agreement recently contracted with Siemens France. Academic partnership includes collaboration with Univ. of Lyon, Oxford and Miami, although the list of publication of team 5 does not include co-authors from these universities.

- ## Appreciation on the scientific strategy and the project

The project presented by team 5 includes the following topics:

- Development of accelerated CSI methods
- Improvement of spectroscopic quantification
- Transfer of perfusion methods (ASL) to the human heart and muscle
- Transfer of spinal cord imaging methods to humans
- Development of multi-atlas based segmentation

The proposed CSI project (combination of ultra-fast imaging and parallel imaging techniques) is definitely challenging and cutting-edge. It relies on top-level academic and industrial collaboration. This project will make it possible for team 5 to further develop its established expertise in CSI.

The transfer of heart, muscle and spinal cord imaging methods to humans are the "natural" continuations of the original and productive projects QASAREM and TRAUMATISM. One of the major strength of this project is its translational aspect. Major validated developments (on rodent models) will be transferred to humans. This translational aspect is challenging but the experience of the team, the availability of source code (on the 1.5T and 3T clinical scanners) and a collaboration contract between Siemens and CNRS will be a guarantee of success. However the PI should bring more detail on their exact methodological contribution, given the fact that diffusion and perfusion methods (including ASL) become more and more routinely available on clinical scanners.

The "image processing" part of the project (development of multi-atlas based segmentation) is made of only 5 general sentences. This questions the ability to maintain competitive research activity in image processing within team 5.

Most projects rely on identified financial resources: ASL and spinal cord projects will be supported by the QASAREM and the TRAUMATISM grants; CSI developments will be partly supported by Siemens France (CIFRE grant); resources for developments in image segmentation are not mentioned.

- ## Conclusion

— Summary

The MR methods team has unique strengths and expertise in the development of MR imaging and spectroscopy. The translational aspect, from mice to human is a specific strength that very few laboratories can match. For example, the team has developed EPI arterial spin labeling methods on small animal and the implementation of this method to the human heart is ongoing.

— Strengths and opportunities

- Team 5 has an outstanding expertise for validating and developing both MR imaging and spectroscopy methodologies, which is rare among similar French labs.

- The research strategy presented by the team leader is clearly established and well focused. It is centered on 2 major topics: perfusion imaging and spectroscopic imaging.

- Team 5 is spreading out a real "methodological culture" in all teams of the unit. For example, the research agreement with Siemens makes it possible for team 3 members to access source code and develop original methods adapted to brain pathology like diffusion spectroscopy.

- Team 5 has taken advantage of the installation of human scanners to establish a research agreement contract with Siemens, giving access to source code and to PhD students for the team. This opens great methodological perspectives.

- Team 5 has established local and international collaborations and plays a central role in the unit.

— Weaknesses and threats

- The number of PhD students in team 5 is low (in spite of 2 recently opened positions).

- The contribution of team 5 members to the technical support group might limit the intrinsic research activity of team 5. In the future, this weakness might be still enhanced with the purchase of two new very high-field MR systems.

- The "image processing" activity is not developed enough to present convincing research results and projects.

— Recommendations

- Team 5 members should be strongly encouraged to achieve "HDR" graduation and to recruit PhD students.

- The installation of new high field MR systems (preclinical and clinical) will require a significant increase in human resources for team 5.

- The "image processing" activity should be strengthened or redefined: research activity in this field can hardly rely on a unique (although highly valuable) person.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
CRMBM - CENTRE DE RÉSONANCE MAGNÉTIQUE, BIOLOGIQUE ET MÉDICALE.	**A**	**A**	**A**	**B**	**A**
MUSCLE [BERNARD-BENDAHAN]	A	A	Non noté	B	A
HEART [BERNARD-BERNARD]	A	B	Non noté	B	A
MR METHODS RESEARCH [BERNARD-KOBER]	A	A	Non noté	A+	A
HUMAN CNS [BERNARD-RANJEVA]	A	A	Non noté	B	A
MAGNETIC RESONANCE OF RODENT MODELS OF BRAIN PATHOLOGIES [BERNARD-VIOLA]	B	B	Non noté	B	B

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Objet : Réponse au rapport d'évaluation - **S2UR120001628 - CRMBM - Centre de résonance Magnétique, Biologique et Médicale. - 0131843H** - de l'unité CRMBM - Centre de résonance Magnétique, Biologique et Médicale

Observations d'Aix-Marseille Université

Université de la Méditerranée believes that several sections of this AERES report are confusing or inaccurate and do not reflect the exact situation. It does not take into account adequately many of the answers, explanations and clarifications which were given and discussed by CRMBM scientists during the site visit. In addition the AERES report surprisingly brings up new questions and interrogations from experts which were not asked or brought up during the site visit.

CRMBM is by no means embarked in a strategy of isolation. It is not *"isolated from the ongoing local federating initiatives"*. The repeated assertions (at least 6 times) made in the AERES report relative to *" the lack of strategic plans on how to interact in the future with major local players"* and *'the poor interest and perspectives'* of the CRMBM teams in the future projects taking place on the Timone campus, CERIMED (Centre Européen de Recherche en Imagerie Médicale) and INT (Institut des Neurosciences de la Timone) is unfounded. All CRMBM teams considered CERIMED as an interesting opportunity for their future research activities considering that it will offer new imaging modalities (PET, optical imaging...) to explore animal models and humans, in perfect complement to multimodal MR techniques already available at CRMBM. Common projects have already been discussed. Similarly, INT and the Brain Dynamic Institute (BDI) are recognized by CRMBM as clear opportunities to strengthen existing collaborations with high level neuroscientists and to build new ones. As a matter-of-fact, CRMBM has established for many years many collaborations with the scientific and medical "neuro" communities in Marseille. There are existing and future projects with teams which will be moving soon to the INT facilities (e.g. ongoing Pharmacog project with O. Blin, EC-IMI grant, see CRMBM report team 3), and existing and future collaborations with key teams from the BDI (*e.g.* common post-doc just hired on the epilepsy project between CRMBM team 3 and P. Chauvel and V. Jirsa at BDI).

CRMBM is not foreign to*"the restructuring of the research system which is happening at both the national and local levels"* but, on the contrary, is a major actor of the national reflexion in the field of multimodal *in vivo* imaging and more widely of bioengineering *(e.g.* P. Cozzone has presided over the committee of experts who prepared the CNRS prospective report on

Jardin du Pharo . 58 Boulevard Charles Livon . 13284 Marseille cedex 07 . France
Tél. : +33 (0)4 91 39 65 00 . Fax : +33 (0)4 91 31 31 36 . www.univmed.fr

these topics in 2009). CRMBM is heavily involved in many existing national and international initiatives and networks (it leads some of them) which are critical for maintaining its competitiveness and ensuring its development, as well as promoting actions reinforcing the recognition and the organisation of the local and French MR communities on the European and international scenes (cf. role of CRMBM members in ESMRMB, IUPAB, ISMRM, Eurobioimaging, CNRS Committees, Co-CNRS, INSERM, ANR, AERES, the NMRInet project of 'Investissements d'avenir" etc.).

SPECIFIC COMMENTS ON SECTIONS 2 and 3

The transition between the founder director and a newer generation of leadership has been carefully planned and successfully implemented over the years, in total agreement and transparency among the current director, the strategic council of CRMBM, CNRS, the University and, for some aspects, the Hospital. CRMBM is in an active phase of evolution ; it has just completed (2008) a major ambitious expansion thrust with the building of a new facility (1000 m^2 expansion of CEMEREM on the hospital site of the Unit) and the purchase of 2 state-of-the-art whole-body MR scanners, for a total cost of 6.5 M€. This operation is rather unique in the country and rare in the world.

In the "Appreciation on the scientific strategy and the project", page 8, the AERES Committee suggests that the policy of sharing resources among research teams may create in the long run tension between teams (*"such a policy has pros and cons... it might create in the long run tensions..."*). This question was also raised by the AERES Committee during the discussion with the team leaders. All team leaders and principal investigators at CRMBM have been adhering to that policy for 25 years. CRMBM has then a "long-run" experience in sharing financial resources for common objectives, demonstrating the viability of this system at CRMBM which operates as a cohesive Research Unit and not as a "Hotel à Projets".

CRMBM interface with the hospital is a major strength and achievement of UMR 6612 (CRMBM-CEMEREM). It is recognized in the "Strengths and Opportunities section of the AERES report (page 5). But the experts wrongfully seem to consider that the partnership with the hospital mostly involve *"services the two platforms provide to the La Timone hospital clinical departments"*. As a matter of fact, "services" constitute a minor part of this long-time established partnership. This exemplary situation involves training of young clinicians (preparation of master degrees, PhD etc.), teaching and continuing education, transfer of know-how to the clinical imaging facilities with an immediate benefit for patients (e.g. imaging of acute stroke, MR exploration in utero ...), joint application and management of competitive clinical research protocols (e.g. PHRC)... Several prominent clinicians are embedded in CRMBM-CEMEREM where they have been conducting their research activities for many years.

Fee-for-service for the hospital and the industry is not a dominant activity in the Unit and not a potential weakness considering the very favorable cost/benefit situation (*"this has lead to a considerable development of service-like activities and puts a heavy routine workload on both technical and research staff"*). On the CRMBM site, the analysis of muscle biopsies (contracture tests) and the MR characterization of biological fluids are conducted by trained

hospital technicians. There is no additional burden on CNRS or university personnel. On the CEMEREM site, fee-for-service activities (mostly international clinical trials with big pharmas) are limited to 3 periods per week out of 24 available (one period = half a day) on our 2 whole body MR scanners. They are essentially managed by a contractual engineer, paid out of industrial contracts.

In their report, the AERES Committee members state in page 5 that *"a potential threat of this diversification is a progressive lack of coherence between team research activities, such as for example the noticeable discrepancy between pathologies for which rodent models are currently developed and pathologies investigated in humans".*
The animal models developed at CRMBM are directly related to the human studies performed in the Unit (heart, brain, muscle), except for malaria. The purpose of the studies conducted on animal models is to go beyond the MRI/MRS characterization of the disease that has been obtained on patients. They often require optimizing or creating accurate murine models of human pathologies, which is a heavy task *per se*. The development of a mouse model to document the cerebral toxicity of *scyllo*-inositol found to accumulate in the brain of chronic alcoholics is a good example of this interplay and cross-fertilization between human and animal research at CRMBM (IREB grant). Another example is the successful on-going translation from mice to humans of MR methods developed for the characterization of spinal cord (ANR contract). The main objectives pursued in animal studies are (i) to achieve detailed characterization of pathogenesis, (ii) to search for new diagnostic/prognostic markers, (iii) to identify potential therapeutic targets, and (iv) to ultimately evaluate new therapeutic strategies. The study of pathogenesis often involves the generation of new mechanistic knowledge, which requires time and a lot of biology, conducted in-house and through selected collaborations (e.g; IBDML, Institut de Biologie du Développement de Marseille Luminy for the EAE and multiple sclerosis project).

TEAM 1, HEART TEAM

The general strategy of the team is well-existing with a focus on "microcirculation alterations and energetic metabolism defects in pathologies with diffuse ischemia, mainly diabetes and transplantation". The track record of the team over the years shows undoubtedly a continuum in these main topics of interest: the Heart team has been working for 30 years on cardiac preservation during transplantation and for 20 years on diabetes.
The team has a number of established long-term collaborations at the local, national and international levels. In particular it has several significant and active international collaborations: Laboratory of Physiology, Physiology Department, Oxford- UK (Prof Kieran Clarke), Centre for Clinical Magnetic Resonance Research, University of Oxford, UK (Prof Stefan Neubauer), Center for Arrhythmia Research, University of Michigan, Ann Arbor, USA (Prof J Jalife), Heart Research Center Oregon Health and Science University, Portland, USA (Dr DJP Barker, Dr KL Thornburg), Developmental Origins of Health and Disease Division, University of Southampton, UK (Dr C Osmond), Danone Institute International. The Heart team is part of an international network of excellence in cardiac MR research which includes University of Oxford, Charité Berlin, Harvard Medical School, University of Calgary. This network is currently filing a large international grant application.

TEAM 2, MUSCLE TEAM

Part of the Committee recommendations is to develop collaborations with developers of "mouse models" and with clinicians from our University Hospital. This is actually what the Muscle team has been doing for the last 20 years (first collaborative paper with clinicians published in 1991 in 'Neurology"!). The team will keep with the research strategy and priority at both preclinical and clinical levels for sound physiologically-driven projects, and not methodology-driven. The complexity of biological phenomena has to be tackled through appropriate multimodal approaches. Such a strategy has been chosen and implemented since the inception of research on muscle metabolism at CRMBM and on that basis the Muscle team has reached international recognition with *"things they are good at and things they are best at"*.

TEAM 3, HUMAN CNS TEAM

A major point is relative to some of the reservations and comments in the AERES report upon the scientific strategy of team 3. In the oral presentation, 3 unifying scientific objectives (of obvious clinical interest in a deliberate translational approach) were explained to justify the human CNS team research strategy across neuropathologies. The objective is indeed to augment knowledge of (i) neurodegeneration and neuro-axonal suffering through development of new non invasive biomarkers (sodium imaging, DTI MR spectroscopy, and MTR statistical maps), (ii) brain plasticity at the structural and functional level in models of focal, system and global CNS injury and (iii) spinal cord injury.

TEAM 4, RODENT MODELS OF BRAIN PATHOLOGIES TEAM

In their report, the Committee members state that *"team 3 strategy clearly differs from that of other teams since all its projects will be conducted on humans, with no attempt to build a common research projects with other CNS team of the CRMBM (team 4 rodent models of CNS pathologies)"*. Further, on p 19, one can read on Team 4: *"Whereas the described projects have potential for clinical translation, there is surprisingly little explicit relationship with the projects of team 3 "Human CNS"*. This is not the exact situation: (i) Angèle Viola (head of team 4) is also an active member of team 3 where she runs with Nadine Girard the research project on brain maturation, (ii) except for cerebral malaria, all the research projects developed in team 4 are directly connected or derived from human studies conducted in the Research Unit (mostly Team 3, e.g. animal models of multiple sclerosis, of stroke, of alcoholism, of arrested brain). The common strategy on MS already exists with both teams working on this pathology and generating complementary information on currently available treatments and promising future therapeutic strategies.

The Committee also mentions that: *« the team leader has contributed to a clinical project on brain maturation but this project does not seem to be a priority any more »*. This allegation is untrue. Angèle Viola still takes part to the human project (one paper has been accepted for publication in 2011, in the *AJNR American Journal of Neuroradiology* with Angèle Viola first

author). In addition, team 4 has obtained the first characterization of a model of arrested brain development through a collaborative work with Laurent Villard (2 papers published, one in *PloS one* in 2007). One the projects presented by team 4 is focused on the development of a model of fetal alcohol syndrome, which is a leading cause of abnormal brain development. This study also involves the assessment of normal fetal brain maturation.

TEAM 5, METHODOLOGY TEAM

The 5-year Master Research Agreement between Siemens and CRMBM has many facets pertaining to all activities at CRMBM with selected priorities. Some methodological aspects are understandably handled by team 5, others, on the application side, are developed by other teams (e.g. team 3).

In the AERES report, the statement *"It was clear that methodologists, among whom are several engineers, would very much like to be able to work as a team rather than being dispersed among the different application teams"* constitutes an extrapolation and a misunderstanding of what had been presented. The Methodology team is currently reinforced (one post doc fellow on an ANR contract, 1 PhD student on CIFRE contract), to widen its asset and notably in preparation of the advent of the possible additional ultrahigh field MR equipment. However the people involved (scientists and research engineers) have confirmed that they particularly appreciate the current arrangement which let them conduct methodology projects (within team 5) as well as being integrated in application projects with other teams, as needed.

En accord avec les deux autres établissements d'Aix-Marseille

Le Président
de l'Université de la Méditerranée

Yvon BERLAND

Le Vice-président du Conseil Scientifique
de l'Université de la Méditerranée

Pierre CHIAPPETTA