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

Section des Unités de recherche

AERES report on the research unit

Neuro-Dol

From the

Université d'Auvergne

INSERM

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: Neuro-DoI

Requested label : UMR_INSERM

Name of the director: Mr. Alain ESCHALIER

Members of the review committee

Committee chairman :

Mr. Luis GARCIA-LARREA, Université de Lyon 1, Lyon

Other committee members:

Mr. Troels STAEHELIN JENSEN, Aarhus University Hospital, Aarhus, Denmark

Mr. Michel POHL, Université Paris 6, Paris

Mr. Rafael MALDONADO, University P. Fabra, Barcelona, Spain

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Mr. André SALAGNAC, CHU

Report

1 • Introduction

- Date and execution of the visit

The visit took place in Clermont-Ferrand on February 18th, 2011. The Committee was composed by an international panel of scientists, each one with recognised expertise in at least one of the areas represented by the teams being evaluated. One of the members could not attend personally the visit, but sent his report and interacted with the Committee on the basis of his appreciation of the written document.

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

The NEURO-DOL project aims at joining together 4 research groups (two Inserm Units and two University labs) all located in the Clemont-Ferrand University & Hospital Campus. The project is based of their common interest in translational neuroscience, and their mastering of a vast array of complementary technical approaches. The explicit driving force of the Project is "to bring together all neuroscientists in Clermont-Ferrand", so as to develop new projects and enhance their international visibility and competitiveness.

The project is organized around 3 main domains: pain (teams 1 and 2), dopamine-related conditions (addition and Parkinson's disease; team 3), and neurosensory biophysics (team 4). Together with their respective research lines, transversal projects are meant to articulate and consolidate the interactions among the groups: development of predictive animal and human pain models based on clinical needs (Teams 1 and 2) pain in Parkinson's disease (Teams 1, 2 and 3); and migraine and intracranial pressure (Teams 1, 2 and 4).

The new Unit will host 58 researchers (38 university, 19 hospital & post-doc, 1 full-time CNRS), 19 technical & administrative, and 18 PhD students. Habilitation to supervise research has been granted to 28 members of the team. According to the AERES translative rules, the full-time equivalents (ETPs) are 21.9 researchers and 14.4 technical-administrative staff.

- Management team

The new Unit will be directed by Alain Eschalier (curently head of Inserm UMR 766), to be replaced by Radhouane Dallel (currently head of Inserm UMR 929) in two years' time. The Director will be assisted by a Directory Board composed by the team leaders plus the chief of the Center for clinical investigation (CIC), themselves as part of the Unit Council including 2 senior researchers per team, 2 technician/administrative, 2 PhD students and 3 post-docs.

- 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)	39	38
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	18	18
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	19	19
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	23	21
N7: Number of staff members with a HDR or a similar grade	29	28

2 • Overall appreciation on the research unit

- Summary

This venture brings together four research teams with different backgrounds, to constitute a common Unit which should associate all the neuroscience workforce in Clermont-Ferrand. The common project line of the new Unit is largely focused on pain research, although this orientation corresponds to the natural history of two of the teams only (T1 and T2), the two others having research lines focused respectively on Parkinson's disease (T3) and sensory receptor biophysics (T4). A number of transversal projects have been conceived to promote conceptual convergence among the teams, but each of the four groups will pursue and develop in parallel its own line of research. The possibility of joining together all the neuroscientific forces of Clermont-Ferrand, strongly backed by the University d'Auvergne, is an appealing project to which this Committee is favourable, notwithstanding the likely difficulties and threats derived from the dissimilar research objectives and heterogeneity of the teams' past and present work. These will be discussed further in the sections below, and with more detail in the sections devoted to each particular team.

- Strengths and opportunities

  - Very good leadership of the Director, who is a respected and well-recognised neuroscientist in his field. His management is appreciated by all the members this Committee had the opportunity to meet, formal or informally, not only researchers but also PhD studients, post-docs and technical-administrative staff.

  - Enthusiastic adherence of technical staff to the project, with some groups already sharing experimental areas and animal housing facilities.

- Strong suport from the University d'Auvergne, as shown by the fervent backing provided during the meeting held by the Committee and a number of high-rank univesity officials, including the Dean and Vice-dean of medical and pharmacy faculties, and the Director of the university hospital. The team leaders and other members of the four groups are prominent actors in virtually al the Degrees, Master and PhD tracks in neuroscience currently held in Clermont-Ferrand university.

- Excellent technological platforms authorising a wide array of approaches in neuroscience, ranging from molecular - cellular biology and immunohistochemistry to behavioral models, clinical assessment and epidemiology. Good (although uneven) capacity to obtain external funding.

- Strong commitment to develop translational, and especially reverse-translational research, with the aim of developing animal models derived from (and hence relevant to) actual clinical conditions.

- Weaknesses and threats

  - More than a common goal, there seem to exist "shared goals" between the teams, with no clear difference between the present project and that of a unit gathering teams 1 & 2, and collaborating on specific projects with teams 3 and 4. The Unit project heavily relies in a continuation of the research lines already established by each of the teams, rather than on a true integrated scientific endeavour, which entails the lack of a clear research focus involving all the teams.

  - Lack of full-time researchers. This was considered as a weakness in the Unit's written document, and also spontaneously during the Committee's discussion with the technical staff. The only full-time researcher included in the project (from Team 4) is fully involved in the study of photoreceptor alignment mechanisms –a project not included in any of the transversal projects of the Unit.

  - Heterogeneity across teams in publication level, international renown and impact (see specific comments below). Heterogeneity in research strategies too: although all teams theoretically apply a translational research to validate in humans concepts derived from basic research, this is (currently) the case for two of the groups only.

  - Low attractiveness, as reflected by the small number of foreign postdoctoral fellows and the lack of new full researchers recruited in the past years.

- Recommendations

Given the lack of a current integrated research line, efforts should be devoted to improve the common dynamics of the future Unit. Increasing the number and originality of transversal projects, including risky ones, should be helpful for this (but may be difficult to implement if each group continues its own research unchanged). Interactions among PhDs and post-docs of different teams should be fostered, as they are effective ways to increase the scientific exchanges and connections across groups (only one PhD student was "common" to 2 temas in the past). The group may consider whether the name NEURO-DOL is appropriate for a research unit whose activities will be only partially focused on pain. Rather than pain-oriented, the project might be better described as one devoted to "the neuroscience of sensory, motor and motivational behaviours".

The Committee considers important to emphasise that the current leader of Team 1 is not only considered to be essential for Team 1 but he will also be instrumental for the future success of the entire new Unit as such. This is important given the possibility that he might withdraw form the project before the end of the grant.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	32
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	1
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0.85
A4: Number of HDR granted during the past 4 years	3
A5: Number of PhD granted during the past 4 years	18

3 • Specific comments

- Appreciation on the results

  * **Relevance and the originality of the research, quality and impact of the scientific output:** In the period concerned by this assessment (2006-2010) the group has published 256 international papers, 45% in journals with IF>5. Eighteen PhD theses have been supervised, and 69 international presentations honored. These figures are sizeable considering a "full-time equivalent" (ETP) of 22 researchers. Relevant results have been produced both in the basic and clinical domains; for some teams, this has represented real breakthroughs in their field. In the basic domain, the groups have often been in the lead for the conception, performance and in-house analysis of results; conversely, in the clinical domain the teams have frequently acted as collaborators, sometimes included in multi-site networks (see detailed comments in each of the teams' appreciation below).

  * **Partnership and valorisation :** Partnerships are multiple and most of them stable. Industrial collaboration and valorisation of results are very good, with 5 patents filed and one startup in operation. Ability to rise external, competitive funding (independent from recurrent institutional support) is high, with >1.5M€ in public or private grants (PHRCs, INCA, Regional Council, NeuroDis, but also pharma and food industry). The teams participate to national multi-site clinical networks, among others in headache and deep stimulation studies. France being leader in multicentric work in these areas, the presence of the teams is fruitful and commendable.

  * **Impact & attractiveness of the research teams :** Attractiveness is still low, if we judge by the few post-docs and the lack of recruitments of researchers in the last 5 years. This is only partially counterbalanced by regular visits of foreign senior researchers. International recgnition, although good to excellent for the Unit Leader, remains limited for most of the other members. Invitations to international conferences and symposia are globally scarce, with substantial differences across teams (see below), suggesting a need to increase the visibility and impact of the research being done. One of the main aims of this joint project is to revert this situation and enhance the international presence of the joint team.

  * **Contribution to teaching and organisational programs :** The contribution of the unit members to teaching and structuration of local academic life is remarkable. The fact that very good scientific work has been produced by individuals with such important clinical and academic duties has impressed the Committee. There is a very important local support to the project from the Clermont-Ferrand University (University d'Auvergne).

* **Appreciation on the management and life of the research unit :** The management and internal life of the individual research teams appear very good, with a number of journal clubs, regular meetings, visitors' lectures and organisation of internal and external seminars. Clear policies have been develped for the allocation of ressources if the Unit is created. Students, post-docs and technical / administrative staff were generally happy with the ambance wthin the labs and willing to pursue the path and to work together. The question whether such organisation will smoothly proceed toward a similar inter-group articulation in the future Unit remains open.

* **Appreciation on the scientific strategy and the project :** The project sets special emphasis in the study of pain mechanisms, and on scientific grounds it appears reasonably feasible within the next 5 years. However, the project does not give an impression of multi-level integration toward a common goal in pain research, as one might expect from a unit labeled 'Neuro-Dol". While there are indeed three transversal projects on pain research involving different team combinations, it appears that each of the non-pain oriented groups (Teams 3 and 4) will continue its pain-independent research, respectively on addiction and Parkinson's disease (T3) and on auditory and eye sensory biophysics (T4), independently of their collaborating in the transversal projects. The name Neuro-Dol may therefore appear misleading. The evolution toward a strong focusing on pain, with teams 3 and 4 driving all their research potential to pain-oriented projects, apears irrealistic. A better option seems to conceive a more "generalistic" unit focusing its forces on *the neuroscience of sensory, motor and motivational behaviours*, with strong translational commitment which would foster originality and cutting edge projects.

4 • Appreciation team by team

Title of the team: Clinical and Basic Pharmacology of Pain

Name of the team or project leader: Mr. Alain ESCHALIER

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	15	15
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3.9	3.9
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form **2.8** of the application file)	9	
N7: Number of staff members with a HDR or a similar grade	8	8

- Appreciation on the results

Relevance and the originality of the research, quality and impact of the results : This is a well-recognized international group in neuropathic pain and their contributions on this particular topic have been very sound. The team has produced original and impacting results in the field of the pharmacology of pain systems and pain-relieving drugs, using a wide number of techniques ranging form molecular and cellular biology and immuno-histochemistry in transgenic mice, to behavioral pain models (rodent and human) and clinical assessment in patients.. Novel insights on pain pharmacology concerns both the results obtained directly within the team's laboratory and related departments (central mechanism of acetaminophen, opioid-dependent action of antidepressants, Edonis postoperative cohort) as well as those worked up in collaboration with other teams, notably in Montpellier and Sophia-Antipolis Universities (T-Ca Channels ; 5-HT2A-linked proteins; TREK-1, Asic and metabotropic Glu-III channels), Santiago de Chile (Dopamine receptors) and Lund (TRPV1 and acetaminophen). The ensemble of these results, with associated patents to both the leader and other fellow members, have positioned the team as an internatonally respected research group.

Quality and number of the publications and other scientific outputs : The group has a good publication track, with 62 papers in international peer-reviewed journals between 2006 and 2010 (one third with IF>5, including most highly ranked journals such as Nature and EMBO). The citation index of the leader (H=32) corresponds to a good recording track in the field of neuroscience; accordingly, he is included as a top scientist in the Essential Science Indicators (field: pharmacology). The average presence of team members in publications is 35%. However, despite the lack of full-time researchers, the team members are first or last authors in 58% of papers (65% if we consider the "equal contributions"), suggesting that they were leading the research in a majority of cases. The group has honoured 75 invitations to lecture in congresses

and symposia, of which 20% were in international meetings. It collaborates with a number of national and international laboratories in the field, as well as with an impressive number of industrial partners. It should be emphasised that such scientific output was obtained despite enormous teaching duties by some of the team members (one member with 385 hours/year and several others with more than 200 hours/year).

Impact and attractiveness of the team. Quality of the links with international, national and local partners : Team n° 1 has developed academic and research links with universities in France and abroad (Montpellier, Lille, Sophia Antipolis, Santiago de Chile, Lund, Barcelona). These partnerships are stable and of good quality, and have given rise to joint publications in good – to very good Journals, to which the team appears to have represented an added value. It is however not always clear which was exactly the role of each collaborator in the published papers. Recruitment of scientists and PhDs is essentially at local level, but we may note two doctoral students having done their cursus in Paris, and one further from China. Support from the local university and regional council is extremely strong. The team has shown ability to successfully apply for competitive funding, and to participate to scientific and industrial clusters. Local and national attractiveness as estimated by external funding is important, with more than 1.5 M€ obtained in 2006-2009 of which 70% was from external non-institutional sources. Attractiveness and scientific impact estimated by invitation to international events is however still limited (16 invitations in the past 4-year period).

- Appreciation on the scientific strategy and the project

As per the written document and the oral presentations, the team will continue, on the one hand, its current work on a number of lines previously explored, and on the other hand will develop transversal projects within the new proposed joint Unit, especially with team 2 also involved in pain research, in what is described as a "joint pain project". The latter considers the pathophysiology and pharmacology of pain, especially "trigeminal pain and migraine, neuropathic pain and visceral hypersensitivity". This appears highly ambitious, as it includes virtually all types of clinical pain with the exception of non-cranial inflammatory pain. The committee appreciates and commends the team's backbone proposal that reverse translational research (i.e. from the clinics down to the models) is to be privileged as a mandatory step to develop preclinical models that are relevant for human pain. This notion has granted meaningful results in recent years, e.g. with oxaliplatine-induced neuropathy, and the team leader -well aware of the insuficiencies of current pain models- is determined to pursuit this path. The Committee would have appreciated more precise data on how this reverse translation will be specifically fostered in the next years, besides the non-selective post-surgical cohort that is being studied. With the exception of the assessment of the role of 5-HT2A receptors at trigeminal and spinal levels, the item on "discovery of new concepts" remains rather vague, especially in what concerns the specific work to disclose mechanisms of neuropathic pain, as well as on the "selected pain syndromes" that will be explored. It is the Committee's impression that most of the work will prolong the past activity of the team on monoamines and ion channels. In this respect the project, although motivating and feasible, appears to privilege the continuation of a previous path rather than incorporate innovative and risky approaches.

The transversal projects with other teams in the proposed new Unit concern mainly pain in Parkinson's disease, and specifically the investigation of the effects of LDopa and deep brain stimulation (DBS) on subjective pain thresholds. The proposed cross-over, randomized and double blind study is an attractive, but not entirely original project, and it is perhaps regrettable that other more innovative joint projects have not been conceived in the field of dopamine and pain. The Committee also notes in this project that only subjective measures are considered, which may represent a caveat given the many different biases present in subjective responses from patients, especially following invasive procedures. Incorporation of objective physiological measures of pain processing (electrophysiological brain responses, spinal nociceptive reflexes, functional imaging data) would be important to ensure the relevance and reliability of results and to increase the originality of this work. Given the clinical commonalities between positive pathological symptoms in the auditory and somatosensory systems (eg tinnitus, hyperacusia and neuropathic pain) the Committee is surprised that no transversal project takes profit of the expertise of Team 4 in the biophysics of auditory transduction to develop byophysical models of the processes leading from sensory deafferentation to system hyperactivity. This may provide important insights, including therapeutical, into the commonalities between tinnitus, hyperacusis and neuropathic pain.

- Conclusion:

  - Summary

An active team with strong leadership, good track and high potentialities in pain pharmacology. Important visibility and publication track of the leader, who is included in the list of top scientists for the 2000-2010 period.

  - Strengths and opportunities

Mastering of a wide range of techniques, from cellular and molecular biology (mainly in collaborative programs) to immuno-histochemistry, behavioural studies and clinical trials. Experience with animal models of neuropathic pain and knowledge of their current insufficiencies. The opportunity to work in close interaction with other teams within the same Unit and benefit from a wider spectrum of cliically-founded hypotheses.

  - Weaknesses and threats

In the Committee's opinion, the main three weaknessess are (i) the lack of full-time researchers, which dampens the weight of the group when collaborating with other labs and reduces international impact; (ii) the temptation to follow existing paths and research lines, which limits the likelihood of breakthrough discoveries, and (iii) a too restrictive collaboration in projects with teams 3 and 4.

  - Recommendations:

Include innovative and risky research axes together with conventional procedures. This committee recommends caution with the models that are used, as some of those explored in the past may not be applicable to humans –thus explaining divergent results relative to clinical work. The new models (oxaliplatin-induced pain, mouse IBS model) may be a better option for that. Include objective measures of pain perception in humans (brain responses) to assess the effects of DBS and/or LDopa. Take profit of the skills of team 4 to develop collaboration on byophysical models tagging the processes that lead from deafferentation to hyperactivity. This may provide important insights into the commonalities between tinnitus and hyperacusis and neuropathic pain. Eefforts to recrute permanent full-time researchers should be highly rewarding.

Title of the team: Neurobiology of the trigeminal pain

Name of the team or project leader: Mr. Radhouane DALLEL

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	10	10
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form **2.8** of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	8	8

- Appreciation on the results

Relevance and the originality of the research, quality and impact of the results : Focused on the mechanisms of trigeminal pain, the team's scientific activity in basic neurobiology has been original and creative, with significant contributions to the study of processes relevant for wind up, spinal mechanisms of allodynia and corticofugal controls in animal models. The clinical work performed so far is largelly independent from these results, rather than being translative, although some efforts are currently done to create genuine progresion from basic results into the clinics.

Quality and number of the publications and other scientific outputs : As a whole, the team has a good publication track with 68 published papers in international journals in the last 5 years (plus 15 'collaborative' articles). 17% of articles appeared in high ranked journals (J Neurosci, Lancet Neurol, Pain, Brain, Arch Neurol). The citation rank of the group members, including the leader, remains however moderate (H=19), reflecting the uneven impact of different lines of research. The overall proportion of team members that participate to the publications is sizeable (~40%). A number of studies presented as emerging from the group did not include explicitely the research unit as the main affiliation of any of the authors. This is especially the case of clinical studies, and suggests that part of this work was not conceived, conducted or analyzed within the team itself, but rather performed as part of the clinical activities in connected networks (e.g. the French headache or multiple sclerosis networks). The actual team's contribution to multi-authored papers to which only one member participates is difficult to assess. However, we note that the team members are first or last authors in an overall 60% of their production (~85% in basic science, ~45% in clinical studies), indicating their prominent role in most of their basic science work. The team has honoured 23 invitations to lecture in international congresses and symposia, of which 11 in Europe or America. It collaborates with a number of national and international laboratories in the field, as well as with an important number of industrial partners.

Impact and attractiveness of the team. Quality of the links with international, national and local partners : Good to very good local and national attractiveness. Quality and stability of partnerships is excellent, particularly the clinical partnerships and collaborations. Good capacity to attract clinicians proficient in headache and trigeminal pain from distant cities in France (eg Nice, Marseille) thanks to a resolute shift toward the inclusion of clinical approaches. Very active team in promoting and enhancing the visibility of pain research. The leader has succeeded in launching and coordinating a French pain network that is now operational, as well as starting a francophone French – Quebec pain network. Links with these partners appear stable and solid. Attractiveness is less in the international domain, and international presence of post-docs is limited despite the potential appeal of the group. Some disproportion exists between administrative and scientific strategical activities and international renown, which remains limited.

- Appreciation on the scientific strategy and the project

Substantial part of the research force will be devoted to continue and develop existing projects, notably on the mechanisms of allodynia, while joint schemes will be developed in parallel, in collaboration with the other teams of the new Unit. Some of the presented projects appear relatively superficial and/or unfocused, with some lack of mechanistic questioning. The joint project with Team n° 1 is the most comprehensive, and considers "the pathophysiology and pharmacology of trigeminal pain and migraine, neuropathic pain and visceral hypersensitivity". Quite pushy and purposefully translational, the specific strategy of this joint project remains however ambiguous. Other collaborations concern pain in Parkinson's disease (with team 3) and pain and intracranial pressure (with team 4). The Committee acknowledges the proven capacity of the team and the energy of its leader to carry out multidirectional work, but also fears that the lack of a clear global strategy may hamper the efficacy of parts of the project. Human potential is solid, and care should be taken to ensure that each of the sub-projects that are foreseen is adequately articulated with the others and thus contributes to foster a general strategy. In this context, the part of the project dealing with studies of potential predictors of chronic pain appears rather vague in its strategy.

- Conclusion:

  - Summary :

A solidly established group in trigeminal pain research, with good track and ambitious projects. Joint projects with other pain groups should icrease its international impact.

  - Strengths and opportunities:

The team has recently developed close partnerships with clinical departments and the CIC which should allow genuine translational research. Multidisciplinarity and collaborative clinical work prompted by the proposed multi-team association should enhance international visibility and attractiveness.

  - Weaknesses and threats:

Cooperation between basic, preclinical and clinical members of the group is not obvious; as a consequence clinical and basic work appear disjoint and the general strategy as a group remains poorly visible. Lack of full time researchers to conduct basic and preclinical work is a risk. The exact status of the team in the conception, conduction and analysis of clinical projects remains ambiguous. The claimed leadership of the team in trigeminal/cephalic pain studies is not yet sufficiently translated in high-quality publications, and some disbalance appears between important funding, high number of researchers involved in a given scientific project and the corresponding output. Lack of collaborative projects with teams 3 and 4.

- Recommendations:

The idea to study the trigeminal system from the basic and clinical point of view is in essence a good and logical one, which potential can fit into projects carried out by Team 1. The committee fears however that too much emphasis is put on one single basic mechanism of allodynia (PKC gamma hypothesis) to explain the various phenomena of clinical hyperexcitability in the trigeminal complex. The group may consider to include other types of animal models or mechanisms in order to explore and understand better the differences and possible similarities of pains in the trigeminal and extra-trigeminal regions. Thoroughly questioning the mechanistic aspects of some of the team's observations, and tackling these in a less restrictive manner would probably make the project gain in importance. It will be important in this respect to have clearer links between the basic and clinical part. Also the team may want to focus their clinical studies and limit the number of different pain conditions so that a a common hypothesis can be explored.

The specific niche of the team's research should deserve more risky projects launching new ideas and innovative views on cephalic pain that, in many aspects, is particular and distinct from somatic pain. Patients in cohort trials should be tested as much as possible with physiological means (not just questionnaires), with efforts devoted to derive mechanisms also from clinical work, so as to develop genuine translational projects that are still lacking. The cellular and molecular approaches should be developed, particularly in combined efforts with Team n°1. Important attention should be also given to improve the international positionning of the Team in this hyghly focused research.

Title of the team: Neuropsychopharmacology of subcortical dopaminergic systems

Name of the team or project leader: Mr. Frank DURIF

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	6	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	9	9
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form **2.8** of the application file)	6	
N7: Number of staff members with a HDR or a similar grade	5	5

- Appreciation on the results

Relevance and originality of the research, quality and impact of the results : Emerging group of researchers and clinicians (created 2004) with special interest in the clinical changes arising from dysfunction of dopaminergic pathways, and the use of dep brain stimulation (DBS) as a tool for therapeutics and functional exploration of Basal Ganglia functions. In the clinical domain, the team has produced interesting clinical data on energy expenditure and weight changes following subthalamic stimulation, with good progression toward subsequent studies on non-insulin dependent increased endoglucogenesis and glucose intolerance in implanted PD patients. The early descriptive work on manic states induced by DBS contacts in the Substantia Nigra (SN) was followed by more sophisticated and elegant functional imaging studies demonstrating on-line limbic activation in correlation with the development of the hypomanic state. In preclinical domains, the team has used nuclear magnetic resonance to assess the impact of dopamine depletion on basal ganglia metabolism in models of Parkinson's disease (mice, rats and primates), and produced important data on Glutamate and GABA increases in the striatum of MPTP-mice, reversed with Ldopa administration, as well as dissociation between ventral and dorsal striatum according to the respective severity of VTA and SN lesion. The team participates to a number of multi-site clinical studies too, mainly in the context of Parkinson's disease (PD).

Quality and number of the publications and other scientific outputs : The team reports 63 international pblications between 2005-2010, mostly in mid-level journals, but with 20% in most highly ranked journals such as J Physiol, Brain, Archives Gen Psych, Ann Neurol or NEJM. The citation rank remains moderate (leader H=20). The average participation of members of the team to published articles is very low (16%) especially in clinical and genetic studies, suggesting that a substantial part of this work was not conceived, conducted or analyzed within the team itself, but rather performed as part of the activity of large-scale national networks or fellow clinicians.

Impact and attractiveness of the team. Quality of the links with international, national and local partners : The team is involved in local, regional and national clinical activities, including neurostimulation networks and industry. Very important local teaching and administrative duties (Direction of Federative Research Institute, responsabilities in Master-1, Master-2 and other educational programs, etc). Local and regional partnerships appear stable, attractivity to students is important at the local level, with good capacity to invite external funding. Five out of 15 tenured members (33%) have an habilitation to direct research (HDR). Team members have gained entrance into important epidemiological PD networks, but this may have been to the detriment of their own availability to conceive, conduct, analyze and expand their own research. Perhaps as a consequence of this, the national and international visibility of the team is very limited, with only 5 national, and no international invitations to lecture in congress or symposia.

- Appreciation on the scientific strategy and the project

Analysis of past achievements shows a good continuity and logical progression of studies within basic and clinical projects, but without real connection between them. This lack of continuity from pre-clinical to clinical work is detrimental to the group, and at odds with the translational programme announced (a similar problem as in team 2). As examples, data on the possible combination of metabolic studies in Acc – striatum and the study of impulsivity in humans are lacking, as is the case for the progression from NMR data in animal models to possible clinical markers. The Committee expects this situation to be reverted in the context of the new multi-team Unit. The project of the group, labelled now "addiction and Parkinson's disease", concerns the disorders of impulse control in Parkinson's disease, primary addiction, and animal models of these. This clearly calls for strong collaborations between clinical and basic research, to relate the pathophysiology of addictive behaviour explored through the recording of human brain activity with the cellular and molecular bases of similar behaviour in animal models of rodents and primates. Serious concerns may arise with regard to the study of the addictive properties of dopamine agonists in an animal model of Parkinson's disease, as 6-OHDA lesions will certainly modify locomotor performance, which may represent a major bias for the interpretation of the self-administration and conditioned place preference results. It is expected that the team will make use of its multidisciplinary capacities and find the way to adequately solve these problems and connect preclinical and clinical work.

- Conclusion:

  - Summary :

Multidisciplinary and multi-competence group allying neurologists and psychiatrists in the domain of Parkinson's disease (past) and of dopamine control of behaviour (project).

  - Strengths and opportunities:

Associating neurological and psychiatric clinical skills together with competence in the manipulation of (i) dopamine depletion models (mice, rat and monkey), (ii) NMR procedures and (iii) deep brain stimulation is undoubtedly an enormous strength. The study of the behavioural disorders associated to Parkinson's disease is a new field of research which offers the opportunity to this young team to find their specificity at the national and international level. Joining a multi-team Unit is the opportunity to reach maturity as a research group, develop renown and international existence.

  - Weaknesses and threats:

Lack of international renown and impact. Lack of full-time researchers and (perhaps as a consequence) lack of real translational work from models to the clinics and vice-versa. Most publications (especially clinical) are still coupled with other 'major' teams, with a very moderate representation of the group in the international major publications to which they participate.

- Recommendations:

Increase the connections with the global group. The team could benefit from using the expertise of team 1 and team 2 to explore further pain in PD in order to connect the teams better and develop cooperation in the domain of the dopamine regulation of pain control. Pain is an almost neglected area in Parkinson's and related disease, with number of unanswered questions –well beyond the simple epidemiological trials of "pain in Parkinson disease". Given the large databases and large experiences of DBS for movement disorders in France there is an obvious opportunity for the team to join forces with teams 1 and 2 and explore various issues related to pain and Parkinsonism.

Go ahead in the research of behavioural disorders associated to PD and extend this research to similar disorders in psychiatry. It could be more appropriate to turn the context of these projects toward the impulsive and compulsive disorders rather than the field of addiction, which is more associated to drug abuse. The study of non-motor symptoms in Parkinson's disease (pain and behavioural disorders) will allow this team to establish the link with the other teams of Neurodol project and to find its specificity with the other teams at the national level.

Title of the team: Biophysics of sensory handicap

Name of the team or project leader: Mr. Paul AVAN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6	6
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
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	8	8

- Appreciation on the results

Relevance and originality of the research, quality and impact of the results : The team "Biophysics of sensory handicap" focuses on the development of non-invasive measurements of sensory cell activity (cochlear hair cells and retinal photoreceptors), with the aim of modelling the neurophysiological interaction of receptors with their adequate physical stimuli. The team has combined reflectometric methods and in vivo electrophysiological recordings to detect sensorineural impairments due to the absence of specific molecules, using mutant mice developed through collaboration with UMR 587 at Pasteur Institute (Pr Ch Petit). Either through genetically engineered mice or by creating damage to the sensory cells (e.g. by overexposure to intense noise), the team has analysed mechanisms whereby a number of molecules contribute to sensory auditory performance. Among the molecules investigated with the use of mutants, at least 4 (Otoferlin, Vezatin, Stereocilin and Pejvakin) have been the object of publications in important Journals such as Cell or Nature genetics, although the actual contribution of the team members to these papers (1 out of 14 co-authors) is difficult to assess.

The team has contributed to establish the molecular origin of sounds re-emitted by a category of cochlear sensory cells, and shown that ability to emit sound from hair cells relies on suppressive masking. This last result may be of importance for future studies of hearing in noise. Although limited, the contribution of the team to these papers appears significant, as it provides the original approach of their reflectometry measurements (otoacoustic emissions), and in at least one case (stereocilin) the leader of the group is clearly indicated as a major contributor in the conception and realisation of the study. In other cases, (e.g. pejvakin) the team leader can be granted for having conceived and performed the experiments on abnormal susceptibility to noise exposure. Should similar genetic features be found in humans, this could represent a significant first step in the prevention against noise trauma, in which individual susceptibility plays a major role but remains presently unpredictable.

Quality and number of the publications and other scientific outputs : The team reports 29 principal articles and (separately) 40 papers qualified as "minor or unrelated to the main themes of the unit". This very honest presentation of the scientific production is much appreciated by the Committee. The average participation of team members to the reported papers is moderate (21%), but it increases steadily from 2006 to 2010. In half of the papers a member of the team is first or last author, and in 35% (10/29) both first and last authors are from the group. International recognition remains modest, with citation index H=22 for the leader. Of 45 invited lectures in 5 years, only a rough quarter (28%) was international.

Impact and attractiveness of the team. Quality of the links with international, national and local partners : Long-lasting, stable and fruitful partnership with Institut Pasteur in Paris. In recent years, researchers from Pasteur come regularly to the team's lab to work in situ, which suggest a growing impact and renown of the group. The Institut Pasteur group seem to have definitely established the Clermont-Ferrand team as its partner for all reflectometry measures applied to genetic studies of deafness. On its own the group succeeded in developing a variety of clinical potential applications of their reflectometry measures for cochlear and retinal explorations. The approach is technically new and worth exploring, and the C-F group has succeeded in setting a national and international network for these explorations. The development of the group in terms of formation to research is illustrated by two PhD students, both from distant universities in France (Paris and Tours). Two PhD thesis and 1 HDR obtained in the period concerned by this report.

- Appreciation on the scientific strategy and the project

Given the theoretical and technical competencies of this group the two main but clearly distinct lines of research are fully relevant. The association with the Institut Pasteur team provides a fruitful and mutual benefit. The exploration of genetic aspects of deafness is extremely promising, and the position of the team in this context seems established for the coming years. The clinical (diagnostic) line of research is still in exploratory phase. Although the first results seem promising, only a very limited number of patients have been reported so far, and a large amount of data on patients groups is still required to set the potential clinical interest. The team has succeeded in involving several clinical groups at national and international level, which should reasonably guarantee that valuable data will be gathered in the following years. The technique involved is new, relevant on theoretical grounds, and worth exploring. This could certainly be performed over a period of about four years. In the context of the future project, a general drawback is the lack of major collaborative projects with the other teams.

- Conclusion:

  - Summary :

The team "Biophysics of sensory handicap" has a distinctive profile relative to the 3 other groups of this multi-unit project. This relatively small team uses resolutely translational approaches; it is the only to include a full-time researcher (CR1 CNRS) and the one presenting with a most favourable percentage of members having habilitation to direct research (90% of tenured researchers have HDR). It is also the only to have launched and supported a startup company that builds and commercialises a system for medical electrophysiology derived from the team's past research (Echodia®). Renown and international impact are low, and as a whole it might have difficulties to stand alone; however, it appears important that it be with the multi-team group, to which it should definitely represent an added value.

  - Strengths and opportunities:

The team has developed original theoretical and technical competencies in a specific domain of biophysics –reflectometry. Its strategy to valorise these is wisely two-faced: the first is based on a successful and long term cooperation with the Institut Pasteur, which has brought extremely rewarding benefits in terms of basic science. The second deals with clinical applications and is still in an exploratory phase; a multi-centric is being established, which should permit in about four years to validate or nuance the proposed approaches.

- Weaknesses and threats:

Excessive confidence in the reliability and clinical applicability of the diagnostic systems derived from their basic research. It remains unclear which were the preclinical tests supporting the diagnostic value of these systems before being put "in the market". Diagnostic validation of phase change detection concern very few subjects and still less patients, thus sensitivity and specificity of the measures for detecting pathology remain unknown. The same may be applied to the detection of intracranial pressure changes in the future joint project, which should need extensive cross confirmation versus standard ICP probes before being accepted as a standard.

- Recommendations:

The research topic of this team being outside the main research activities of the Unit, the presence of additional collaborative projects with other teams of the Unity should be of outmost importance. There is a great collaborative potential that should be taken into consideration. The importance of pain research in the Neuro-Dol project suggests that the team should consider the inclusion of hyperacusis and tinnitus as models relevant for the development of positive symptoms following sensory deafferentation, which may be of importance for the understanding of neuropathic pain mechanisms. Each new translated application in these or other domains should be extensively tested in patients' samples.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
NEURO-DOL	**A**	**A**	**A+**	**A**	**A**
NEUROSENSORY BIOPHYSICS [ESCHALIER-AVAN]	A	A	Non noté	A	A
TRIGEMINAL PAIN AND MIGRAINE [ESCHALIER-DALLEL]	A	A	Non noté	A	A
ADDICTION AND PARKINSON'S DISEASE [ESCHALIER-DURIF]	B	B	Non noté	A	B
FUNDAMENTAL AND CLINICAL PHARMACOLOGY OF PAIN [ESCHALIER-ESCHALIER]	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**

UNIVERSITÉ
D'AUVERGNE
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Clermont-Ferrand, le 8 juillet 2011

Le Président

et

Le Vice-président du Conseil Scientifique

à

Monsieur Pierre Glorieux
Directeur de la section des unités de recherche
AERES
20 rue Vivienne
75002 Paris

OBJET : Rapport d'évaluation S2UR120001919 – NEURO-DOL – 0631262E

Direction de la Recherche

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N/réf. :DR-IR/AL/2011 N°216

Monsieur le Directeur,

Je vous prie de bien vouloir trouver ci-joint les observations de portée générale concernant le rapport d'évaluation de l'unité « NEURO-DOL» dirigée par le Professeur Alain Eschalier, envoyé le 20 avril 2011, observations que j'approuve bien évidemment.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de mes sentiments les plus cordiaux.

Professeur Philippe Dulbecco
Président de l'Université d'Auvergne

Professeur Alain Eschalier
Vice-président du Conseil Scientifique

Reply to the AERES report on the
NEURO- UNIT, UNIVERITY OF AUVERGNE
Director: Alain ESCHALIER

(Note: *in blue and italic are the comments from the AERES report*)

We thank the committee for their appreciative remarks and recommendations. We want to take this opportunity to address some points raised by the committee and highlight what we feel are some minor misunderstandings and omissions in the report.

REPLY TO THE SPECIFIC COMMENTS ON THE UNIT

University, School and Research Organization representatives

As mentioned in the report other representatives than Ph. Dulbecco (President of the University) and A. Salagnac (Vice-Director of the University Hospital) were present: T. Orliaguet (Dean of the Odontology Faculty), J. Fialip (Dean of the Pharmacy Faculty), P. Clavelou (Vice-Dean of the Medicine Faculty).

Introduction

Management team.
Alain Eschalier will be replaced by Radhouane Dallel in 3,5 years' time from 1st January 2012.

Overall appreciation on the research unit / Specific comments

We just want to mention that the President of the University was involved in the "the fervent backing provided during the meeting held by the Committee and a number of high-rank university officials".
We appreciate that the committee considers that joining together all neuroscience forces in Clermont-Ferrand is an appealing project, notwithstanding difficulties and threats we will discuss below.
We are pleased to read that the committee feels the technical staff very enthusiastic about the project. This is absolutely true and very important for the success of the unit. The excellent available technological platforms and the very good relationship maintained with researchers and students contribute to this unity.

Scientific strategy and project
Whether we do have '*a common goal*' is obviously a critical issue.
Three different topics and several transverse projects were indeed presented. We understand that this organization look more like '*shared projects*' from '*a unit gathering teams 1 & 2, and collaborating on specific projects with teams 3 and 4*" than '*a true integrated scientific endeavor*' for a Unit. However, we do think that initiating such transverse projects will serve as a trigger to common dynamics for our new Unit. Pain was selected as a common topic for these transverse projects because (1) there are two teams (out of four) specialized in pain research, (2) team 1 and 3

have previously collaborated within this field, and (3) we are convinced that such a field will provide us with a rapid onset of integrative work.
Indeed, beyond this initial step, we plan to develop scientific projects with actually '*a clear research focus involving all the teams*' – thus following committee's recommendation – : e.g. dopamine and sensory, motor and motivational behaviors. Such scientific integration should be facilitated by our decision to co-direct PhD students on transverse projects and share technical approaches and facilities. Moreover, that all our teams be involved in both pre-clinical and clinical research – not so frequent in France – will certainly help us to build up a homogeneous unit. Finally (not so unexpectedly) combining such different expertise might be a chance to very original scientific approaches in poorly or unexplored fields: e.g. pain in Parkinson's disease and migraine and intracranial pressure.
We want to emphasize that we are strongly committed to lead neuroscience up to an excellent level in Clermont-Ferrand and we will thus take all committee's recommendations into account to reach this goal.

Lack of full-time researchers.
Though we achieved a good scientific production – according to committee's own statements – with a lack of full-time researchers, we agree, as stated in the written document, that this lack is a weakness. Through improving our attractiveness, we plan to welcome full time researchers and have PhD students applying to Inserm or CNRS. Moreover, we are discussing with the university for having teacher/researchers with reduced teaching duties (Institut Universitaire de France, chaire mixte…).

Translational research.
As mentioned by the committee, we are strongly committed in developing translational or "reverse-translational" research; thanks to the specificity of our four teams which all include basic researchers as well as clinicians and perform both basic and clinical studies.
The committee argues that only Team 1 and 4 currently perform translational research. We want to stress the point that Team 2 is developing a translational research too, assessing DNIC impairment in animal models of migraine and looking for such pathophysiological mechanism in patients with chronic migraine. Together with the pre-clinical study of the involvement of descending serotonergic and dopaminergic controls in DNIC, such a demonstration might lead to new concepts for managing migraine-evoked allodynia (see below).
From an improvement of knowledge on pathophysiology of impulse disorders and addictions in animal models of Parkinson's disease, Team 3 will develop new concepts to treat these disorders in Parkinson's disease. To date, no therapeutic management is available to improve impulse disorders in PD.

Low attractiveness.
We agree we need to improve our attractiveness to increase the number of foreign postdoctoral fellows. Efforts are made in that sense regarding both post-doctoral fellows and researchers (see specific team replies below).

Unit leader.
Alain Eschalier thanks the committee for its highly positive comments regarding his activity. Nevertheless, he wants to make clear that he will stop managing the Unit on September 2015, though he will certainly stay a member of this Unit beyond this date. This will provide enough time to Denis Ardid and Radhouane Dallel to be ready to manage Team 1 and the Unit, respectively. Their current experiences and their willpower led us to consider that they will be able to draw the

Unit, ensure its future success which will be strengthened by its good collective atmosphere and the decrease of the average age of its members.

Relevance and the originality of the research, quality and impact of the scientific output.
We appreciate the positive committee's comments regarding the relevance of our scientific results and specifying '*the fact that very good scientific work has been produced by individuals with such important clinical and academic duties has impressed the Committee* '. Regarding clinical studies, we agree that we have acted as collaborators but we also would like to point out that we have initiated several clinical works (see team replies) including multi-site work (eg Edonis study, around 3000 post-surgery neuropathic pain patients).

Partnership and valorisation.
We would like to precise that we have created two start-up (one for Team 1 and one for Team 4).

REPLY TO THE SPECIFIC COMMENTS ON THE TEAMS

TEAM 1 (A ESCHALIER)

- We thank the committee for its review and very positive assessment, but also for its constructive recommendations. We particularly appreciate comments made on scientific production regarding teacher/researchers heavy teaching duties.
- We will take into account comments made on our international attractiveness and attempt to welcome more foreign students (eg we will welcome a Spanish post-doctoral fellow in the next weeks) and scientists (we will recruit an external assistant professor in the next years).
- We would like to clarify the "reverse translational" strategy we will develop in the next years: (i) by working on clinically effective analgesics (in terms of both analgesic and adverse effects); (ii) by setting-up new relevant animal models (eg post-infectious colonic pain) or assessing so far poorly investigated pain associated symptoms (eg assessment of cognitive or emotional pain components); (iii) by determining human pathophysiology (Edonis study and studies focused on patients suffering from IBS) to propose relevant new targets. We think this strategy is rare and therefore original. Moreover several topics are new and risky: dissociation of analgesics and adverse effects of morphine which could lead to a totally, never reached, novel concept; neurochemical investigation of the supra-spinal components of neuropathic pain in animals; assessment of changes in ionic channels expression in IBS patient's colonic biopsies.
- We fully agree with the committee's recommendations regarding animal pain models, therefore our "reversed translational" strategy, more risky that the "benchside to bed" strategy, was chosen due to our awareness of model insufficiencies pointed out by the committee.
- Regarding the three mentioned weaknesses and recommendations: (i) we are attempting to recruit full-time researchers and to obtain reduced teaching duty of teacher/researchers; (ii) we include more innovative and risky paths (see above) but we take into account the committee's comments to do more; (iii) we will reconsider our collaborative work with team 3 and 4 according to the committee recommendations.

TEAM 2 (R DALLEL)

Thanks to the committee for their constructive critical comments. We are pleased to see that the committee believes that '*the idea to study the trigeminal system from the basic and clinical point of view is in essence a good and logical one*' and that our scientific projects is 'ambitious'.

We would like to underline the specificity of our team – '*A solidly established group in trigeminal pain research*' as stressed by the committee – as being the only one in France and one of the very few in Europe involved in translational research on trigeminal pain and migraine. A quick survey of articles published in *Pain* (the premier and most respected journal on pain) in 2006-2011 with the search terms 'trigeminal pain', 'rat' and 'mouse' retrieves 30 papers, out of which 6 are from European laboratories, including 4 from our own group (Coste et al., 2008; Lapirot et al, 2009; Miraucourt et al. in press; Lapirot et al. in press).
In addition, the committee acknowledges our '*very good local and national attractiveness*', our strong involvement in '*promoting and enhancing the visibility of pain research*' and '*the proven capacity of* (our) *team … to carry out multidirectional work*'.

We would like to address the following issues raised by the committee.

APPRECIATION ON THE RESULTS

The Committee notes that '*Attractiveness is less in the international domain, and international presence of post-docs is limited despite the potential appeal of the group*.'
Although we do agree with the Committee that increasing recruitment from abroad should be encouraged, may we note that, in the past four years, 1 of 2 post-docs and 3 of 7 PhDs did come from abroad (Chile, Mexico, Syria). For the time being, 1 of 3 post-docs and 2 of 7 PhDs come from abroad (India, Lebanon, Tunisia). We will try of course to further improve these figures in the future.

APPRECIATION ON THE SCIENTIFIC STRATEGY AND THE PROJECT

It thus appears as if '*substantial part of the research force will be devoted to continue and develop existing projects, notably on the mechanisms of allodynia'*. And the committee '*fears however that too much emphasis is put on one single basic mechanism of allodynia (PKC gamma hypothesis) to explain the various phenomena of clinical hyperexcitability in the trigeminal complex.*'
The PKC gamma hypothesis is only a limited part of our project that is about the basic mechanisms of tactile allodynia, one of the most disrupting symptoms of pathological pain. We plan to investigate **a whole range of molecular and cellular mechanisms**. We will explore how changes in polysynaptic circuits of medullary dorsal horn (MDH) can account for focal mechanical allodynia, and delineate the role of descending inhibitory controls in widespread allodynia. Please, note that we are developing two cellular and molecular techniques to investigate these questions in our laboratory. To explore the functioning of MDH neuronal networks, we will use *in vitro* electrophysiology to record (with the patch-clamp technique) from visually recognized (infrared microscopy) MDH neurons. We are also developing laser capture microdissection and gene array analysis to assess gene expression in subclasses of MDH neurons.
Finally, we want to stress the point that a substantial part of our research force will be actually devoted in **developing a totally new project on migraine, thus a '***risky project launching new ideas and innovative views on cephalic pain that, in many aspects, is particular and distinct from somatic pain'*. Accordingly, the name of our team is now: '**Trigeminal pain and migraine**'.

The following committee's comment suggests that clarification is needed: '*The joint project with Team n°1 is the most comprehensive, and considers "the pathophysiology and pharmacology of trigeminal pain and migraine, neuropathic pain and visceral hypersensitivity". Quite pushy and purposefully translational, the specific strategy of this joint project remains however ambiguous.*'
First, each of teams 1 and 2 will go on with its own projects: the pharmacology of neuropathic pain and visceral hypersensitivity (Team 1), the pathophysiology of trigeminal neuropathic pain and migraine (Team 2). In addition, teams 1 and 2 will cooperate to implement two joint projects:

(1) Addressing the role of 5-HT_{2A} receptors in animal models of pains in the trigeminal (Team 2) and extra-trigeminal regions (Team 1): basic, preclinical research;
(2) Assessing the prevalence and characteristics of postoperative neuropathic pain at 3 and 6 months after surgery: clinical research. We have already initiated a large epidemiologic study (> 3000 patients) and data analysis is on-going. We will extent this study by assessing the genetic risk factors of neuropathic pain (the project is supported by Inserm and by a national PHRC 2010).

The committee '*fears that the lack of a clear global strategy may hamper the efficacy of parts of the project*'. Clearly, we need to better explain our '*general strategy as a group'* since it *'remains poorly visible'*.
Our global strategy is to perform translational research focused on two clinical pain symptoms: focal mechanical allodynia and widespread extracephalic cutaneous allodynia. Such strategy can be summarized by the table below. It shows the '*links between the basic and clinical part*' and how '*each of the sub-projects that are foreseen is adequately articulated*':

	Local, dorsal horn mechanisms of focal mechanical allodynia	**Role of descending inhibitory controls in widespread allodynia**
Basic, preclinical research	From tactile information to pain: changes in synaptic processing within medullary dorsal horn circuits (including PKCγ interneurons) in animal models of trigeminal neuropathic pain and migraine.	1. Anatomy and pharmacology of Diffuse Noxious Inhibitory Controls (DNIC): involvement of serotoninergic (from the rostral ventromedial medulla) and dopaminergic (from A11) descending controls. 2. Can deficient DNIC account for widespread allodynia in animal models of chronic migraine?
Clinical research	Role of nerve compression, demyelination and deafferentation in trigeminal neuralgia, a clinical model of focal mechanical allodynia.	Can deficient DNIC account for widespread allodynia in patient with chronic migraine?
	Analysis of potential predictors of chronic pain (collaborative project with team 1)	

CONCLUSION :

Weaknesses and threats:

Whereas it was true that '*Cooperation between basic, preclinical and clinical members of the group* (was) *not obvious, as a consequence clinical and basic works appear(ed) disjoint*', this issue is being improved in the project.
We have **focused** our **basic and clinical research projects on only two questions**: focal mechanical allodynia and widespread extracephalic cutaneous allodynia (see above) **to make clinical and basic work joint.**
Basic, preclinical and clinical members of the group have the opportunity to sit together at least **twice a week** (every Monday and Tuesday).

The committee is concerned about '*The exact status of the team in the conception, conduction and analysis of clinical projects* (being) *ambiguous'.*
All the clinical projects are designed and managed by members of our group.

In agreement with the committee, we '*focus* (our) *clinical studies and limit the number of different pain conditions so that a common hypothesis can be explored*'. We have selected three clinical conditions: trigeminal neuralgia, a typical human model of mechanical allodynia; chronic migraine and burning mouth syndrome, two human models of widespread allodynia.

'Lack of collaborative projects with teams 3 and 4.' This might be a 'copy and paste' mistake since the committee acknowledges somewhere else in the report '*Other collaborations concern*(ing) *pain in Parkinson's disease (with team 3) and pain and intracranial pressure (with team 4)*'.
Recommendations:

The committee suggests to '*include other types of animal models*'. As indicated in the project, we will address the above questions in **three animal models** of pain, including a new animal model of migraine developed by our team.

We agree with committee's recommendation that '*patients in cohort trials should be tested as much as possible with physiological means (not just questionnaires),…*'.
We plan to (1) use Quantitative Sensory Testing (QST), (2) record trigeminal reflexes and laser-evoked potentials, (3) assess DNIC; that is, measure pain intensity for a 'test' stimulus (heat stimulus on the hand) before, during and after the application of a noxious 'conditioning' stimulus (foot in cold water), (4) use functional as well as conventional magnetic resonance imaging and panoramic radiographs in addition to (5) administering questionnaires for anxiety, depression (State-Trait Anxiety Inventory, Beck Depression Inventory, Pain Catastrophizing Scale) and addiction (Iowa Gambling Task).

'*The cellular and molecular approaches should be developed, particularly in combined efforts with Team n°1*.' We agree with this recommendation. We have recently introduced in our laboratory two cellular and molecular techniques: in vitro electrophysiology in brain slices and laser capture microdissection and gene array analysis (see above).
Moreover, it has to be emphasized that the NEURO-DOL project aims at joining together 4 research groups mastering a vast array of complementary technical approaches with a major commitment in developing cellular and molecular approaches.

Finally, it is worth mentioning that since the visit of the committee, three additional articles have been published: Lapirot et al., Pain, in press, 2011; Miraucourt et al., Pain, in press, 2011, Dualé et al., Reg Anesth Pain Med, in press, 2011. We also obtained four grants (altogether: 300 000 €): from the Neurodis (creation of young research team) and Apicil foundations, Pierre Fabre laboratories and the Ministry of Foreign Affairs. And, the university has recently given us a position of associate professor (MCU).

TEAM 3 (F DURIF)

•We thank the committee for its review and for its recommendations. We would just bring some remarks from the evaluation of our team

Quality and number of the publications and other scientific outputs

As reported by the committee, we are participating to several studies including national networks in the field of psychiatry and neurology with a relatively weak impact of our team in published articles. However, we are also promoter of several national research programs who are ongoing in the field of addictions and deep brain stimulation of subthalamic nucleus, validation of behavioral scales in Parkinson's disease, impact of botulinum toxin in the treatment of dystonia in Parkinson's disease. These studies will give international publications with a strong participation of our team. In the future, an effort could be done to limit our participation to collaborative national studies with strong scientific impact such as genetic studies (for which a national network is mandatory) in the aim to focus the researchers of the team to the "heart" of our project.

Appreciation on the scientific strategy and the project

One of the part of our project, perhaps badly explained in our project and during the oral presentation of the team, is to join the preclinical and clinical projects of the team. Firstly, we would like to use our expertise in NMRS to explore the metabolic activity of brain areas implicated in addiction in animals. We have recently submitted an article on the metabolic profile of the NAc after dopaminergic lesion in the mouse : Does MPTP intoxication in mice induce metabolic changes in the nucleus accumbens? An 1H nuclear magnetic resonance spectroscopy study. Carine Chassain , Guy Bielicki, Carole Carcenac, Anne-Claire Ronsin, Jean-Pierre Renou, Marc Savasta, Franck Durif. (submitted). We also are assessing the metabolic profile using 1H NMRS in the motor and the limbic part of the striatum in rats during STN-DBS (collaborative project with Kerkerian Lydia-, Marseille-ANR 2011 submitted). We finally use 1H NMRS in parkinsonian patients to look at the metabolic profile in the striatum to quantify Gln+ Glu and gaba and if this first study is a success, we propose to test this approach in patients with addictions. This project is however risky due to the relatively low field of our magnet using for clinical research (3T) compared to the spectrometers used in animals (9.4-11.7 T). The methodological development in NMRS performed in animals will help to do this project.
Secondly, we would like to assess other behavioral disorders than drug addictions in animals. A recent post-doc recruited in our team this year who has an expertise in the domain of food behavior, will explore food behavior in animal model of PD. In the field of the clinical research, we have several projects to study the addiction to antiparkinsonian drugs, and also the binge eating using metrological, epidemiological, and physiopathological approaches with imaging (Pet-scan, fMRI).

Concerning the animal models of Parkinson's disease and lesion of the SN, we explore animals after motor recovery (1 month) giving ability to assess the behavior of animals using CPP. Furthermore, lesion of VTA does not change the locomotor performance of the animals. Thus, we think this model of lesion is acceptable to study the addictive properties of dopamine agonists.

Our transversal project is to develop collaboration with team 1 and 2 in the field of pain and Parkinson's disease. Clinical trials are ongoing (stomatodynia and Parkinson's disease, effect of STN-DBS and Ldopa on pain In Parkinson's disease. On a preclinical field, we have a project to study allodynia in animal models of PD (rat) and after lesion of the VTA. Our preliminary data demonstrated the presence of allodynia in SNc 6-OHDA denervated rats. This neuropathic pain process was present in the 6-OHDA lesioned rats for more than 2 months post-lesion. Furthermore the intracisternal injection of dopamine receptor 2 agonist decreased the neuropathic behavior in the 6-OHDA lesioned rats suggesting important role of the lack of dopamine in the induction/appearance of the neuropathic pain.

Conclusion-Recommandations

Owing to the multidisciplinary aspect of our team allying neurologists and psychiatrists , we have chosen to do a new project focusing only on impulse disorders and addictions in PD. In the aim to have reconnaissance on this project, we did avoid scattering in other domains of behavioral disorders in PD. Of course, the development of the team with recruitment of full researchers could permit to assess other behavioral dimensions in PD but also in other psychiatric pathologies. Pain and Parkinson's disease is a transversal project which is in progress in the clinical field. We would like to develop the preclinical approach with shared PhD students or post-doc from team 1 and 2. Finally, we totally agree with the committee to the obligation to have full researchers in our team. Discussion will be done of this point with the university.

TEAM 4 (P AVAN)

We thank the committee for their fair evaluation and constructive suggestions aimed at encouraging the clinical validation of our novel reflectometric equipment. We would like to bring to the committee's attention the following remarks addressing some of their concerns.

'Among the molecules investigated with the use of mutants, at least 4 (Otoferlin, Vezatin, Stereocilin and Pejvakin) have been the object of publications in important Journals such as Cell or Nature genetics, although the actual contribution of the team members to these papers (1 out of 14 co-authors) is difficult to assess.'

Similar to the Nature paper mentioned a few paragraphs further in the report, these papers followed the conventional rule that the last co-author is the most important senior researcher in charge, then the importance of the involvement is in reverse order. Paul Avan was ranked 2 or 3 in this respect. The part played by the Clermont lab, as acknowledged elsewhere by the AERES committee, was to assess the impact of the missing molecule in vivo. We could thus show, in Cell, that no there was no neural activity up to 115 dB, thus that no putative rescuing process was at work. For the pejvakin model published in Nature Genetics, our in vivo tests proved that the molecule acted in neurons, whereas antibodies (later found to be aspecific), by marking the outer hair cells, led to a misinterpretation. For vezatin, we implemented the in vivo stress tests revealing accelerated evolution.

'Diagnostic validation of phase change detection concern very few subjects and still less patients, thus sensitivity and specificity of the measures for detecting pathology remain unknown.'
A paper entitled 'Unstable distortion-product otoacoustic emission phase in Menière's disease', by P.Avan, F.Giraudet, B.Chauveau, L.Gilain, T.Mom, all members of team 4, has just come out in Hearing Research (Impact Factor: 2.2; now available online at doi:10.1016/j.heares.2011.03.006). It reports on results on 41 definite Menière patients followed up at least 3 times over a period of 3 months. This paper was not mentioned in our presentation, being still in the submission process.

Paper 'Otoacoustic emissions: a new tool for monitoring intracranial pressure changes through stapes displacements', Hear.Res 1996, 94, 125-139, by Avan et al., reported on 21 patients with increased ICP (intracranial pressure) and direct ICP controls through a spinal tap in parallel (an average of 8 measurements per ear at different, directly measured ICPs). This was not mentioned, as only our papers in the last 5 year-interval were cited. Thus the patented methods have already been controlled in several sizeable cohorts of patients.

Yet we are well aware of the urge for confirming our new technology in more cohorts, as aptly pinpointed by the committee. The risky strategy of building the equipment and putting it in the market before validating it fully was made necessary by the pressing need to have portable, ergonomic equipment to replace off-the-shelf, makeshift cumbersome devices. This turned out to be instrumental for building a multicentric network for clinical validation. Of late, the Echodia system has been included in protocols in AP-HP and AP-HL hospitals (Prs Sterkers, Dubreuil, ENT) and in a bicentric validation study that we are conducting together with the ICU in the neurosurgery department of the CHU at Clermont and with the Neurology Dept at Leiden (Pr. Ferrari, Drs Vein & van Oosterhout; IRB approval just granted). Last, we have just completed a manuscript reporting on our successful non-invasive follow-up over a period of 30 months of 50 patients having received a surgically implanted ventriculo-peritoneal shunt for chronic adult hydrocephalus.