# INMED - Institut de neurobiologie de la Méditerranée

Rapport Hcéres

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

Section des Unités de recherche

# AERES report on the research unit

## Institut de Neurobiologie de la Méditerranée

# From the

## Université Aix-Marseille 2

February 2011

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Le Président de l'AERES

**Didier Houssin**

Section des unités de recherche

*Le Directeur*

**Pierre Glorieux**

February 2011

# Research Unit

Name of the research unit: Institut de Neurobiologie de la Méditérannée

Requested label : UMR_S INSERM

N° in the case of renewal : UMR_S_901

Name of the director: Mr. Alfonso REPRESA

# Members of the review committee

## Committee chairman:

Mr. Pascal LEGENDRE, Université Pierre et Marie Curie, France

## Other committee members

Mr. Serge CHARPAK, Université Paris Descartes, France

Mrs. Isabelle DUSART, Université Pierre et Marie Curie, France, CNU representative

Mr. Urs GERBER, Brain Research Institute, University of Zurich, Switzerland

Mr. John G JEFFERYS, University of Birmingham, UK

Mr. Florian LESAGE, University of Nice, France, INSERM CSS Representative

Mr. Christian LÜSCHER, Medical Faculty, University of Geneva, Switzerland

Mr. John PARNAVELAS, University College London, UK

Mr. Dietmar SCHMITZ, University of Medicine, Neuroscience Research Center, Berlin, Germany

# Observers

## AERES scientific advisor:

Mrs. Thérèse JAY

## University, School and Research Organization representatives

Mr. Pierre CHIAPPETTA, Université Aix-Marseille 2

Mrs. Catherine LABBÉ-JULLIE, INSERM

# Report

## 1 • Introduction

- Date and execution of the visit : February 10-11th 2011

The site visit took place on February 10th and 11th 2011. It started by a general presentation by the head of INMED Alfonso Represa and a presentation by each leader of the 11 teams over the two days. Each presentation was followed by a discussion with the committee members and after each discussion, the committee members had a 10 min door-closed meeting . Next, the committee members spoke consecutively with the researchers, the students and postdoc currently present in the laboratory and, with the technical and administrative personel. A discussion also took place with the representatives of the University of Aix-Marseille2 and INSERM. The last part of the second day was reserved for a closed meeting of the committee during which the first conclusions of the visit were formulated.

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

INMED is located in Luminy campus at Marseille. This Institute was created in 1989 by Dr Ben Ari and belongs both to INSERM and Université de la Méditérranée. Its main field of research is the study of the development of local neuronal networks of the brain both in physiological and pathological conditions (Epilepsy, Prader-Willy syndrom etc.).

In 2006 this institute was composed of 8 teams. It grew up to 12 teams from 2006 to 2009 with the arrival of new teams either isolated or associated, (team Prader-Willy syndrome; team Genetics of Epilepsies, team Pathophysiology of synaptic plasticity and the FRM team; Maturation of GABAergic microcircuits).

In 2009 Mr. Represa replaced Mr. Ben Ari at the head of INMED. Y Ben Ari is still in the Laboratory as a team manager (Team Developmental sequence, Infantile Epilepsies and Neurological disorders).

In the future (2011-2015) this Institute will be composed of 11 teams. This is due to the departure of two teams (including one team AVENIR) and the fusion of two teams. In addition, one of the AVENIR team (Maturation and plasticity of cortical maps) is proposed to become a full INMED team.

- Management team

The new management strategy of the laboratory comprises a scientific council involved in the strategic evolution of the lab (recruitment of new teams, new scientists, development of new platform etc.) and a laboratory council with elected and nominated representatives for helping the direction in research orientation, research of grants, technology transfers, budget management, as well as improving working conditions within the lab (Human resources management, formation and training).

- 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) | 4 | 5 |
| N2: Number of full time researchers from research organizations (Form 2.3 of the application file) | 28 | 26 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 30 | 15 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 18 | 16.4 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 14 | 11 |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 25 | |
| N7: Number of staff members with a HDR or a similar grade | 21 | 20 |

## 2 • Overall appreciation on the research unit

- Summary

The change in the directorship represented a challenging transition, which has, however, been very successful.

INMED made substantial efforts during the past 2 years to increase the strength and the independency of the scientific teams. The past 4 years INMED teams made highly original scientific contributions to their fields of research. The production is very good with more than 100 papers over 4 years, some of them published in the best journals (Science, Nature neuroscience, Neuron etc). The number of grants obtained by the different teams is impressive.

The global project is original and the interactions with clinicians and geneticists will allow this institute to continue performing high quality research. The feasibility of the global project is strengthened by the arrival of many young scientists and new teams, the development of highly efficient new technical platforms and the combination of classical and innovative technologies as for example fast calcium imaging and in vivo patch clamp recordings.

A senior scientist created an original teaching program ("tous chercheurs") to promote scientific research and to initiate High school and college students to experimental procedures. In addition this teaching program allows diffusing scientific knowledge to associations of patients.

- Strengths and opportunities

This laboratory has an excellent level of publication and a very good international recognition.

It is one of the best laboratories of electrophysiology in Europe. The teams developed new techniques and new animal models and they attracted many international Post docs.

They recently developed projects using human tissues. Accordingly the laboratory increased its interactions with clinicians.

The arrival of new teams that will develop research area related to pathology, epigenetic and environment strengthen the general project.

There are strong interactions between the different teams which strengthen the quality of the research project.

Most of the teams have a very good level of funding from external sources. They have stable collaborations with foreign partners.

Overall the general project is strongly supported by the University as exemplified by obtaining a « Chaire d'excellence » and by INSERM as exemplified by the number of researcher positions.

The creation of an original teaching program ("tous chercheurs") makes this laboratory an example for teaching the scientific knowledge to non-specialist and to High school students. The teaching strategies have an international recognition as exemplified by a recent publication in PLOSbiol.

- Weaknesses and threats

Some small groups perform too much collaboration that are out of the scope of their research area, which can be detrimental for their own projects.

The quality and the efficacy of the animal facilities are poor.

The administrative staff is not enough; therefore too many administrative responsibilities and tasks are devolved to the team leaders, which could decrease their efficacy in making research.

- Recommendations

The comity strongly encourages the director and the different members to continue on the same way, developing high impact scientific projects in a studious and friendly atmosphere.

The Institute should be helped to improve the animal facilities on the "Luminy site".

A general recommendation to alleviate administrative work, which pertains to the whole institute, is to create a position for an administrative assistant with a research background, and qualified to coordinate and help with the submission of grants and with other scientific bureaucratic responsibilities.

- Production results

The laboratory has an excellent scientific production. Since 2006 this laboratory has published 128 per reviewed papers some of them being published in high ranked journal (Science, Neuron, Nature Neuroscience, PNAS, TNS, J Neurosci. Etc)

| | |
|---|---|
| A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research | 5 |
| A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research | 26 |
| 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 (Form 2.10 of the application file) | 5 |
| A5: Number of PhD granted during the past 4 years (Form 2.9 of the application file) | 15 |

# 3 • Specific comments

- Appreciation on the results

The past 4 years INMED teams made highly original scientific works that contribute to a better understanding of the development of the local neuronal networks and the determination of the impact of altered developmental processes on the functional properties of adult networks that translate into pathologies such as epilepsies and mental retardations.

By using innovative techniques and preparations, as for example high resolution bi photon imaging, isolated hippocampus preparation and in vivo recordings, they described a new step in the maturation of hippocampal and neocortical network activity involving intrinsically oscillating correlated neuronal assembly before the emergence of synaptically driven activity.

They showed that kainate receptors are selectively involved in the genesis of the theta activity in O-LM neurons.

They found that shortly before offspring delivery, GABA become transitory inhibitory in the embryo in response to maternal oxytocin release, thus preventing anoxic episode damages during delivery.

They found that developing hippocampal networks follow a scale-free topology, and they discovered a subtype of immature interneurons possessing widespread axonal arborisations that regulate the entire dynamic of the network.

Using an animal model of mental retardation related to double cortin mutations, they found that migration disorders produce alterations not only on neurons that fail to migrate but also in their programmed target area. This phenomenon is likely to play a major role in cortical dysfunction of DCX brain.

In addition INMED also developed collaborations with clinicians. The teams built new strategies based on the use of human resected materials (Collaboration with Pediatric neurosurgery departments at Foundation A Rothschild and Hospital Necker in Paris) and on the development of new animal models to better understand network developmental related disorders observed in epilepsies and mental retardations. For example, by combining electrophysiology, calcium imaging and morphology they showed that the high excitability of Sturge Weber cortical neurons may contribute to increased network activity. Moreover they also demonstrated that GABA mainly plays an anticonvulsive role in this epileptic syndrome.

Finally INMED developed a new platform to generate animal models of neurological disorders by an in utero transfection approach. This platform is now fully functional but has already led to the production of an animal model of double cortin mutation syndrome.

INMED has a high rate of publication. They published 102 original papers from 2006 to 2010 in good journal to high ranked journal including 2 Science (2006 and 2009)+ 2 Science in collaboration, 1 Nature Genetic (2009), 1 PLOSbiol (2010), 1 Neuron (2007), 1 PNAS (2006), 12 J Neurosci. Etc They also published many reviews in high ranked journal such as TINS, Current opinion in Biol, Ann review etc.

And they obtained 2 Patents

From June 2010 INMED teams published 26 very original papers including 1 paper in Science and 3 papers in Nature Neuroscience (Manzoni's team), They also published one paper in Neuron, one in Brain, one paper in J Neuroscience, several papers in Hum. Mol Gen, one review in TINS, one in Curr Op Biol etc.

They participated to books (28 contributions) and also to domestic presentations (4 to general public).

They were often invited abroad : 92 invited conferences in foreign countries including invited conferences in international meeting, 46 oral presentations to international meetings and more than 60 poster presentations

They Organized 9 national congresses or workshops and 2 satellite international Meetings (SFN, EMBO)

In the last 4 years, 15 students passed their PhD.

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

Some of the INMED staff members obtained High awards. The previous director being still a member of INMED obtained the highest prize of INSERM, the prize of the European Society of Epilepsy, the Rotary BRAIN research Prize and he is Doctor Honoris Causae at Liège University (Belgium).

The new director was Lauréat FRC rotary club, operation Espoir en tête 2009

The leader of the team "Maturation of functional cortical GABAergic microcircuits" was a winner of a Liliane Bettencourt grant, obtained a FRM team distinction and a ERC starting grant from European community.

INMED staff members are often invited to seminar series or meetings. They also participate as reviewer of juries for thesis and HDR. They also act regularly as reviewers for international journals.

INMED teams reach a very good level of attractiveness and a very good international visibility. In the past 4 Years INMED teams attracted 31 post docs. Among them 14 post doc have work in the institute for a mean period of 2 years. 12 postdoc came from foreign countries including USA (2), Canada (1) and Japan (1).

INMED attracted over 16 new researchers with permanent position and a PI (Chaire d'Excellence" C Rivera). They also attracted a very good team (O Manzoni).

Their ability to raise funds and to successfully apply for competitive funding is impressive: 22 ANR grants, 4 European projects in addition to AFM, FRM, FRC-rotary grants and regional grants (region PACA).

The teams have stable collaborations with foreign partners and some of them participate to international or national scientific networks.

INMED organized satellite meetings to international meetings and workshops. For example EMBO meetings series every year and an European winter school in Austria in 2009. They organized symposia for the French society of Neuroscience and the laboratory director is a member of the organizing committee for 2011 meeting of the French Society of Neuroscience

INMED include a space for biotech companies and 2 patents were obtained by INMED staff members.

The institute develops or integrates networks gathering together clinicians and geneticists. It is also engaged on the creation of a new biotech company aimed to improve the valorization of INMED discoveries (INSERM transfert).

In the past 4-years, INMED made significant effort to improve its socio-economic partnerships.

INMED organizes every year practical workshops to make the general public understand the latest advances in research.

INMED is actively involved on the diffusion of science.

The group created an original teaching program ("tous chercheurs") to promote scientific research and to initiate high school and college students to experimental procedures. In addition this teaching program allows diffusing scientific knowledge to associations of patients.

- Appreciation on the management and life of the research unit

The change of direction was a sort of challenge being now strongly successful.

INMED made substantial efforts during the past 2 years to increase the strength and the independency of the scientific teams. Accordingly, every team got financial supports from various sources including ANR and Europe.

Under the new director management the institute sustains active collaboration between teams resulting in a greater efficiency in research activities and reduced costs. The head of the laboratory also promoted the development of new links with geneticists and clinicians to improve the transfer of knowledge and to help the redefinition of specific scientific objectives and to promote future programs.

One of the original new features of the management policy is the creation of a scientific laboratory council to help the director in defining new research orientations, in improving technology transfer and resource management, in determining the best strategies to obtain grants, etc. Such a collegial direction non solely makes all scientists responsible for the fate of the institute but also allowed the institute to built sophisticated technical platforms, which certainly strongly improved the quality of the scientific production of each team.

This last 4 years INMED attracted over 16 new researchers with permanent position. They recruited 4 "chargés de recherche" INSERM, 1 "directeur de recherche" INSERM, 1 Professor (Université de la Méditerranée) and 1 "Chaire d'Excellence". They attracted from other labs 6 young researchers (CNRS, INSERM or associate professor : MCU).

In addition INMED attracted 1 team from Institut Magendie in Bordeaux (1 DR1 INSERM;1 CR1 CNRS; 2 Postdocs; 1 technician; 6 PhD students, among them 4 will defend their thesis in 2011 and 2 in 2012).

Under the new direction, INMED strongly improved the contribution to local education and training. The institute developed or contributed to several educational programs in Marseille and Paris. Professor and associate professors belonging to INMED have standard teaching activities but INMED also provided advanced courses for master students.

INMED is actively involved in the diffusion of science. Remarkably, the creation of an original teaching program ("tous chercheurs") to promote scientific research and to initiate High school and college students to experimental procedures is highly original and was successful: during the last 4 years all researchers from the institute trained 92 graduate students and hosted 112 school classes (about 3250 students).

In addition this teaching program, they used similar strategies to diffuse scientific knowledge to associations of patients, and INMED organizes every year practical workshops to make the general public understand the latest advances in research.

- Appreciation on the scientific strategy and the project

Understanding neuronal networks development is the main project of INMED. It is important to note that almost all teams analyze several aspects of the physiological and pathological development of the merging neuronal network in the developing brain.

The feasibility of the general project is strengthened by the arrival of new teams and of several young scientists as well as of a translational partnership with geneticists and clinicians. It is obvious that the comprehension of brain pathologies and the development of new therapeutic strategies require first a good knowledge of how pathology alters neuronal networks construction and operation.

In their future project they will address important questions allowing to elucidate the rules and factors that govern and modulate important developmental steps of neuronal network construction, and to identify steps and phenotypic checkpoints susceptible to be being important for a proper construction of the mature brain. Finally, pathologies linked to environmental factors (addictive behavior, viral infections and nutritional paradigms) will also be considered in this project with the aim of challenging the respective roles of genes and environment on brain construction.

The feasibility of this project is excellent according to the complementary competences of each team. The high level of interactions between the teams and the presence of very good technical platforms are also strong guaranties for the feasibility of this long-term project. The project is strengthened by the use of a multi disciplinary approach (molecular biology, morphology and electrophysiology), the combination of classical and new technologies (Electrophysiology in vivo, ex vivo and in vitro; imaging techniques using fast calcium imaging; voltage sensitive dye imaging combined with electrophysiology; single particle tracking; optogenetics; in utero brain transfection), the use of several in vitro preparations and the development of new animal models. For example, newly developed in vivo techniques have been introduced to perform pharmacological profiling of the activities in the maturing brain and allowing whole-cell recordings in freely moving rats.

INMED has the necessary financial resources to conduct this ambitious project with an average income of 3700 K€ per year. The only concern is the animal facilities of INMED that must be improved significantly. This is especially important since they will use increased numbers of animal models including transgenic mice. The "Université de la Méditerranée" has the project not formalized yet to build a large scale OPS animal facilities, but a better interaction between the University representatives and the different research institutes appears to be required to warrant the success of this project.

## 4 • Appreciation team by team and/or project by project projet (to be pasted as many as needed)

Title of the team 1 :Developmental sequences, infantile epilepsies and neurological disorders

- Name of the team or project leader: Yehezkel BEN ARI

- Staff members

| | Past | Future |
|---|---|---|
| N1: Number of researchers with teaching duties (Form 2.1 of the application file) | 1 | 0 |
| N2: Number of full time researchers from research organizations (Form 2.3 of the application file) | 4 | 6 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 4 | 4 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 2 | 2 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 1 | |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 3 | |
| N7: Number of staff members with a HDR or a similar grade | 2 | 3 |

- Appreciation on the results

This team has a long history of developing and pursuing exceptionally creative avenues of research. Most of the work is inspired by their seminal observation that in immature CA3 pyramidal cells GABA is excitatory rather than inhibitory. Subsequent work characterized the underlying mechanisms, the roles in normal brain development, and the pathological consequences leading to neuro-developmental disorders when this process is disturbed. More recently, efforts have been initiated to translate these findings into therapeutic applications. Specifically, the team leader and coworkers have collaborated with clinicians and have found that bumetanide modifies chloride gradients in the brain, which shows promise in curtailing seizures and which reduced symptoms in patients with infantile autistic syndrome.

This group published 72 papers (2006-2010) including top journals such as Science, Neuron, J Neuroscience. Several publications emerged every year from collaborations within INMED and also with external international researchers. 15 theses were completed for all of INMED (2006-2010) – unclear how many of these were from the Ben-Ari group.

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

The leader of the team obtained 4 awards, 28 invitations to conference and symposia. The team attracted foreign and French post-docs to the Marseille region, including numerous highly qualified post-docs. Moreover, targeted recruitment of various specialists has helped to maintain an excellent level of technical expertise at INMED.

The lab was able to raise 1,550,615 € ((2006-2010) through grants, although part of this sum is shared in the context of 2 EU grants (EU FP6 and EU FP7). In addition they received a Marie-Curie Fellowship.

The team is collaborating with 5 external labs and is part of the EU FP7 consortium

The demonstration of the importance of altered neuronal chloride gradients in the developing nervous system has had a major impact on numerous domains of neuroscience.

With respect to potential economic benefits, the laboratory has three granted patents stemming from their work.

In addition, the team leader has instituted a training program for MDs and PhDs in France and has organized a European winter school for young researchers. He also frequently gives lectures for general audiences including on radio and television.

- Appreciation on the scientific strategy and the project

For the period 2012 to 2015, the team has presented a strong proposal focusing on the investigation of infantile epilepsies. These projects represent a further step in their endeavor to translate findings in the laboratory during the past several years into therapeutic applications. Y Ben-Ari heads a strong team, many of whom have worked together with him for numerous years. In 2013, he plans to step down as leader, and the team will be split into two groups.

INMED has demonstrated an exceptional record for successful interactions among the different laboratories. The various teams readily share expertise, knowledge, and equipment, reflecting an equitable distribution of resources. The team leader has recently proposed an original hypothesis whereby he posits that neurons that fail to migrate properly become “misplaced”, such that they can no longer respond to normal physiological cues. As a result, he suggests these cells are suspended in a terminal immature state, in which they trigger pathological electrical signals. Several of the proposed projects are designed to substantiate this hypothesis.

Cutting edge techniques include the implantation of a multi-patch robot permitting the recording from 6 neurons at a time. In addition, the lab will use the chloride sensitive dye clomeleon to track developmental shifts in gradients. Finally, INMED has created a post genomic platform for the creation of new mouse lines that model neurological disease.

- Conclusion
    - Summary

This team is exceptionally productive, publishing regularly in top research journals. Their work and hypotheses have international impact on the field of neurodevelopment and epilepsy. With the extensive experience and solid track record of this laboratory, it is certain that they will achieve most of the goals outlined in their research plan.

    - Strengths and opportunities

INMED is housed in a modern facility with excellent infrastructure and a carefully thought out organization of teams with complementary expertise. This team drawing on several decades of experience in basic research, is now ideally suited to translate their findings into treatments for patients. In fact, they have recently begun with clinical tests of bumetanide to regulate neuronal chloride gradients. Thus, this laboratory has a strong vision of which biological and medical problems they are trying to solve, and has clear experimental strategies in how to address these issues. They are studying important questions concerning the potential amelioration of infantile epilepsies, which can markedly affect neurodevelopment and the future quality of life of afflicted individuals.

    - Weaknesses and threats

As mentioned above, in 2013 this team will be divided into two groups.

The first group is well funded and will consist of 3 postdocs and 1 PhD student. However, the other group, consisting of 1 postdoc and 2 PhDs, does not have independent funding at present, which the evaluating committee sees as a potential problem if the ANR grant proposal for which team leader of the second group is applying is not successful.

    - Recommendations

The evaluating committee suggests that the first group should be given the status of a fully independent team early during the year 2012, in order to facilitate a smoother transition when the actual team leader steps down as the team leader. A very special care should be given to the transition between one to two teams.

Title of the team 2: Early activity in the developing brain

- Name of the team or project leader: Rustem KHAZIPOV
- 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) | 1 | 1 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 2 | 2 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 0 | 0 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 0 | |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 2 | |
| N7: Number of staff members with a HDR or a similar grade | 1 | 1 |

- Appreciation on the results

This is an excellent group with a creative PI. The group has published excellent papers in the best journals. The group is still in contact with the Buzsaki lab in the USA, which definitely represents an asset, without interfering with the independence of the PI.

This team did some major discoveries on the development processes leading to mature cortical networks.

They discovered a central role of peripheral embryonic activities on the regulation of the merging cortical network electrical activity. Using a multidisciplinary approach they discovered that spontaneous movements of premature human neonates trigger delta-brush oscillations in the central cortex in a somatotopic manner suggesting that spontaneous fetal movement provide sensory stimulation and drive electrical oscillation in the developing somatosensory cortex contributing to the formation of cortical body map. They showed that spontaneous retinal waves are transmitted and drive electrical activity in the visual cortex, which again suggest that the interaction between the retinal waves and the spindle bursts in the cortex contributes to the development of the visual cortex In addition they demonstrate that cholinergic inputs facilitate V1 spindle burst in the visual cortex and that the early development of visual processing is governed by a conserved intrinsic program that switches thalamocortical response properties in anticipation of patterned vision. They also shown that spindle burst oscillations of neonatal rat barrel cortex are driven by thalamocortical and intracortical glutamatergic synapses and are compartmentalized by GABAergic synapses.

They discovered that depolarizing action of GABA in the immature CNS is highly plastic and it is subject to hormonal regulation. Effectively they have shown that the production of oxytocin by the mother during delivery induces a transient excitatory-inhibitory switch in the action of GABA in the neonate.

Finally they demonstrate that the depolarizing action of GABA required to be excitatory in the presence of a voltage-gated persistent sodium current in postsynaptic neurons (neuron 2010).

This small team has an excellent scientific production with 2-5 papers per year. Since 2006 this team has published papers in high ranked journal (1 in Science in 2006, 1 in Neuron 2010, 3 in J Neuroscience in 2006, 2007 and 2010) including one review in Physiological reviews, one in TINS,

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

Considering the general interest and the impact of the work produced by the team leader, his international visibility is rapidly increasing with 15 invited conferences to international congresses. The team leader organized one TINS/INMED conference in 2006.

Sufficient funding is secured to carry out the current projects. The team is working well and has a number of highly motivated scientists.

- Appreciation on the scientific strategy and the project

The project is focused on the network mechanisms and physiological roles of spindle-bursts in cortical development.

Their central hypothesis being logical with previous team's data is that spindle-burst and delta-brush are endogenous thalamocortical oscillations, driven by the sensory periphery and implicated in cortical maps formation.

The project is divided in 4 tasks

In a first task they will determine the neuronal network involved in spindle bursts generation including the thalamic participation, the intracolumnar and horizontal spread of spindle bursts and the impact of he developmental changes in GABA signaling from excitatory to inhibitory in their generation

In a second task they will explore the relationship between the developmental changes in spindle-bursts and delta-brushes and their switch to adult activity patterns with the developmental changes in the sensory signal processing in somatosensory, visual and auditory systems.

In a third task they will determine the physiological role of the spindle-bursts.

Their main hypothesis is a competition via spindlebursts between sensory inputs for their cortical representations.

In a last task they will address the question of the role GABAergic interneurons in the generation of the early activity patterns in vivo with a special attention to the physiological impacts of pathological plasticity in GABA signaling in neonatal hypoxia, epilepsy and pain.

This project addresses interesting questions of early neuronal development with very creative approaches.

The projects are feasible and much preliminary data provides also proof of principle of some of the basic hypothesis.

The team has a good size, but will certainly grow over the next few years. Resources allocated to this team are well invested.

The team has established an impressive array of cutting edge technological approaches. We were particularly impressed by the creating use of caged GABA in vivo (pipette filled with ruby-GABA and photolysis through a fiber inserted into the pipette). These experiments carry the potential to study the polarity of GABA transmission in vivo and yield some definite answers on long-standing questions in the field.

- Conclusion
    - Summary

This group with a creative PI carries out research with great rigor and care.

    - Strengths and opportunities

The team has a creative use of cutting edge techniques. They raise very interesting research questions and have the potential to provide definitive answers. This team is still in an ascending phase.

    - Weaknesses and threats

The PI will have to ensure that his independence is not questioned. He should be more active to promote the visibility of his lab. With great stories at hand, he can definitely have an impact that will boost his career.

    - Recommendations

This team is very successful and the PI is encouraged to maintain the same quality of research, productivity and funding.

Title of the team 3: Alterations in cortical development and epileptogenesis

- Name of the team or project leader: Alfonso REPRESA/ Carlos CARDOSO

- Staff members

| | Past | Future |
|---|---|---|
| N1: Number of researchers with teaching duties (Form 2.1 of the application file) | 2 | 2 |
| 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 (Forms 2.2, 2.4 and 2.7 of the application file) | 3 | 0 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 2 | 2 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 0 | |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 3 | |
| N7: Number of staff members with a HDR or a similar grade | 1 | 3 |

- Appreciation on the results

Malformations of cortical development (MCDs) are recognized causes of mental retardation and epilepsy. This team aims to understand the pathological basis of brain malformations. They propose to focus on the pathophysiological mechanisms responsible for epileptogenesis. Specifically, they aim to use genetic, molecular biological and imaging approaches to study both normal and abnormal cortical development. Their main results are:

- Identification of a mutation in a locus on 5q14.3-q15 responsible for a new PNH syndrome, and development of an experimental design that allows for rapid functional evaluation of the role of candidate genes in neuronal migration.

- Establishment of an animal model of Periventricular Nodular Heterotopias, using in utero electroporation of RNAi vectors, which allows for determining the functional consequences of flilamin 1 mutations in neuronal migration and cortical layering.

- Analysis of the relationship between altered cell migration induced by doublecortin gene knockdown in utero and cortical activity. They discovered that rats became pro-epileptogenic following such knockdown, thus demonstrating that subtle developmental alterations of the cortex can yield epilepsy.

- Finally, deregulation of glutamate homeostasis (block of glutamate transporter) that can lead to epileptic paroxysmal burst, could involve the activation of extrasynaptic NMDA receptors.

The number and quality of publications, communications and other outputs by the group is very good. The team published 22 papers and 10 papers in collaboration since 2006. The team leader published 7 papers as last author, some in very good journals.

The group appears to have a good balance of expertise, and have established collaborations locally and with well-known groups in France and internationally.

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

Members of the group have been represented well in international scientific activities (>10 invited conference per year). The team was successful in raising in excess of 1.5 million Euro from national and European organizations.

The participation of group members in stable scientific networks within France and with foreign partners is satisfactory.

- Appreciation on the scientific strategy and the project

In this project, the team will investigate whether the epileptogenic foci involved ectopic neurons, the normotopic cortex or both by taking advantage of new rat models of cortical malformation disorders obtained using in utero RNA interference. The ambitious goal will be to ultimately suggest new therapeutic strategies to ameliorate epilepsy in patients.

To address these questions, they will utilize molecular biological tools to selectively manipulate the excitability of ectopic/normotopic neurons (optogenetic) and to describe their connectivity in vivo. With this approach they hope to understand how these neurons participate in the generation of seizures.

- In a first task they will perform in vivo functional assays using RNAi in rodents to identify new PNH genes

- In a second task they will determine the mechanisms of genesis of MCD associated to Flna mutations and lissencephaly linked to mutations in the transcription factor ARX. This part of the project is supported by preliminary results showing disruption of radial glial cells associated with Flna mutations. Because it was supposed that ARX mutations could alter GABA neurons development they will evaluate the impact of different ARX mutations on neuronal survival, migration and differentiation, by targeting pyramidal cell neuroblasts or interneurons, in vitro and in vivo.

- In a third task they will performed a morphofunctional analysis of heterotopic networks. For example, they will evaluate the axonal distribution of “ectopic” neurons and identify their target cells as well as the functional properties of this abnormal network.

- In a last task they proposed to determine the functional repercussions of cortical migration disorders and then they expect to identify the seizure-generating structure and its connectivity and then to generalize their data to patients with cortical malformations associating ectopic neurons.

The proposed scientific project outlined on is logically laid out. One of the main attractions is the multidisciplinary approach of the proposal.

- Conclusion
    - Summary

This is a strong team with good output, good scientific environment and good funding. The project is logical and well organized. This team is productive, publishing regularly in very good journals. Their work and hypotheses have international impact in the field of neurodevelopment and mental retardation. With the extensive experience of the team leaders, it is certain that this team will achieve most of the goals outlined in their research proposal.

    - Strengths and opportunities

The scientific proposal, although somewhat ambitious, will have important scientific implications. Identify new genes that play important roles in neuronal migration is an important issue and to analyze the link between genotype and phenotype and identify the process leading to developmental alteration of neuronal circuit will give results of great interest for better understanding neuronal network development processes as well as the consequences of their alteration on CNS diseases.

    - Weaknesses and threats

There is some uncertainty as to whether the proposed experiments to understand the generation of epileptic seizures in animals will achieve the stated goal (to ultimately propose novel therapeutic strategies for human pathology: task4).

    - Recommendations

A reflection must be done for some of the proposed experiments in task4 related to the generation of epileptic seizures They should be more convincing about the final goal of this part of the project (to ultimately propose novel therapeutic strategies for human pathology).

Title of the team 4: Role of KCC2 and BDNF in construction of cortical and hippocampal neuronal networks

- Name of the team or project leader: Jean-Luc GAIARSA / Igor MEDYNA

- 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) | 2 | 2 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 6 | 1 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 3 | 3 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 0 | |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 6 | |
| N7: Number of staff members with a HDR or a similar grade | 3 | 3 |

- Appreciation on the results

This is a consortium of two research groups where one focuses on the secretion of BDNF in neuronal cultures and the trafficking and expression of KCC2. The link is given by the observation the KCC2 expression is modulated by BDNF. As such this is an interesting question. They see their work in relationship to synapse development.

The output of the two teams this past 4 years is really correct (14 papers). The two PI already published papers as coauthors in J Neurosci (2008) and in Mol Neurol (2009). In addition, the team leader of the first team (BDNF) was a co-author in Physiol review paper (2007). He published 2 papers in J physiol and in Commun Integr Biol as a the last author in 2008, 1 paper in J Neurosci ( last author) in 2009 and 1 paper in EJN in 2010 (last author). The second team leader (KCC2) published 1 paper in J Physiol in 2006 and he was a co-author in a Hippocampus paper and in an Annal Neurol paper in 2006. He was first author on 1 paper published in Sci Stke in 2007. He also collaborated to two papers in 2008 (1 An J Hum genet and 1 MCN) and was co-author on a paper published in J Neurochem in 2010.

Both PI list a number of collaborations, which in some instances have led to publications (For example 1 paper I Annal Neurol in 2006).

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

The first team leader (BDNF) has been invited to one conference per year on overage, most in specialized meetings.

The team will be complemented with a chair of excellence sponsored by the University, which will strengthen its potential.

The second team leader has an ANR grant that runs until 2011 and the ANR grant of the first team leader ran out in 2010, which indicate that new financial supports must be obtained to secure the project.

- Appreciation on the scientific strategy and the project

The project aims at studying maturation of synaptic networks and the role of BDNF and KCC2 in this process. A special focus will be on inhibitory neurons. Some of the crucial tools have been established by the team (e.g. fluorescent probe to follow BDNF secretion) but others remain to be developed. The currently available data from

preliminary experiments suggest that over expressed BDNF is secreted while the cell is spontaneously active and that this BDNF is then reuptaken by neighboring cells. The experimental strategy to study KCC2 trafficking and the readouts to assess synaptic maturation need to be defined.

The team is well funded until 2011 and new support needs to be secured. The arrival of another PI as a chair of excellence will strengthen the team, but there will certainly also be a need for a reorganization of the resources.

The project could benefit from additional focus on molecular mechanism of the basic question stated. Ultimately the team will have to address the concern that their main experimental approach relies on BDNF over expression, when in fact the goal is to study the role of endogenous BDNF.

- Conclusion
    - Summary

This is a group with two PIs who have made interesting contributions to the field. The funding situation is somewhat uncertain. The project is interesting, and will rely on some elegant tool that the team has already developed (proof of feasibility). The team should be commended for this. On the other hand, the elaboration of the common project should be pursued: one would like to see a more systematic approach and clear strategy to test the basic hypothesis. The strategy for testing the basic hypothesis is still fuzzy; hopefully the team will benefit from the arrival of the chair of excellence and review the planned experiments.

    - Strengths and opportunities

The arrival of a chair of excellence PI can be an opportunity to reorganize the groups and streamline the project.

    - Weaknesses and threats

The fact that in the very near future the group will have three PI's also carries a risk, as a common culture will have to be defined. The funding may run out shortly.

    - Recommendations

The main challenge of this new team is to build a common project. They are on the way. The focus should be on the strengths of the preparation the PIs propose to use (culture system). Before addressing questions of network maturation they should deepen the investigation of the molecular mechanisms that govern BDNF release from dendrites and BNDF uptake in neighboring cells on the other hand.

Title of the team 5 : Pathophysiology of Temporal Lobe Epilepsy

- Name of the team or project leader : Valérie CREPEL

- Staff members

| | Past | Future |
|---|---|---|
| N1: Number of researchers with teaching duties (Form 2.1 of the application file) | 2 | 2 |
| N2: Number of full time researchers from research organizations (Form 2.3 of the application file) | 2 | 2 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 1 | 1 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 0 | 0 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 0 | |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 3 | |
| N7: Number of staff members with a HDR or a similar grade | 1 | 2 |

- Appreciation on the results

The research of this team seems high quality and original. Their big story is on the role of kainate receptors in EPSPs in newly formed synapses in epileptic tissue. In my opinion this group made a very major contribution to this line of work, and I think they may have initiated it. The point is that this is a big issue because the slow time course of this receptor will make it rather strongly pro-epileptic.

The team's papers are high quality: Neuron and Annals are top of their subject rankings, while having a decent proportion of their papers in J Neuroscience in itself makes them internationally competitive. The number of papers is OK but not spectacular: 7 over 5 years for ~3 postdoctoral staff is only justified by the relative difficulty of the work and the time taken to manage chronic models.

Collaborations look reasonable. The transgenic model is appropriate to the work. The report suggests to me that the author was a bit embarrassed not to have already used transgenic animals, but I think it is important to use new(ish) technologies only when they help address the question being addressed and not just for the sake of keeping up with trends.

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

The team leader has a good number of invited talks in international conferences. She appears to have received several honors from French organizations. Her team is small but high quality: she has recruited members with pretty good track records and from several countries. The two current postdocs arrived with first authorship on papers in high profile journals: one in Science and PNAS, so serious players for their stage of career. The rest of the team comprises two PhD students and two masters students.

The team appears to have two major grants.

The team leader plays a creditable role in funding committees and in teaching. Her international collaborations have not yet resulted in full publications, but the three that she identifies do sound as though they make sense, and we are reasonably confident they will deliver valuable benefits over the coming review period.

This research is not likely to impact on medical practice in the near future, or even the mid-term, so "concrete results" are unlikely to impact on the general public in the foreseeable future. However several members of the team have contributed to public awareness of science through more popular papers, and they also have contributed to more general popular reviews for scientists too (Epilepsy Currents, Neuroscientist, Phil Schwartzkrion's encyclopaedia).

- Appreciation on the scientific strategy and the project

The plan looks like a strong line of work that builds on the lead that the group has in the role of kainate receptors in chronic epileptic tissue. The various tasks represent an intelligent integration of in vitro and in vivo methods, primarily electrophysiological, but with appropriate use of selective antagonists and transgenic mice. The use of in vivo patch clamping is a particular strength.

- Conclusion
    - Summary

This is a tightly focused program of work, centered on the role of kainate receptors in chronic temporal lobe epilepsy. It uses state-of-the-art recording methods, and a good synthesis of in vivo and in vitro methods. For the size of the team it is ambitious but I think it can be delivered.

    - Strengths and opportunities

The team has one excellent researcher (CR2 INSERM) and one excellent postdoc and a real sense of direction and leadership. The several projects all complement the general issue of kainate receptors in epilepsy, so they show a focus which increases the likelihood of substantial advances. The in vivo patch clamping which is going to yield really exciting results is particularly impressing.

    - Weaknesses and threats

As a minor point, we are concerned about the team leader's level of contribution to teaching, administration and grants committees. It is important to keep in mind that the presence on funding bodies needs to balance the benefit of being seen in the national arena (and to play a decent part in managing scientific funding) against the cost in time and effort and loss of research time.

    - Recommendations

The team leader must control her level of contribution to teaching, administration and grants committees to avoid damaging her small team's research performance. Otherwise the research is exciting and the committee looks forward to seeing the results.

Title of the team 6 : Maturation of functional cortical GABAergic microcircuits

- Name of the team or project leader : Rosa COSSART

- 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) | 2 | 2 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 4 | 4 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 0 | 0 |
| 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 2.8 of the application file) | 2 | |
| N7: Number of staff members with a HDR or a similar grade | 2 | 2 |

- Appreciation on the results

This team studies the development of GABAergic network activities in the rodent hippocampus and neocortex, using optical and electrophysiological methods. In the past 4 years, the team has principally focused on the generation of coherent activity patterns using multibeam multiphoton microscopy and targeted whole cell recording, in vitro. The scientific output has been excellent and the team is one of the most prominent in the field of neuronal networks. In brief, the team reported for the first time (in 2007) a particular non-synaptic coherent activity, named synchronous plateau assemblies (SPAs) in the hippocampus. It then deciphered the sequence of coherent activities in the neocortex, demonstrating that both SPAs, eNOS (early network oscillations) and GDPs (giant depolarizing potentials) coexist and appear within a fixed time frame. Recently, the team identified a subclass of GABAergic interneurons (Hub neurons) that drive GDPs in the hippocampus. All these findings are considered major contributions in the field.

In terms of publications, the quality of the works is attested by the impact of the journals in which they were published. As a leader, R. Cossart published 2 studies in J. Neurosci. (2007, 2008), 1 in Neuron (2007) and 1 in Science (2009). Finally, R. Cossart also published 2 reviews in 2010 (J Physiol. Role of NMDA receptors in early oscillations; Curr. Opin. Neurobiol. Role of interneurons on the emergence of network activity) that clearly indicate that she is internationally identified as a leader in the study of early network activity.

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

The cooperation of this team with other teams on site has provided excellent scientific results. In particular, the team has been associated with studies on the role of oxytocin in the transient switch of GABA actions at birth (Science, 2006), as well as with the controversy on the depolarizing role of GABA (J. Neurosci. 2011).

The team leader's collaborations have led to the publication of ~20 studies from outside INMED, which appeared mostly in mid-level journals.

The impact of her work is also evidenced by the high number of invited talks (about 25 talks)

The team is very productive despite its small size with all the work done by postdocs and PhD students. For the period of 2006-2010, 3 doctoral students were directed by the team leader.

To conclude, the results are impressive and they justify the awards obtained in France (ANR Jeune Chercheuse, Coup d'élan de la Fondation Bettencourt, Equipe FRM) and internationally (ERC Starting Grant 2010-2015).

- Appreciation on the scientific strategy and the project

Three major projects are currently being followed. The first one continues the study on Hub neurons. The team wants to map Hub neurons during development: when do they appear? Which interneuron subtypes do they involve? What is their synaptic connectivity? The second project aims to determine the role of SPAs in the maturation of GABAergic networks. The last project is new, addressing the role of early synchronization in two models of epilepsy and involves several collaborations. These projects are ambitious and at the cutting edge of available methods and techniques. The team has the necessary expertise and financial support to achieve their goals.

- Conclusion
    - Summary

This group is one of the few in the world with the theoretical and experimental expertise required to dissect the functional mechanisms and roles of early network activities in the maturation of the brain. The leader has worldwide recognition in the field and is strongly supported financially (FRM equipe, ANR Jeune chercheuse, ERC starting grant). The scientific production and impact has been constantly at the highest level during the last years.

    - Strengths and opportunities

As mentioned above, the team is a leader in this field. Their productivity is excellent. The projects are at the cutting edge but with little risks. The projected milestones are realistic.

    - Recommendations

Maintain the same quality of research, productivity and funding. The discovery of Hub neurons has been very important and their further characterization in the hippocampus as well as their investigation in the cortex should take precedence over studies on epilepsy.

Title of the team 7 : Genetic of isolated and associated epilepsies

- Name of the team or project leader : Pierre SZEPETOWSKI
- Staff members

| | Past | Future |
|---|---|---|
| N1: Number of researchers with teaching duties (Form 2.1 of the application file) | 3 | 1 |
| N2: Number of full time researchers from research organizations (Form 2.3 of the application file) | 2 | 2 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 3 | 1 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 0 | 0 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 5 | 2 |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 1 | |
| N7: Number of staff members with a HDR or a similar grade | 1 | 1 |

- Appreciation on the results

This team has only recently started at the unit so they do not have an extensive track record here – just one paper in Epilepsia. Previously the PI worked at another institute in Marseille and averaged about 3 papers per year, some in very good journals.

The research itself is good. There is an element of chance in searching for genes that cause diseases, and the group has had successes. Human medical genetics generally involves relatively large, often international, teams; judging by the numbers of authors that applies to some of the pre-INMED papers, and it is reassuring to see that the PI is last (presumably senior) author on several of those in high impact journals.

The recent arrival of the team makes it hard to test the stability of partnerships from its base in INMED, but the recent past does give grounds for optimism.

The big story that lays the foundation for the next 4 years is the SRPX2 gene and its association with abnormalities in the speech area. In my view this looks interesting and well worth pursuing.

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

The team leader so far does not seem to have given talks at international conferences, but has given 4 in national meetings. We hope that would improve in the coming years. The team has 5 full time staffs, and at least one of them has an excellent publication record. None are from outside France. The remainder of the team comprises one student and two technicians.

The team leader clearly has participated in large scale international clusters – that is essential to build cohorts for most studies in clinical genetics. If he is planning to focus on the consequences of the SRPX2 mutation then the nature of the research networks will change and probably be smaller. The present summary suggests that his ideas are sensible enough but it is too early to see whether they work – essentially INMED's strong point is the animal models, physiology and histochemistry that will be key parts of finding out how the mutation causes the disease state. One of his new grants is for a postdoctoral physiologist for 2 years, which increases his ability to exploit the potential of INMED – identifying physiological phenotypes for gene mutations really needs a skilled physiologist who is committed to the project, and whose career depends on a productive outcome.

The team leader participates in teaching to a creditable degree, but not excessively so there are no concerns about teaching eroding research time. The team leader also has presented at a couple of public events, which contributes to public understanding of science – again reasonable but far from excessive.

- Appreciation on the scientific strategy and the project

The plan looks sensible. Taking the genetic mutation and following its consequences to understand the symptoms and disability it causes is a good idea. Studying a condition that affects speech in a rodent model will have its challenges given the limited linguistic scope of the average rat or mouse, but the evidence of migration errors in the human tissue does provide a viable end point for the animal model. A key issue will be to show rescue of the knocked out/down gene, both with the wild type rodent and human genes. Without that rescue, the idea of testing the effect of the human mutation would at least need a different strategy, if it were possible at all. In that case, the PI may need to develop alternative plans rather quickly.

Tasks 1 and 2 seem to be a continuation of the molecular genetics and molecular biology of speech disorders and needs a different kind of research network, which will be delivered by links with Lyon and Strasbourg. The increasing effectiveness of outsourcing for gene sequencing and other molecular technologies makes this work achievable in a centre that is not primarily molecular. It represents a continuation of a proven line of work.

Tasks 3 and 4 concern Srpx2 and are discussed above. They seem particularly interesting to the members of the panel. The commitment of a grant-funded physiologist to build links between the molecular expertise of the core team to the physiological expertise of INMED is to be commended, and greatly increases the likelihood of success. This work will make good use of one of INMED technical strengths, namely in utero electroporation, to knock down Sprx2 in the rat neocortex.

Task 5, on environmental factors during pregnancy potentially impacting on migration defects seemed to be less well developed than the other tasks, at least in the material available to us. We do not have enough evidence to form an opinion on its strength or feasibility.

Overall, the multidisciplinary approach to this disease is appreciated, and could really be cutting edge.

- Conclusion
    - Summary

This team is new to INMED so it is too early to tell whether it will prosper here. It is not clear how common the SRPX2 mutation is, but the thrust of the account seems to be that the work will generalize to other neurological conditions impacting on speech, which clearly is a big burden on patients and careers. The genetics and molecular biology of this team will be nicely complemented by the electrophysiology, animal models and histology that is the strength of the host institution, and this connection will be greatly strengthened by the appointment of a researcher dedicated to work on it.

    - Strengths and opportunities

Much of this project focuses on the mechanisms by with a pathogenic mutation causes the associated disease. We like the approach, which recognizes that finding the mutation is a long way from explaining the disease. As mentioned in the summary, INMED is a good place to develop this approach. The other parts represent continuations of proven approaches developed in the team's previous institution.

    - Weaknesses and threats

Staffing levels are low for a molecular genetics team, but the committee accepts the argument that the availability of high-quality molecular technology companies has reduced the scale of academic enterprise required to be competitive.

    - Recommendations

If the funding position is OK, then the key step is to build effective collaborations with the teams that can deliver the required physiology and other phenotypic analyses. The commitment of the postdoctoral electrophysiologist on one of the PI's new grants is important to make this kind of collaboration work.

Title of the team 8 : Neurodevelopment, genetic and epigenetic: investigation of Prader-Willi syndrome

- Name of the team or project leader: Françoise MUSCATELLI-BOSSY

- 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) | 1 | 2 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 1 | 0 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 0 | 0 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 1 | |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 1 | |
| N7: Number of staff members with a HDR or a similar grade | 1 | 1 |

- Appreciation on the results

Prader-Willi Syndrome (PWS), a rare neurogenic disease, is characterized by a range of physiological, endocrine and behavioral disturbances. This team aims to use genetically modified mouse models to study the pathophysiological role of two genes thought to be involved in PWS: Necdin and Magel2. Elimination of these genes is known to affect vital functions such as breathing and feeding. So, it is hoped that the proposed studies will help to understand PWS and reveal new physiological, cellular and molecular pathways involved in vital functions, which might be altered in other diseases.

The group leader joined the Institute in 2008. The group is very small, comprising 2-3 other scientists and a couple of postgraduate students. As a result, the number of publications and outputs of the group, as acknowledged in the report (p.90) by the leader, is limited. But from June 2010 the group published 1 paper in Hum Mol Genet (2010), has 1 paper in revision in Plos One and one submitted paper.

As it is a new group, with one scientist joining last year and another this year, there has not been sufficient time for the team to establish long and stable partnerships.

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

The team leader is clearly a well known expert in the field of PWS. She and her colleagues collaborate with scientists locally, nationally and with a laboratory abroad.

Invitations and participation of members of the group to international conferences and symposia are limited. However, the team leader is an expert in the field of PWS. She and her colleagues collaborate with scientists locally, nationally and with a laboratory abroad.

Two established French scientists joined the group recently.

Recruitment of PhD students and postdoctoral fellows is limited.

As far as we can see, there is only one 3-year ANR grant to support the work of the group, with plans to apply for additional funding. However, the group was awarded two small grants (30KEur) recently as well an equipment grant jointly with another group.

- Appreciation on the scientific strategy and the project

The project, outlined on pages 92-95 of the report, aims to use mouse models to: 1) identify cellular and physiological pathways altered in PWS; 2) reveal links between cellular and molecular mechanisms and physiological functions; 3) elucidate the function of Necdin and Magel2 in neuronal development; 4) establish cellular and mouse models for pharmacological screening.

The feasibility of the project is sound.

- Conclusion
    - Summary

Small new team with limited resources yet, modest publication record in recent years, but a possibility for expansion in the foreseeable future by the arrival of two other scientists. From June 2010 the group published 1 paper in Hum Mol Genet (2010), has 1 paper in revision in PlosOne and one submitted paper which indicates that productivity is increasing.

    - Strengths and opportunities

The team leader is a recognized authority in the very specialized field of Prader-Willi Syndrome. The proposed project is sound and feasible.

    - Weaknesses and threats

Modest publication record in recent years, but as mentioned above productivity is increasing.

    - Recommendations

Every effort should be made by the group to sustain their increasing productivity and to publish their work in order to increase their visibility and compete successfully for grant support.

Title of the team 9: Physiological and pathological oscillations in the basal ganglia

- Name of the team or project leader : Constance HAMMOND

- 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) | 1 | 1 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 1 | 0 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 2 | 2 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 1 | |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 3 | |
| N7: Number of staff members with a HDR or a similar grade | 1 | 1 |

- Appreciation on the results

Abnormal bursting activity in the basal ganglia is a hallmark of the Parkinson's disease. Whereas this bursting activity is believed to alter integration of cortical signals, very few is known about its mechanisms of generation. The team has obtained original results that highlight some of the cellular mechanisms underlying this dysfunction. It has shown that in the absence of dopamine, GABAergic interneurons burst and generate repetitive IPSCs in medium spiny neurons (J Neuroscience, 2009). Dopamine deprivation was obtained by dopaminergic denervation using 6-hydroxydopamine treatments. Gigantic spontaneous GABAergic activities in the striatum that reflect the same signature pattern of dopamine deprivation were also observed in mouse models of Parkinson's disease (PINK1 KO mice and mice surexpressing alpha synuclein A53T) (manuscript in preparation). The team has also shown that in conditions of acute dopamine depletion or chronic dopaminergic denervation, the subthalamic nucleus network generates bursts of glutamatergic currents that propagate to the entire extrastriatal network (Neuroscience). These bursts jam the activity of all the extrastriatal target nuclei of the subthalamic nucleus.

The development of a novel in vitro preparation of the mouse basal ganglia has been published in Neuroscience. The team leader is also the first author of two reviews in "Trends in Neurosciences" and "Movement Disorders". Two more collaborative articles were published in "Neuron" and "Chemistry and Biology". All these publications are of quality. At first glance, their number seems modest but it is proportional to the small size of the team and to the teaching activities of its group leader. Another reason for this moderate production is the development of a new research theme that will become the centre of the research project for the next period (see section "appreciation of the scientific strategy and the project").

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

Reputation of the team is attested by the number of invited lectures given by its group leader (10 conferences). The other members of the team have presented their results in more than 10 scientific meetings (oral presentation and posters). In 2007, the team leader has been awarded a national award, the "Palmes Académiques", for her long lasting efforts in science teaching and vulgarization.

The team leader is at the origin of the program “Hippocampe”/"tous chercheurs" that has introduced 6000 high school students to the scientific method by carrying out mini-research projects at INMED. This creative approach has been published in Plos Biol. The team succeeded to raise money for funding its research. Grants were from ANR, FRC and France Parkinson. The team recently attracted a foreign post doc, a second one should join the team in 2011.

- Appreciation on the scientific strategy and the project

The research project fits the central theme of INMED on the maturation of neuronal circuits to benefit from the internal expertise. It focuses on the developmental activities of the basal ganglia and on their alterations during development that may underlie late motor disorders in familial forms of the Parkinson's disease. The hypothesis is that an early genetic insult to the neuronal population of midbrain dopaminergic (mDA) neurons of the substantia nigra affects the developmental sequences of activities in the basal ganglia. The team wants to understand whether this leads to the formation of immature and/or misplaced or misconnected neuronal ensembles that will subsequently affect DA neurons or make them more susceptible to stress.

The team has already characterized the developmental activities of the control striatal network. The next steps comprise: 1. Identification of the sequence of immature activities of mDA neurons and evaluation of their ability to release DA across development; 2. Study of the developmental activities of the subthalamic nucleus (second target of DA and cortical neurons); 3. Evaluation of the impact of Parkinson mutations on the development of mDA neurons and related targets. These studies will carried out using patch clamp recording and ultrafast two-photon calcium imaging on in vitro brain slices from control TH-GFP or Nkx -GFP mice or double transgenic mice PINK1-KO/TH-GFP, A63T SNCA/TH-GFP. We suggest that the team takes into account well established cell type-specific differences in the neuronal population that will be studied. For example VTA DA neurons and SN DA neurons differ in many ways, which may be of significance for Parkinson's disease, as the VTA DA neurons are more resistant to neurodegeneration. Also in the striatum, medium spiny neurons fall into essentially two classes, direct and indirect pathway neurons. It may therefore be of interest to compare the two groups in some of the experiments proposed.

- Conclusion
    - Summary

Whereas rather small, this research team uses its solid experience in electrophysiology of the basal ganglia to obtain original results in the field of the Parkinson's disease. Its research project is solid and the questions are clearly identified.

    - Strengths and opportunities

The project is in harmony with the general research theme of INMED. The planned addition of two post docs should help to increase the team's productivity.

    - Weaknesses and threats

There is no grant extending after 2011, and the funding of this project is not yet secured.

    - Recommendations

Every effort should be made by the group to increase the funding of the project.

Title of the team 10 : Pathophysiology of synaptic plasticity

- Name of the team or project leader : Olivier MANZONI / Pascale CHAVIS
- 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 | 2 |
| N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file) | 2 | 3 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 0 | 0 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 1 | 1 |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 3 | 1 |
| N7: Number of staff members with a HDR or a similar grade | 2 | 3 |

- Appreciation on the results

This is a small team, which has made significant contributions in the past few years to our understanding of synaptic mechanisms underlying drug addiction and of processes regulating the maturation of synapses during development. Specifically, their work has for the first time shown that drug addiction (cocaine) in rodents impedes synaptic plasticity. In addition they found that application of cannabinoids induces the removal of presynaptic cannabinoid receptors from axonal terminals. They have also identified an important function of reelin, namely the modulation of cell surface trafficking of NMDA receptors. These findings have been published in the highest ranking journals.

This group published 17 papers (2006-2010) including in top journals such as Science, Nature Neuroscience, Neuron, J Neuroscience.

7 theses were completed in this group between 2006 and 2010.

This team has several publications every year from national and international collaborations.

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

The team leader obtained 1 award and had 17 invitations to conferences and symposia

The team attracts a steady stream of highly qualified research scientists and students, approximately one third from abroad.

The team was able to raise 1,713,088 € (2006-2010) through grants, and in addition received three fellowships to finance the positions of one postdoc and two doctoral students.

The team is collaborating with 10 national and 12 foreign labs but at present is not participating in formal scientific networks, although they plan to apply for a European Community Research consortium grant.

Research from this team has identified new mechanisms elucidating the synaptic basis for drug addiction. These findings will be of importance in the development of new therapies to combat the serious problems of addiction afflicting modern societies. Recently, their work (Nature Neuroscience 2011) has demonstrated a link between malnutrition and synaptic dysfunction in emotional disorders.

The team leader has in past acted as a consultant to pharmaceutical companies (Sanofi.Aventis, Scientia). At present he has a patent pending.

The two senior scientists were founding members of the European Synapse Summer School (PENS).

The team leader is a good communicator and has given numerous interviews about his work on French television and radio, and for newspapers.

- Appreciation on the scientific strategy and the project

For the period from 2012 to 2015, this team aims to characterize deficits in synaptic plasticity occurring in neuropsychiatric disorders, such as mental retardation, autism, schizophrenia, depression and addiction. Next, they will evaluate a variety of pharmacological and nutritional strategies designed to restore normal synaptic plasticity. They present promising preliminary data in their report that support the feasibility of their experimental approach. The questions they address are extremely important for basic research as well as for potential clinical applications. Considering their strong track record, in terms of publications and the attainment of past goals, it seems clear that this dynamic team will grow and succeed in making further advances in the coming years.

This team moved from the Institut Magendie in Bordeaux to INMED a few months ago. The motivation for this change was that INMED hosts several laboratories with expertise in synaptic mechanisms, and thus provides a better research environment to investigate the pathophysiology of synaptic plasticity. In addition, they will be able to benefit from the excellent infrastructure at INMED.

The Manzoni lab implements several cutting-edge technologies in their experimental protocols. They have performed live imaging with single-particle tracking of reelin and of cannabinoid receptors using semi-conductor quantum dots. They will also obtain large scale recordings of entire neuronal networks in prefrontal cortex and nucleus accumbens to map functional connectivity, which will be important to achieve their goal of determining the critical periods of synaptic plasticity for different classes of synapses. Finally, they are utilizing optogenetic approaches involving photostimulation of channelrhodopsin-2 expressed in subpopulations of neurons to characterize spike timing-dependent protocols of synaptic plasticity.

- Conclusion
    - Summary

The team leader has assembled a dynamic, productive team, which despite its relatively small size, is publishing high impact papers on a regular basis. They are addressing questions of great importance, with respect to both the discovery of new synaptic mechanism as well as the translation to clinical applications.

    - Strengths and opportunities

This team has recently moved from Bordeaux to INMED. Their main topic of research, the pathophysiology of synaptic plasticity fits in well with the considerable experience in synaptic and network mechanisms of many of the laboratories in INMED. In fact, this team has already initiated collaborations with the other groups here.

A particular strength of the team is their focus on the problem of drug addiction, which is an acute problem confronting modern societies. They have published a number of important breakthroughs on this subject recently.

This team will benefit greatly from the excellent infrastructure and expertise at INMED and will be able to even increase their productivity in the future.

    - Weaknesses and threats

No significant problems. However, this team is rather small with few permanent positions, which can be a hindrance for the continuity of some of their projects.

    - Recommendations

This team should continue with their current successful strategy, which will certainly lead to many further breakthroughs in the future.

Title of the team 11 : Maturation and plasticity of cortical maps

- Name of the team or project leader : Ingrid BUREAU

- 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 (Forms 2.2, 2.4 and 2.7 of the application file) | 3 | 1 |
| N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) | 0 | 0 |
| N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file) | 0 | |
| N6: Number of Ph.D. students (Form 2.8 of the application file) | 1 | |
| N7: Number of staff members with a HDR or a similar grade | 0 | 1 |

- Appreciation on the results

This team (only one PI) has been created recently (Avenir team from 2007). The publications of the PI during the last "quadriennal" were therefore mostly signed out of the INMED, but for 2 (one review in J Physiol and original data in Frontiers in neural circuits 2011). The publications signed out of the INMED are, nevertheless, related to the project developed at INMED and of extremely high quality (2 Plos Biol, 1 Nat Neurosci, and 1 J Neurosci) underlining the high potential of this team. Their recent INMED publication is an important contribution in the field of understanding how brain encodes information from the external word and use them to adapt behavior. Indeed, their data reveal that associative learning alters the canonical columnar organization of functional ascending projections and strengthens transcolumnar excitatory projections in barrel cortex. These phenomena could participate to the transformation of the whisker somatotopic map induced by associative learning. It is a basic science of very high interest involving state-of-the-art technology.

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

The PI has been invited recurrently in international conferences. She is one of the internationally recognized expert people on Laser Scanning Photostimulation (LSPS). She participated to international teaching programs to present LSPS. The PI got highly international competitive grants such as HFSP and Avenir. The team is well integrated within the unit (two collaborations with two other teams).

- Appreciation on the scientific strategy and the project

The project is a very ambitious project. Indeed, the challenge taking by the PI for the next "quadriennal" is to explore in vivo associative plasticity of whisker-evoked responses using multi-electrode arrays. The PI has the competence to perform such a project. However, due to very high competition in this field and the size of the team, it is very important to find a niche. They also propose to perform two projects in collaboration with 2 other teams: i) investigate the potential relation between cortical plasticity and learning performance by studying the effect of inactivation of FRMP specifically in the somatosensory cortex (using a specific Cre mouse line) on learning deficits, ii) study the effect of cortical dysplasia on network construction. Although these projects are of interest, it is important to avoid dispersion at this stage of the PI career. Overall, the project should bring important breakthroughs.

- Conclusion
    - Summary

It is a very promising team, with a very challenging project based on an excellent technical expertise.

- Strengths and opportunities

This small team is located in an adapted environment making the project feasible beside the size of the team.

- Weaknesses and threats

The field of research is highly competitive, and the PI should therefore keep in mind to develop its own niche.

- Recommendations

The PI should keep in mind to develop its own specificity and focus the activity of the team in developing its own project.

| Intitulé UR / équipe | C1 | C2 | C3 | C4 | Note globale |
|---|---|---|---|---|---|
| INMED-INSTITUT DE NEUROBIOLOGIE DE LA MEDITERRANÉE | A+ | A+ | A+ | A+ | A+ |
| DEVELOPMENTAL SEQUENCES, INFANTILE EPILEPSIES AND NEUROLOGICAL DISORDERS [REPRESA-BEN-ARI] | A+ | A+ | Non noté | A+ | A+ |
| MATURATION AND PLASTICITY OF CORTICAL MAPS [REPRESA-BUREAU] | Non noté | A | Non noté | A | A |
| MATURATION OF CORTICAL GABAERGIC MICROCIRCUITS [REPRESA-COSSART] | A+ | A+ | Non noté | A+ | A+ |
| PATHOPHYSIOLOGY OF TEMPORAL LOBE EPILEPSY [REPRESA-CREPEL] | A+ | A | Non noté | A+ | A+ |
| ROLE OF KCC2 AND BDNF IN CONSTRUCTION OF CORTICAL AND HIPPOCAMPAL NEURONAL NETWORKS [REPRESA-GAIARSA-MEDYNA] | A | A | Non noté | A | A |
| PHYSIOLOGICAL AND PATHOLOGICAL OSCILLATIONS IN THE BASAL GANGLIA [REPRESA-HAMMOND] | A | A+ | Non noté | A | A |
| TEAM EARLY ACTIVITY IN THE DEVELOPING BRAIN [REPRESA-KHAZIPOV] | A+ | A+ | Non noté | A+ | A+ |
| PATHOPHYSIOLOGY OF SYNAPTIC PLASTICITY [REPRESA-MANZONI] | A+ | A+ | Non noté | A+ | A+ |
| NEURODEVELOPMENT, GENETIC AND EPIGENETIC: INVESTIGATION OF PRADER-WILLI SYNDROME [REPRESA-MUSCATELLI-BOSSY] | A | A | Non noté | A | A |
| CORTICAL DEVELOPMENT DISORDERS AND EPILEPSY [REPRESA-REPRESA] | A | A+ | Non noté | A | A |
| GENETICS OF EPILEPSIES, EITHER ISOLATED OR ASSOCIATED (GEIA) [REPRESA-SZEPETOWSKI] | A | A | Non noté | A | A |

**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**

# General observations on AERES report of the research unit

## Institut de Neurobiologie de la Méditerranée (UMR 901)

# From the

## Université Aix-Marseille 2

19 April 2011

Institut de Neurobiologie de la Méditerranée (INMED) - Institut National de la Santé et de la Recherche Médicale (INSERM)
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UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Objet : Réponse au rapport d'évaluation - **S2UR120001642 - INMED-Institut de Neurobiologie de la Mediterranée - 0131843H** - de l'unité INMED-Institut de Neurobiologie de la Méditerranée

Observations d'Aix-Marseille Université

The University of Aix-Marseille, will help the unit to improve its animal facilities.

Specific comments of teams are detailed below:

**Team 1: Developmental sequences, infantile epilepsies and neurological disorders (Y. Ben-Ari & N. Burnashev)**

As suggested by the committee the team is evolving though a transitional phase anticipating smoothly the retirement of his present director. Independence is already in progress for sub-team 1, which has just got a Fritz Thyssen research grant in collaboration with Dr A. Becker (University of Bonn) providing financial support for the proposed project. As for the second sub-team, the evolution over the next two years, in terms of recruitment of post-docs and grant application success, will clarify if it emerges as a new team (the project itself was not criticized) or if it integrates other INMED teams (some options have already been debated at the INMED scientific council).

**Team 4: Role of KCC2 and BDNF in construction of cortical and hippocampal neuronal networks (J.-L. Gaiarsa & I. Medyna)**

The indicated weaknesses are 1) the present of three PI's in the team and 2) the lack of funding.

1) Dr. Claudio Rivera recently obtained a chair of excellence at the University of Aix-Marseille. He will join the group during about 2 years until he could create his own team. As noticed by the visiting committee, the arrival of Claudio Rivera in the team is a great opportunity. Claudio Rivera is a word know specialist of KCC2 expression and regulation by BDNF. He has a great experience in molecular techniques. He will help the team to study "the molecular mechanisms that govern BDNF secretion and uptake by neighbouring cells" as recommended by the committee. In the future, the team headed by Dr. Rivera will study the contribution of KCC2 in the emergence of pathological conditions and on the plasticity of glutamatergic synapses. We will of course maintain a close collaboration between the two future teams.

2) *"The experiments strategy to study KCC2 trafficking needs to be defined"*. As stated in the application form, the team has developed different molecular tools to study the trafficking and function of KCC2 such as 2 shRNAs to silent KCC2, 2 non-active mutated forms of KCC2 and numerous chimera proteins composed of KCC2 and different fluorescent

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proteins (EGFP, Phluorine). These molecular tools were used successfully to modify the neuronal expression of the KCC2 allowing us to discover a critical role of the KCC2 in the formation of functional GABAergic synapses (Chudotvorova et al., J. Physiol, 2005) and in the maintenance of neuronal resistance to different neurotoxic treatments (Pellegrino et al., J. Physiol., 2011 published during the evaluation period).

*"The main experimental approach relies on BDNF over expression, when the main goal of is to study the role of endogenous BDNF".* As stated in the application form, the major portion of our previous work, as well as future projects, is devoted to study the action of endogenous BDNF on the maturation and plasticity of GABAergic synapses. The team has shown that ongoing synaptic activity in acute hippocampal slices can trigger a secretion of endogenous BDNF that in turn contribute to the functional maturation of GABAergic synapses (Fiorentino et al., J. Neurosci. 2009; Kuczewski et al., J. Physiol. 2008). Team has also developed an immuno-staining assay (based on the detection of the phosphorylated form of CREB) and ELISA to measure and monitor endogenous BDNF secretion in acute living hippocampal slices (Kuczewski et al., J. Neurosci. 2008; Kuczewski et al., J. Physiol. 2008; Kuczewski et al., J. Neurochem. 2011. The team will combine in future experiments these approaches with electrophysiological recordings on acute slices and cultures to evaluate the activity-dependent proteolysis and action of BDNF in the developing hippocampus.

*"The focus should be on the strength of the preparation used (culture system)".* As stated in the application form, in addition of using culture system (heterologous expression systems, primary neuronal and organotypic slice cultures), the team will use in vivo and ex-vivo (living acute brain slices) models. Our previous publications illustrate that we can successfully use a combination of different preparations and techniques that are appropriated to asked questions. For instance, we have used knock-out mice, neuronal cultures, acute hippocampal slices, intact hippocampal preparations, electrophysiological recordings, immuno-staining, Ca2+ imaging and time lapse imaging to study activity-dependent secretion and action of BDNF on developing GABAergic synapses (Fiorentino et al., J. Neurosci. 2009).

**Team 7: Genetic of isolated and associated epilepsies (P. Szepetowski)**

*1/ Appreciation on the scientific strategy and the project: 'A key issue will be to show rescue of the knocked out/down gene, both with the wild type rodent and human genes. Without that rescue, the idea of testing the effect of the human mutation would at least need a different strategy, if it were possible at all. In that case, the PI may need to develop alternative plans rather quickly.'*

Rescue experiments with both the rat and the human genes were indeed obtained and shown during the visit – hence supporting the feasibility of this task.

Rescue with the rat gene had also been mentioned in the file provided prior to the visit: '*In utero* experiments (...) that included rescue experiments with wild-type rat Srpx2 actually demonstrated altered pattern of radial neuronal migration in the embryonic cortex.'

*2/ Appreciation of the results: 'This team has only recently started at the unit so they do not have an extensive track record here – just one paper in Epilepsia.'*

Since start at INMED (Jan 2009), the team has got six INMED-labeled publications (all in 2010), five of which with PI as last and senior author. Two publications were in Human Molecular Genetics, two in PLoS One.

*3/ about financial support: 'This team is new to INMED so it is too early to tell whether it will prosper here.' 'If the funding position is OK'*
Since its integration at INMED the team got two grants (including an ANR) and participates to two additional collaborative grants. In total the team obtained 386 000 Euros from a total of 1 240 000 Euros in 2010, securing the development of the proposed project.

**<u>Team 8:</u> Neurodevelopment, genetic and epigenetic: investigation of Prader-Willi syndrome (F. Muscatelli-Bossy)**

As the Committee correctly pointed out, the team moved recently to INMED in 2008, to pursue its scientific project. Thereof the size of the team has been reduced to the PI, a PhD student and a contractual technician, for about three years. Despite this transitory situation, the team published 7 original articles, 5 as last author for the PI over 2006-2010. Furthermore, one patent has been internationally registered and, presently, clinical trials are ongoing. During this period, the PI obtained competitive grants to support the team research including salary for technician and students (475K€) and has already secured 362K€ for the next period. To strengthen the team in the future, the PI has successfully attracted two tenured senior scientists with strong expertise in Neurobiology (joining the team in 2011).

*1- in the "Conclusion": "Small new team with limited resources yet...."*
During the 2006-2010 period, the team raised a total of 475K€ (EC, AFM and Le Jeune). Moreover, for the next following 5 years period, we already have secured 362K€ (including an ANR grant coordinated by the PI; 610K€ overall and 235K€ for the team) and obtained an FRM grand equipment grant with two other INMED groups (380K€).

*2- "modest publication record in recent years"*
The team published 7 original articles, 5 as last author for the PI (1 Hum. Mol. Genet. (IF: 7.4) and 1 J. of Neuroscience (IF: 7.2)). One international patent (EP10305545, Ref. MUSCATEL09731NC, Applicant: INSERM Country FR) has been obtained.

*3- "The team leader is a recognized authority in the very specialized field of Prader-Willi Syndrome."*
As highlighted by the reviewer, Prader-Willi is classified as a rare disease (1/15000), but the scope of our research is not limited to only a rare disease. Indeed, *in vivo* studies on mouse models reveal new physiological, cellular and molecular neuronal pathways involved in vital functions, particularly at birth time. Consequently, our work is of importance for more fundamental and general biological mechanisms.. This is supported by the fact that the PI has been invited to give a talk in two international meetings not focused on PWS. Our publication record also confirms that our work concerns a wide audience in Biology (genetics, development, and neurobiology). One more indicator for this specific aspect is the diversity of ongoing international collaborations.

4- *in the Appreciation on the results*: *"The number of publications and outputs of the group, as acknowledged in the report (p. 90) by the leader, is limited."*
The number of publications during this period is not impressive but they do constitute sound publications mainly because they are based on *in vivo* investigations with an integrative approach. Indeed, considering the list of publications (and one patent), the grants, the collaborations and attractiveness, it is clearly not limited.

*5- in the Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners. She and her colleagues collaborate with scientists locally, nationally and with a laboratory abroad."*
The PI has three European collaborations: Pr. Swaab Dick (Amsterdam, Netherlands), Pr. De Backer Olivier (Namur, Belgium), Dr Brunelli Sylvia (Milan, Italy) and two international collaborations: Dr. Fainzilber Mike (Tel Aviv, Israel) and Pr. E. Deneris (Cleveland, USA). Three publications have been issued from these collaborations and one is in preparation.

*6-"Invitations are limited"*
A total of 7 European/ international meetings were attended as an invited speaker during the 2006-2010 period: European Meeting on Prader-Willi, 2008, Cambridge (UK); International symposium on Respiratory control, 2008, (France;, NGF international meeting, Katzir conference, 2008 (Israël); European workshop on PWS: 23-25 September 2007 (Amsterdam); IPWSO meeting, 2007, Cluj-Napoca (Roumania); International meeting on PWS , 2006, Toulouse; Scientific European meeting experts of the Prader-Willi French association,2006, Marseille (the PI was the organizer).

**<u>Team 11:</u> Maturation and plasticity of cortical maps (I. Bureau)**
*"The PI should keep in mind to develop its own specificity and focus the activity of the team in developing its own project":*

The intentions are to give priority to investigate the plasticity and role of somatosensory cortical circuits in associative learning. The setting of in vivo recordings with multi-electrode arrays within the team is a logical extension to our approach in vitro (LSPS) as the two techniques complement each other in the functional investigation of circuits. This development will consolidate our niche since the two techniques were never combined before. The study on a mouse model of Fragile X syndrome is entirely within the scope of the project because the knock-down of FMRP was shown to deteriorate the learning performance of mice. The team goal is to correlate this deficit with abnormalities in the plasticity of neuronal circuits in conditional mutants that display the mutation in the somatosensory cortex only. This study is already ongoing. In contrast, the developments of collaborative projects with the teams of A. Represa and O. Manzoni teams are conditioned by the hiring of new post-docs. These projects will allow to better understand the relationships between the pattern and the function of cortical circuits.

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