INM - Institut des neurosciences physiopathologie et thérapies des déficits sensoriels et moteurs

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Sensory pathology, neuroplasticity and therapies

From the

University Montpellier 1

University Montpellier 2

CNRS

INSERM

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

July 2010

Research Unit

Name of the research unit: Sensory pathology, neuroplasticity and therapies

Requested label: UMR CNRS, UMR_S INSERM

N° in the case of renewal:

Name of the director: Mr Jean-Luc PUEL

Members of the review committee

Committee chairman

Mr Thomas JENTSCH, Leibniz Max-Delbrück-Centrum für Molekulare Medizin, Berlin, Germany

Other committee members

Mr Yvan ARSENIJEVIC, Jules Gonin Eye Hospital, Lausanne, Switzerland

Mr Jos EGGERMONT, University of Calgary, Alberta, Canada

Mr Jonathan ASHMORE, University College London, London, UK

Mr Rob BROWNSTON, Dalhousie University, Halifax, Nova Scotia, Canada

Mrs Maria FITZGERALD, University College London, London, UK

Mr Marco CATANI, Centre for Neuroimaging Sciences, London, UK

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

Mrs Francine BEHAR-COHEN, CSS INSERM member

Mrs Françoise DENOYELLE, CSS INSERM member

Mr Martial RUAT, CoNRS member

Mr Jean-Marie CABELGUEN, CNU member

Observers

AERES scientific advisor

Mr Christophe BERNARD

University, School and Research Organization representatives

Mrs Catherine LABBÉ-JULLIÉ, INSERM

Mr Alexis BRICE, INSERM

Report

1 • Introduction

• Date and execution of the visit

The site visit took place on January 19 and 20, 2010 and was conducted by an international team of scientists who are experts in the areas of research of the 6 research teams that were evaluated. The director of the Unit and the teams (team leaders and members) gave presentations of 40-60 minutes which were followed by intensive discussions with members of the committees. Furthermore, laboratories and technical platforms were visited and the associated Avenir team and start-up companies presented themselves.

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

The Unit is located in the INM (Institut de Neurosciences de Montpellier) on the campus of the Saint-Eloi Univesity Hospital campus, to where INM moved in February 2004. The new Unit, the subject of this application, will succeed INSERM unit U583 which was created on January 1st 2003 and which was directed by Christian Hamel since then. U583, in turn, emerged from three previous units (U254, U336, U432). U583 focused on the investigation and treatment of neurological sensory pathologies and was constituted of 4 teams that were concerned with retinal blindness, physiology and pathology of the inner ear, neurobiology of the somato-sensory system, and spinal cord pathology. U583 has efficiently interacted with the clinics and several start-up companies originated from the Unit. The Unit has steadily increased in size with a total gain of 13 researchers/clinicians between 2005-9. It has had an impressive scientific output with 245 papers in journals with an IF>1 since 2005 (mean IF 5.5) , 67 of them in journals with impact factors >7 and 14 with IF > 10 (of the latter 3 papers with first or corresponding authors from researchers that are now at the Unit (excluding reviews)). The new application for a Unit builds on this strength and now proposes the formation of 6 research teams. Whereas most of these teams emerge from the previous teams and continue to focus on sensory systems, the sixth team is a new addition and adds aspects of glial tumors, stem cells and plasticity as new research areas. There is also a general trend for the teams to emphasise more translational aspects than hitherto, including topics such as stem cell biology and gene therapy.

• Management team

The proposed Unit will be directed by Jean-Luc Puel. The director will be assisted by a steering committee that meets every month and that includes all team leaders, additional researchers for teams with more than 10 members and the general secretary. There will be , furthermore, a Laboratory Council that includes several elected researchers, technicians or administrative staff, as well as representatives of the PhD students and postdoctoral researchers. The Unit is to be overseen on a regular basis by a Scientific Advisory Board that includes two foreign scientists.

- 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)	19	23
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	17	17
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	27	25
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	7	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	26	12
N7: Number of staff members with a HDR or a similar grade	23	26

2 • Overall appreciation on the research unit

- Summary

In structuring the new INSERM Unit, the INM plans to build on the strength of the existing U583 and that had focused on the physiology and pathology of sensory systems and that contains several excellent groups with international visibility. New team leaders have emerged from within the units, creating new independent teams concerned with, for example, the vestibular system and the development of the somatosensory system. The inclusion of the new team 6 intends to extend the research to the human central nervous system and brain plasticity. The presence within the INM of an independent Avenir Junior Group working on developmental aspects of the nervous system further strengthens the Unit. The links to the clinic will be further reinforced, as will be the collaboration with start-up companies. Together with new projects on stem cells and gene therapy there is a certain shift from basic research towards translational aspects. The commendable focus on the physiology and pathology of several sensory systems, including projects aimed at curing relevant pathologies, is combined with a multidisciplinary approach that is supported by several up-to-date technical platforms accessible for all research teams. Many of the proposed projects are promising and feasible, with some of them having potentially a high impact for both basic science and in translation, a feature particularly of some high risk projects. Some projects will be carried out in collaboration between different teams with complementary expertise.

- Strengths and opportunities

Major strengths of the Unit are:

- Several very good to excellent groups with international visibility.
- Synergy of research topics that are concerned with several sensory systems (vision, hearing, equilibrium, somatosensation).
- Multidisciplinarity, broad spectrum of techniques.
- Excellent technical platforms and infrastructure, large number of qualified technicians.
- Strong interactions with clinical groups and with start-up companies that have emerged from the Unit, translational research; 9 patents have been applied for or have been granted since 2005.

- Every team has obtained good funding from various agencies, foundations and companies.
- The leader of the Unit fosters excellence in research and has encouraged researchers to become new team leaders.
- Several members are very active in teaching, 26 theses have been defended between 2005-09 and 12 are ongoing.
- Excellent public dissemination of own research results and science in general.

Weaknesses and threats

- Many groups extend research to stem cells and gene therapy, often without being already internationally competitive in these areas or a clear plan to develop this expertise, for example through recruitment.
- There are doubts whether inclusion of Team 6, with its main focus on human gliomas, will strengthen the Unit or rather detract from the Unit's focus on sensory systems.
- No broad discussion within the Institute of future common research directions.
- Compared to permanent staff, postdocs and Ph.D. students feel poorly integrated and represented, and there is insufficient encouragement and travel funds for them to attend conferences.
- Small number of international staff, including postdoctoral researchers and graduate students.

Recommendations to the head of the research unit

- Focus on existing expertise and strengths of the teams; it might often be better to go more into depth rather than extending research to other areas for several teams may have too many projects in parallel.
- Although translational research is important, teams should not focus on this to the exclusion of pure basic research.
- Publications should not be unduly delayed by the conditions surrounding the establishment of intellectual property (e.g. by patent applications).
- With the current increase in stem cell and gene therapy projects, a field which is already highly competitive, it may be necessary to include a new team or even several teams with an established and a high-level expertise in these areas.
- Reconsider whether inclusion of the new Team 6 will strenghten the Unit; if extension of the Units's interests to central processing of sensory input is desired, a team concerned with CNS neurophysiology and/or anatomy may be better suited; an alternative (or additional) strategy is to consider strengthening the translational aspects of existing groups (see above).
- Continue with the stratgy of fostering successful researchers to become independent and to present work at international meetings, to develop their own scientific profile, and to emerge as new team leaders.
- Organize annual retreats of the Unit to foster discussions and interactions.
- Organize journal clubs to make sure that postdocs and graduate students present papers and their results (in English). Improve participation and representation of postdocs and graduate students in decision-making for the Unit.
- Increase efforts to recruit researchers internationally. It is conceivable that this may be easiest to achieve at a postdoctoral level.
- Allocate funds for common projects between different teams.

- Production results

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	40
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	17
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD granted during the past 4 years	12

3 • Specific comments on the research unit

- Appreciation on the results

The overall productivity of the Unit has been very good. It has made very important contributions in the fields of sensory physiology and pathology. Several human disease genes have been discovered, which was facilitated by close interactions with the Reference Centre for Genetic Sensory Diseases organized by the leader of Team 1. The impact of mutations is being studied using sophisticated mouse models and their phenotypes are being investigated by a broad spectrum of techniques including high quality morphology and electrophysiology as well as behavioural assessments. These mouse models reveal pathophysiological mechanisms, are being used to develop therapeutic approaches (e.g. gene therapy), and are directly relevant to the understanding of human disease. In other approaches, important basic questions have been addressed, concerning for example synaptic transmission at ribbon synapses of cochlear inner hair cells and at calyx synapses in the vestibular organ, or the specification of different types of sensory neurons in the somatosensory system. Novel in vitro systems have been developed that are useful for investigating basic mechanisms and for testing influences of substances such as hormones or drugs. The translational research led to the filing of 9 patents since 2005, to collaborations with industry and to the founding of start-up companies which collaborate closely with some teams of the Unit.

The Unit is internationally competitive and visible, in particular since it combines several excellent groups working in closely related fields of sensory physiology and pathology. The productivity is generally high as evidenced by the number of publications (245) between 2005 and 2009, with 12 papers (excluding reviews) with IF>10 (3 of those with first or last author from Unit). Between 2005 and 2009, 26 students from the Unit were awarded their Ph.D. The medical relevance of the research is underscored by collaborations with clinicians and the pharmaceutical industry, patents and the emergence of start-up companies from within the Unit.

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

The member laboratories have been awarded 17 prizes and awards, e.g. 'Prize Innovation-Research ADER', 'Young Investigator 2009' from Languedoc-Roussillon Region, and 'Prix société internationale d'oto-neurologie 2008'. The Review Panel, however, likes to mention that the awards are not extraordinary and that that few team leaders have been invited to international conferences and symposia.

The Unit has been able to recruit several promising young investigators trained in excellent laboratories, four of whom returned to France from postdoctoral positions abroad. This includes the leader of an independent Avenir team which nicely complements the research of the Unit. The number of postdocs (currently 8, none from abroad) is rather low compared to 40 permanent researchers). The recruitment of foreign scientists needs to be increased.

The Unit has been successful in obtaining competitive funding, with about 4 million Euro over 5 years of external funding from various sources. For instance, in 2008, 299 k€ was obtained from European Union, 97 k€ from national public sources (ANR), 246 k€ from charities (e.g. AFM), and 33 k€ from private sources (e.g. companies). This compares to 532 k€ for scientific funds and 2816 k€ for salaries from Internal Resources (INSERM, CNRS, Universities). The Unit participates in several European networks (Nanoear, EVI-GENORET, RESCUE, ad starting 2010 E-RARE). A particular strength is the collaboration with clinical researchers, which is facilitated by the location on the campus of the University Hospital, and the establishment of the Reference Centre for Genetic Sensory Diseases. The strong translational aspects have led to a number of collaborations with large pharmaceutical companies (Pierre Fabre, Ipsen, Solvay Pharma) and the foundation of three start-up companies with whom indivual teams collaborate closely.

The Unit participates actively in European networks (E-rare, ERA-Net for research programs on rare diseases, and Nanoear, an Integrated Project of the EU focusing on drug delivery via nanoparticles) and there are a number of individual collaborations with foreign partners, often in the US.

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

A particular strength of the Unit is the focus on sensory systems, combined with multidisciplinary approaches and complementary expertise that provide excellent opportunities for synergy. The creation of several, highly competent technical platforms available to all teams guarantees high technical standards. An animal facility has been established a few years ago and includes laboratory space which is essential for translational research such as creating mouse models for human pathologies. The Unit intends to extend this facility to be able to accommodate more mice, and aims to establish a new standard screening procedure for sensory deficits in mice. In addition, it is planned to further strengthen the morphological platform by STED microscopy and EM tomography. The leadership has encouraged the emergence of new, largely excellent, team leaders from within the Unit. Several promising younger scientists have been recruited, some of whom may soon emerge as new group leaders. Together with the presence of excellent, internationally well-known researchers in the field of vision and hearing, this recipe was and remains the basis for the success and visibility of the Unit.

Another important plus of the Unit is the strength in translational research, involving both the inclusion of clinicians and collaborations with the hospital, as well as the interactions with industry and start-ups. In the plan for the new Unit, this aspect is further stressed, with several teams having initiated or planning projects involving stem cells and gene therapy. Whereas this may seem as a logical step forward, the review panel was sometimes concerned that these projects may not be internationally competitive. Extending research into these directions may require importing external expertise in the form of a new team or at least in the establishment of strong and lasting collaborations with external groups. The panel felt that the inclusion of a new group mainly focussing on gliomas (with some projects on stem cells as well) would not strengthen the technical expertise of the Unit and may rather 'dilute' the focus on sensory systems.

Whereas the organization of the Unit has allowed the emergence of new team leaders and new cutting-edge projects, we encourage the leadership to foster the emergence of further independent researchers e.g. from within the two largest teams. Furthermore, the Unit could profit from more scientific discussions and interactions between scientists and groups, thereby fully exploiting the outstanding opportunities for synergy.

The Unit has an active seminar program (163 internal and 98 external seminars between 2005-9) and organizes regular 1-day seminars (Journée de l'INM) with a mixture of high-profile external and internal speakers. The Review Panel recommends that this program is complemented by journal clubs and a retreat. Members of the Unit organized 6 national or international meetings (2005-9).

Many members of the institute are rather heavily involved in teaching, with 23 professors and associate professors. They teach at the medical school, the faculty of pharmacy, in neurophysiology and neurosciences. The teaching has been recognized and fostered by 7 PEDR Excellence Awards. The number of Ph.D. students has increased from 18 (2005) to 24 (2009). Additional teaching is carried out in the framework of professional licences and master programs. Scientists from other institutes, including from abroad, are hosted for some time to teach them specialized techniques.

In order to facilitate the training and scientific interaction of young postdocs and PhD students and to encourage appreciation of their research in the context of the wider international arena, the Committee recommends that a senior member of the Unit is formally appointed as a Mentor or Facilitator of Training. In this role they would help organise critical reading and analysis, presentation skills, applications for travel funds etc. across the Unit.

There is a fairly large number of technical staff (35), which justifies setting up a "conseil des ITA" with an ad hoc representation to the "conseil d'Unité". This is a must-do. This will ensure that the technicians have the capacity to formally communicate concerns, and ensure transparency in decision-making. It will also provide the capacity for the technicians to formally provide input to the unit as a whole in technical matters, such as for the acquisition of new major equipment.

The technicians wish a greater transparency regarding the policy for promotions. For example, technicians allocated to platform appear to have priority over those belonging to specific groups. Some ITAs wish to remain associated to research teams, a process that management appears resistant to. In general, ITAs express major concerns regarding the management policy of "mutualisation".

The maintenance of the animal facility raises some concern. Six ETP would be needed, and there is a clear lack of competence regarding genotyping.

There are several issues that need to be addressed. For example, one key staff has been employed on a 10-month contract/year by the University for the past 8 years. This trick enables the university to maintain a non-permanent position for someone who should have obtained it a long time ago.

Although the "conseil d'unité" includes ITAs and students, the real decisions appear to be taken by a team composed of the head of the unit, team leaders and other researchers.

These constitute important and vital (for the Unit's life) issues that must be satisfactorily addressed by the Head of the Center.

- Appreciation on the project

The overall concept is excellent and certainly provides a solid basis for research for 4 or more years. It builds on the concentration of expertise on sensory physiology and pathology that is unique for the Unit and combines top-level basic research with translational aspects. Many of the projects are very feasible, whereas others are high-risk, but cutting-edge and with the promise of providing break-throughs if successful. Examples are the generation of new mouse models for mitochondrial diseases affecting both vision and hearing, projects focusing on synaptic transmission at hair cells, and dissection of the specification of somatosensory neurons. These projects are highly original.

On the other hand, the Review Panel was sometimes concerned that, instead of focusing on their existing strengths, some groups tackle too many projects which could be thought of as extending into areas in which they lack solid expertise.

- Existence, relevance and feasability of a long term (4 years) scientific project

Many of the projects are long-term, such as the generation and analysis of disease-relevant mouse models, the establishment of new therapeutic approaches, or the investigation of developmental specification of sensory cells. The number of projects is certainly more than enough for a research program of four years. Several projects will almost certainly lead to interesting, highly relevant results, while others are more risky but potentially have a high payoff. In addition, there are some projects (e.g. in stem cells and gene therapy) which seem to have little chance to compete successfully at the international level if no more resources are provided. The proposals of Team 6, was not clearly linked to the overall aims of the Unit and was felt unlikely to be competitive without strong cutting-edge expertise in human brain imaging and stem cell technology.

— Existence and relevance of a policy for the allocation of ressources

About 60 % of the INSERM funding is needed for common expenses; the remaining 40 % is distributed to teams on the basis of merit (impact factor of the publications from the two previous years) and ETPs (number of equivalent full time researchers), on a 50/50 ratio. Support from both universities Montpellier 1 and Montpellier 2 is entirely used for common equipment and consumables. A part (10 %) of all private contracts obtained by teams are retained for overhead costs.

Special support is given to emerging groups and new teams by the INM. One to three grants (5,000 to 10,000 euros each) have been allocated to emerging groups in previous years, selected by the scientific advisory board of the INM. To help the installation of the AVENIR team in 2009, the INM did not retain the 60 % of the INSERM funding, thus this team kept 100 % of its funding. In 2010, the INM will retain only 25 % of the AVENIR team funding instead of 60 % for other teams.

— Originality and existence of cutting edge projects

There are several very original and cutting edge projects. The Review Panel was particularly impressed with the risky, highly original projects concerned with generating mouse models for mitochondrial diseases and with the projects investigating the developmental specification of sensory neurons. The investigation of synaptic transmission at hair cell synapses in the organ of Corti and in the vestibular system also promise very interesting results. Furthermore, the ongoing search for new genes causing blindness or other disturbances of vision, as well as deafness, promises new and unexpected results that may lead to new cutting edge projects. This line of research is greatly facilitated by the the Reference Centre for Genetic Sensory Diseases and has been very successful in the past.

4 • Appreciation team by team

Team 1: Genetics and therapies of retinal and optic nerve blindness

Team leader: Mr Christian HAMEL

- Appreciation on the results

The team has obtained a long-standing international recognition of their work on retinal dystrophies and inherited optic neuropathies (ION). The reputation is mainly based on the identification of gene mutations inducing retinal degeneration as well as ION and on the characterization of patient affected by retinal dystrophies and ION. Concerning gene identification, two main works have had an international impact: the discovery of the RPE65 gene in certain forms of LCA and the identification of the OPA1 gene in dominant optic atrophy (degeneration of the optic nerve).

The study of the RPE65 gene function by different groups (including Team01) has allowed the development of therapeutic approaches such as chromophore analogue delivery or gene therapy. This last strategy is now already being tested by 3 different groups in the world with preliminary success, showing the feasibility of gene therapy against ocular diseases. A clinical trial is also planned in France in collaboration with another team. The team's recent work was dedicated to elucidating the role of the different partners involved in the chromophore synthesis, including RPE65. Their results identified the FATP1 protein, which activates LRAT and represses RPE65 activity. The external control of the activity of these two enzymes may help to decrease toxic products known to be implicated in retinal degeneration in certain diseases. The team revealed that the control of enzyme activity is more complex than expected and is surely mediated by other members of the FATP family. Such knowledge may have a great impact on the understanding of the control of chromophore generation and in consequence on therapy developments.

Concerning ION, the team has identified mutations in two nuclear genes (OAP1 and OAP3) encoding intramitochondrial proteins. OP1A gene codes for a protein with multiple functions and the results generated by the team markedly improve the understanding of the function of this gene (9 papers): it was identified that the OPA1 protein controls apoptosis, mtDNA maintenance and mitochondria activity. No therapeutic approaches exist so far, but the elucidation of these different mechanisms should help to discern the adequate targets. The group has published good to excellent papers in this field.

Concerning genetic studies, the group is continuing to obtain success with linkage analyses and mutation identification in autosomal recessive diseases and in ION. They have identified new genes such as EMA, OPA7 and DOA Plus which should also have an important impact in the field.

Team 1 is constituted of 8 researchers : 3 on retinal dystrophies, 1 PU/PH, 2 CR1 Inserm, 3 PhD students and 2 post Docs, 5 on ON 1 DR2 CNRS, 1 CR1 Inserm, 1 PU, 2 MCU, two PhD students and 2 post Docs.

- 58 publications: 22 as first or last authors.
- 50 International publications and 25 didactic publications.
- **In 2005:** 4 papers on the topic of the team (ophthalmic genet 2.6, IOVS 3.6, Mol Cell Biol 31, Annal Neurol 9) with mean impact factor of 11.5, and 6 papers in collaborations on other topics (JPET 3.9, cell death Diff 4.7, gene 2.7, Eur J Human genet 3.9, J cell Biol 9, Life Sci 2.6, J exp Med 15) with a mean Ip at 5.9.
- **In 2006:** 3 papers on the topic of the team (IOVS 3.6, AJ0 1.5, J Med Genet 2.4) and 10 papers in collaboration on other topics (among which 2 JBC 5.8, Oncogene 7.2, Nature Genet 24, EMNBO J 10, Nature Med 28) with mean IP 7.8.
- **In 2007:** 7 papers on the topic of team (Cell death diff 4.7, Exp Cell Res .9, Ophthalmic genet 2.6, J cell Physiol 3.6, Gene Ther 4.5, Human Mut 3.4, Am J Human Genet 11) and 2 papers on other topics in collaboration (Ann Neurol , AJO).
- **In 2008:** 3 papers on the topic of the team (AJO, Ann Neurol, Brain) mean IP 6.5 and 3 papers in collaboration on other topics (IP 3.6, 2.3, 6 .8).
- **In 2009:** 4 papers on the topic of the team (AJO, Ophthalmic Genet, Human Mut 3.4 , Am J Human genet 11) Mean IP 4.6
- 4 papers in collaboration on other topics (neuropsychopharmaco 6.8, Neurobiol aging 5.9, Plos Pathog 9, Int J Biochem cell Biol 4.2) with mean IP 6.4

In conclusion, very good level of publications on the subject of the team and excellent level of publications in collaborations on other subjects.

The level of publication has lowered during the last four years but very good well-cited papers have come from this team.

Presentations at meetings

- 10 invitations to international meetings, 15 invitations to national meetings, numerous poster presentations.
- 6 Master 1; 5 Master 2
- 5 PhD students (6 others are currently in progress)
- The patent of “OPA7 neuropathy” is in preparation but not yet deposited.

Very good integration in the institute with 7 publications emerging from collaborations with several teams in the institute.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners
  - 28 invitations to symposia and international conferences
  - Good partnerships with biotechs to develop new therapeutic tools and methods.
  - Fundings sound very efficient for the last years to hire postdoc (3) and PhD students (6): PHRC (390 KE for national clinical project), Fondations 200 KE/ year, Maturation project and retina France (60KE/ year).
  - The team has obtained a European grant (e-Rare, 170KE/3 years)
  - The success of this team in the genetic field is based on national and international networks bringing a large cohort of patients to identify genes involved in retinal dystrophies and in ION.
  - The patent of “OPA7 neuropathy” is in preparation but not yet deposited.

- Appreciation on the strategy, management and life of the team
  - Communication in the team seems to be appreciated between researchers.
  - Creation of a university diploma in genetics of the retina and optic nerve.
  - Master course.
  - 3 team members have active teaching activity.
  - DU retinal dystrophy every two years, participation to master degree, centre national de reference maladie rare.
  - The team has organized both clinical and laboratory activities to develop phenotyping and genotyping.
  - A European consortium has been created to collect 2000 families with recessive RP in 3 years.

- Appreciation on the project

After several years dedicated to gene identifications and patient characterizations, the team is focusing more on the understanding of gene function, and on therapeutic approaches, partly based on previous seeding studies. Nonetheless, the activity that built the strength of the team (genetics of retinal dystrophies) is still a matter of interest and of cutting-edge knowledge.

The main goals are:

- To identify some of the genes that are responsible for unexplained retinal dystrophies (around 40% of the patients).
- To prevent toxic oxidated by-products (lipofuscin) accumulation.
- To develop gene therapy for Usher syndromes and Stargardt diseases.
- To identify which genes control OPA1 function.
- To study the role of the different OPA protein subtypes.
- To develop gene therapy for dominant optic atrophy.

Concerning gene identification, the proposed project is based on preliminary results obtained by linkage analyses. Two new loci have been identified in patients affected by autosomal recessive RP. The team has numerous families to perform adequate analyses. A similar strategy is proposed for a large cohort of dominant forms of ION.

The group has identified OPA7, and has shown new genotype phenotype correlations associated with specific mutations in OPA1 (DOA plus). In addition, it described a new clinical entity (EMAP) for which the gene(s) remains to be found. The strategy used sounds pertinent and efficient to maintain the team in an international position.

In several retinal dystrophies, a decrease of the visual cycle kinetics (responsible for the formation of the chromophore) is thought to alleviate the course of the degeneration, which could be done by decreasing the generation of lipofuscin. The present project aims to reduce the presence of the chromophore by mimicking the interaction of RPE65 (a key enzyme of the chromophore isomerization) with the FATP1 inhibitor protein (function identified by the team). A library of peptides will be tested to inhibit RPE65 activity. The target sounds interesting and feasible, but the applicants need to pay attention to not decrease RPE65 activity too much, as this is known to induce retinal degeneration. The proposed project will help to determine the limit of chromophore reduction allowing photoreceptor survival and a significant decrease of A2E product. A small decrease of RPE65 activity should alleviate the course of Stargardt and Best diseases.

The development of gene therapy to treat Usher syndromes is of high relevance and importance, knowing that this disease affects first audition and then vision, leading to a major disability for the patient. The goal to generate photoreceptors from patient skin fibroblasts by inducing pluripotent cells is a very interesting approach. This should be an important tool to understand the degeneration process in this model. However, an in vitro gene transfer approach appears to be of low added-value to develop gene therapy. Indeed, so far AAV vectors are the best to infect photoreceptors in vivo. However, they show very low efficiency in vitro. Thus, the rationale of the in vitro approach is not obvious and merits deeper explanation. The establishment of a reliable iPS system to generate photoreceptors is a long and costly process. In consequence, the use of this system to test vector activity sounds expensive in the amount of human work for the benefit that can be expected from the experiments described here. The proposed in vivo model sounds more appropriate.

The idea of screening dog samples to detect mutations in the Usher genes is of great interest and very original, and will provide a fantastic tool for in vivo gene therapy testing. Similar approaches done by the applicant were already used for the RPE65 gene, and lead to preclinical studies for gene therapy in French and English groups.

The next project considers a better definition of OPA1 function. Indeed, the same mutation can lead to either severe phenotype or no abnormalities. The hypothesis is the possible role of a second gene controlling OPA1 function. The applicants aim to study SNPs (single nucleotide polymorphisms) in a large cohort of available patient DNA samples. Such approach may confirm or infirm the hypothesis which sounds pertinent in view of previous studies showing that some SNPs render certain patients more susceptible to specific retinal dystrophies.

To perform a deeper analysis of OPA gene functions, the team plans to generate different knockout and knockin mouse models to analyse impaired regulation of the mitochondria in these different transgenic animals. A very elegant approach is proposed to study the equivalent human LHON by generating mutation in mouse mitochondria and then by transferring these mtDNA in ES cells devoid of mtDNA. In case of success, this will lead to the generation of a cell line bearing the LHON mutation.

The knowledge acquired by the above-mentioned experiments should allow to develop therapies for dominant ocular atrophies. Two strategies are proposed, one by gene therapy and the other by a pharmacological approach. The gene therapy proposal is pertinent, but the group needs to be reinforced to be competitive. The strategy to stimulate mitochondria activity sounds very promising.

The majority of these projects are partially supported by external funding.

- ## Conclusion

— Summary

The project proposes to develop a major effort in understanding the function and the regulation of genes previously identified by the team and to develop therapeutic tools. The hypotheses emitted about the gene functions appear valuable and important to solve. So far, the reason for OPA mutation to predominantly affects retinal ganglion cells is not yet understood and the proposed projects may help to dissect the different functions of the OPA isoforms controlling mtDNA replication and mitochondria activity. In parallel, the excellence in patient phenotyping linked to the gene identification strategy is still very efficient to identify new genes responsible for retinal dystrophies. Animal and cell models will need to be generated to validate the different therapeutic strategies. The project might be too ambitious and technical difficulties were not well anticipated.

— Strengths and opportunities

- The will to continue to dissect the function of the OPA proteins and their regulation mechanisms (many published and preliminary results).
- The team is a reference clinical centre for rare disease.
- Development of a large animal model for the Usher syndrome by genetically screening a large cohort of affected dogs.
- The phenotyping/genotyping strategy (large cohort of patients due to active national and international collaborations) which made the international reputation of the group.
- The will to develop therapeutic strategies using different tools (gene transfer, pharmacological agents).
- Excellent expertise, technical skills and complementarity of the different partners in the team.
- Translational research from clinic to basic research and back to clinic for therapy.
- Good financial support mostly through associations.

— Weaknesses and threats

In general, the choice of therapeutic approaches sounds very pertinent. Nonetheless, iPS cells do not seem appropriate to test vectors. First, because the generation of a reliable cell line is very difficult so far and often not reliable. Secondly, vectors often show a different tropism in vitro in comparison to an in vivo situation. In consequence, such approach will be poorly informative towards identifying adequate vectors for in vivo paradigms. Nonetheless, iPS cells derived from patients are very interesting as models to study the degeneration process and to validate the therapeutic gene of interest (not the vectors), thus this strategy is pertinent to retain as a perspective.

— Recommendations

The team has generated high impact papers during several years feeding the field of genetics and retinal degeneration. A period of less impact publications (but the production is still very high) can be noted during the last years, but this seems to correspond to a change of strategy with a deeper implication in gene function mechanisms. Nonetheless, the results presented during the commission visit show that the team is capable of continuing to identify new genes and loci involved in retinal as well as nerve dystrophies. The gene identification strategy will no doubt continue to generate high impact publications, as well as the work on the biology of genes involved in dystrophies. For therapeutic approaches, new tools were and are necessary to be developed and a new field of investigation is in the process of being apprehended. Because this strategy is very demanding, the commission recommends to develop a sub-team or a platform to produce the vectors of interests in situ, in order to be independent and to well run the gene therapy projects. This will allow to have a good feeling about the quality of the produced vector and to test many different constructs (envelope, promoters, etc.).

It would be nice to promote the visibility of some members who will also enhance the general visibility of the team. In consequence, the project of this team merits to be well supported thanks to their recent results and the potential of the project.

Team 2: Deafness, tinnitus and therapies

Team leader: Mr Jean-Luc PUEL

- ### Appreciation on the results

The team leader is an established senior researcher. The team's goal has been set to study and treat cochlear hearing loss and the associated side effects such as tinnitus. The restriction to cochlear problems has the great advantage that local application of drugs (instead of systemic) becomes potentially feasible in clinical practice without the common and annoying side effects of systemic application. This group has been one of the first to pursue this line but currently other groups are following suit. The range of research represented in this team is wide ranging.

Over the past period they identified VGLUT3 as the IHC vesicular glutamate transporter and established that mutations in VGLUT3 are causing DFNA25 related deafness. Although the results were published at the same time as a competing group in the US, the work from this team unequivocally demonstrated its significance for hearing, by having expertise on whole animal neurophysiology.

The peripheral mechanisms of tinnitus associated with an arachidonate-sensitive NMDA receptor mechanism at the cochlear afferents has been explored. The work used a wide range of techniques using rat models, and the mechanisms proposed are both novel and of interest in developing tinnitus ameliorating drugs. It seems clear that this range of approaches is critical for any laboratory working on tinnitus. A related set of mechanisms have been explored to investigate the involvement of synaptic circuitry in tinnitus states at the cochlear inner hair cell synapse, using anxiolytics again using a rat-model as well as the modulation of afferent tonic firing by the lateral efferents. These are all original results.

Protection of hair cells against noise trauma has been a key theme. The translation of the work into the clinics is at an early stage, although it is gratifying to see that tinnitus cohorts are being monitored (4.1) and a further cohort of presbyacusis patients are being followed (4.2), both of which may represent valuable resource.

The team has concentrated on treatment strategies so far for the prevention of salicylate- or noise-induced hearing loss and tinnitus by intra-cochlear NMDA application. Immediate post trauma treatment results have also been obtained, which are highly significant.

The team takes basic approach aimed at the hair cell ribbon synapse and at the potential regeneration of hair cells. More conventionally the team has identified an interesting regulatory cofactor of the Na/K ATPase in the stria vascularis and this may indeed prove to be a factor involved in some forms of deafness if the link can be made.

Finally the major effort of the team has been to develop gene transfer methods. It is hard to assess the impact so far as with all translational projects on a short time scale. Both gene transfer and stem cell approaches have been explored with results published indicating promising leads. There are good links to local and national biotech companies. In brief the team is a clustering of high quality packages.

In the 4.5-year report period, Team 2 'Deafness, tinnitus and therapies' produced 76 peer-reviewed basic research publications and 15 clinical publications. Given that there are 8 basic researchers and 3 clinical ones this averages out to about 8-9 papers per researcher (for each category).

In the basic research category, the team published 26 papers (34%) in journals with impact factor >3, of which 11 were published in journals with impact factor > 7. This reflects the good to excellent quality of the publications. It is difficult to judge the theses since there was no access to those, but 6 were defended in the report period. A significant fraction the papers are multi authored as expected from an integrated team research.

The team has been very active in presenting at conferences: 50 invited presentations, 27 oral presentations and 42 poster presentations; these data average to about 26 conference presentations per year.

Some of the preliminary work particularly on the ribbon synapse has been carried out in conjunction with high quality internationally placed groups. Of note is the work carried out in conjunction with the Moser group in Göttingen. There is every reason to expect that this may continue to be a long-term collaboration.

- 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 been honored by many (33) invitations to speak and conferences. There are notably 15 other invitations from the basis science section and 4 from the clinical section of the team. The figures illustrate the impact of the team and its national and international contacts.

This information was not clearly available. It is clear that one CNRS position in the team has been recruited from Germany, and a student has also been recruited from a francophone country, but on the whole the group is composed stably from local expertise.

The funding model in France is different from that in North America. All grants were for non-salary only: INSERM provided 190 kEuro. A sizeable Tinnitus Research Initiative grant (200 kEuro/2 yrs) was obtained to study tinnitus. There was a 276 kEuro from the European Commission 6th Framework Programme (NanonEar). A drug delivery grant of 358 kEuro from ITMO Technologies pour la Santé. Another large grant was from the Foundation pour la Recherche Médicale for hair cell regeneration : 298 kEuro. Together with some smaller grants the non-industrial funding totalled 1,200 kEuro. Industrial funding amounted to 277 kEuro. Several salary grants were paid for by industry, typically for one engineer, one postdoc and one PhD student/yr.

The team collaborates with the Tinnitus Research Initiative, a large international privately funded organization, and in a European Commission Framework. They have international collaborations with Göttingen University, Geneva University, Iowa University and Washington University and with two INSERM units in Paris and two groups in Montpellier. The team members participate in 5 editorial boards and review for 18 respected journals. There were also international collaborations with groups in Austria, Portugal, and Japan.

There are 6 joint publications from the Austria collaboration and a high-impact publication from the U. Michigan collaboration. In addition 3 patents are held together with industry.

- Appreciation on the strategy, management and life of the team

Three researchers have University appointments with about 190-hrs/yr commitments for teaching and training. Most other basic researchers teach in some special courses between 3-18 hrs/yr and participate in the Hearing Aids School, and the Masters programs in Audiology and Neuroscience. The basic researchers also supervise Masters and PhD students. Two clinicians have University positions, and one clinician is employed by the hospital.

- Appreciation on the project

This project is a continuation of a previous 5 yr project that was very successful but with an enhanced emphasis on cellular and molecular processes. The topic has changed somewhat from the "control of afferent neurotransmission mechanisms, regulation of potassium homeostasis, degeneration of sensory epithelia and genetic deafness" to "Ribbon synapses of the inner hair cells, Degeneration, Repair and regeneration in murine models to reproduce human deafness and to envision gene therapy, as well as translational research". The changes in the topic are extremely relevant to the field internationally.

The finding that the SNARE complex may not be involved directly in transmitter release in the ribbon synapse will be further explored. The phenotype of the DFNA25 deafness will be studied in a knock-in mouse. This includes studying the vulnerability to noise and age-related hearing loss, and further therapeutic strategies to prevent hearing loss, notably glutamate clearance activation and excitotoxicity prevention using dopamine agonists will be explored.

The computational model of the ribbon synapse looks very interesting – there are precedents for this modelling exercise, but the reasons given here are cogent and well argued. Based on curve fitting of the round-window recorded auditory nerve ensemble activity it will be explored how to extract signs of correlated neural activity between auditory nerve fibres. The hope is to detect changes in temporal firing properties (serial correlation) and in synchrony across fibres (parallel correlation). This will in principle form the basis for extracting such changes from promontory recorded neural activity in humans with tinnitus. These are inverse modeling problems that are very difficult to uniquely solve; when the initial model has of the order of 50 parameters it only becomes feasible when only a few parameters are deemed to be responsible for the expected changes.

The basic projects therefore are quite feasible and likely to yield results. The deliverables are realistic. The translational aspects are promising but the reviewers wonder about the practicality of the promontory testing of spontaneous activity in humans, as impedance between the electrode and promontory, leaking impedances through epithelium moisture levels etc cannot very well controlled. All of these assumptions still assume that chronic tinnitus is a peripheral phenomenon, which is advocated by Team 2 but a view not widely held outside this Team.

The team members are actively pursuing additional grant applications.

We find both basis research projects (2.1 and 2.2) with their subprojects representing cutting edge research. If the non-classical SNARE proteins can be identified this will be a major step forward.

- Conclusion

— Summary

The project aims at building mouse models for deafness; including presbycusis that will allow genetic studies of deafness and tinnitus that is, assuming that most problems arise in the inner hair cell synapse. A large amount of activity is projected for a detailed study of the ribbon synapse and its recovery from short duration insults. The translational aspects include approaches to record spontaneous activity from the auditory nerve in humans in order to objectivate tinnitus and monitor changes induced by drug application. For that purpose implantable drug delivery systems will be developed. If the cochlear application of NMDA blockers and other drugs can cure CHRONIC tinnitus in humans then they have clearly shown that tinnitus has a cochlear origin or can be modified by cochlear activity. This would be important information.

— Strengths and Opportunities

The team integrates clinical work and basic research on deafness and tinnitus. Although the clinical research so far has mainly been in the field of cochlear implants; this may in effect be an advantage in devising objective measurements of auditory nerve activity in humans. The basic research teams are well qualified in the molecular aspects of deafness and tinnitus. It would be important to compare salicylate-induced changes to noise-induced changes with respect to spontaneous auditory nerve fiber activity. The translational aspects of the project can potentially provide exciting opportunities in the study of tinnitus and some its manifestations in humans. It would be important to know if the murine model transfers easily into the human one.

New recruits to the established team ensure an infusion of new techniques, age structure and make the team highly competitive. If the team can develop cellular and molecular approaches to hearing while keeping whole animal expertise alive, it will be a very valuable resource hard to match anywhere else in the EU.

— Weaknesses and threats

The most annoying and clinically manifest forms of tinnitus to the patients are to be those that arise past the

stage where local drug application in the middle ear/cochlea can do anything about it. This assertion has however never has been tested. Thus the peripheral model explored here is mainly geared (rightfully) to the prevention and early intervention aspects of hearing loss and tinnitus. The perfusion salicylate model is technically elegant and beautiful, but in humans salicylate (in the form of aspirin) is applied systemically. In contrast, it is known that this drug also affects the central nervous system GABAergic activity (as does noise-induced hearing loss). What the team has to do eventually is to extend their peripheral model work to incorporate more central aspects; this is not in the current set of proposals but that may need to wait until the next research program.

International recruitment is not strong and few international links make the team more fragile than need be. This is particularly true as the interest in tinnitus in the international arena is growing very fast and it is important that this team keeps its edge. The projects also depend on the success of several ANR funding applications over the next year.

— Recommendations

This is clearly a team that can be considered among the top 10 in the world in this field. The balance of molecular / cellular and systems auditory neuroscience needs to be kept under constant review and the existing expertise in neuropharmacology should be maintained. Attention also needs to be paid to maintaining and strengthening national and international collaborations. The younger researchers in the team need to emerge in the near future with appropriate responsibility being allocated.

Team 3: Pathophysiology and therapy of vestibular defects

Team leader: Mr Christian CHABBERT

- ### Appreciation on the results

This is a new team which has spun out of team 2 in 2008, but with a specific interest in the vestibular system. It includes researchers who have worked on inner ear mechanisms but have been primarily associated with non-cochlear tissues. The vestibular system field which has attracted a smaller number of researchers than the cochlea, but all those who now work on vestibular system probably owe something to this grouping of researchers at Montpellier over the past three decades. The results obtained over the past period arise from the following interests.

The development of ionic channels in vestibular hair cells and neurones (2.1.1) have been mapped in good detail and reported, stemming from ground-breaking work by one researcher and his students over the past decade.There has been good work, published in high impact (>7) journals exploring the formation of synapses in co-cultured systems in vitro and this has allowed this group to study the mechanisms of endolymph production in an accessible system (2.2.1). Much of this latter work has yet to be published and so is difficult to evaluate at this stage.

The team has also been working on mechanisms of neurotransmission in collaboration with members of team 2. Using expertise in in vitro systems, the team has used calcium imaging to study the mode of action of an antivertigo drug Vastarel and its active component trimetazidine. The H3 receptor antagonist, betahistine, has also been studied and It is reported that they have now identified a new compound, SR1001 (subject to a patent) which reduces the excitability of vestibular primary neurones. This is important .

The publications are included in the listed output of team 02 under the appropriate team members. Although there are high impact factor papers, the number of papers per group member, 3, is quite low There must be some concern that effort has been diverted to setting up a spinoff company. There are however identifiable publications:

- Peer reviewed papers from the team in 2005-2009: 13.
- Patents : 3.
- Websites: 3.
- Spinoff companies: 1 Sensorian (established June 2009) a drug discovery company.

A new recruit to this team holds the position of Professor of Neuroscience at UMP1, as well as being associated with U583. To date there are currently no postdocs from outside the immediate UMP environment. There have been short term collaborations with visitors coming to this group and plans to recruit a US postdoctoral fellow from the US.

There have been successful applications for project seedcorn (e.g FDF, or ANR and PRSS, CNES). There are proposals to apply to HFSP, the Swiss Health Ministry and other sources. The outcome of these applications is not known at the time of writing.

There are a number of collaborators listed, in Bern (2.1), and in Rochester, USA (2.2) both excellent links to maintain and cultivate.

A spin off company, Sensorion was established in June 2009 in response to a) a demand for vestibuloplegic compounds and b) to develop therapies for vestibular injuries. The company is based on a new use for an existing and trialled compound, with the result that the product may be brought to market in a short period. The company is well conceived and well organised. It is integrated with Team 3 activity.

- Appreciation on the strategy, management and life of the team

All academic members of this team have allocated hours of teaching at the University of Montpellier 1 or 2.

- Appreciation on the project

The team consists of researchers with an interest in basic ionic mechanisms, but with the inclusion of a new team member there is the potential to identify and develop stem adapted to the vestibular system. This member has expertise to identify rare stem cells using FACS methods, and the use of such approaches e.g.together with the organotypic culture would be novel.

The projects specified with varying degrees of detail, but the deveopment of an in vitro assay system ford an assay of drug argets in the vestibular system is common to all. The first cluster of projects concerns the mechanism of regulation of endolymph factors. The first project (2.1.1) aims to clarify whether there is a link between calcium metabolism (in rats) and otoconial shape, which in turn might be related to benign paroxysmal vertigo. The techniques are primarily morphometric, but a proposal to manipulate the oestrogen receptors in the inner ear using a KO mouse need to spelled out clearly. The second project (2.1.2) addresses Menières disease by using an organotypic culture of the mouse end organ to investigate whether pressure hormonal factors can regulate vestibular endolymph potentials. Although this is nominally a hypothesis driven proposal, it is weaker at this point than the others as there are few preliminary data other than the cultured system itself.

The second cluster of projects investigate vestibular transmission are designed to explore ways of rebuilding the sensory synapses and identifying stem cells which might be able to rebuild the epithelium. The projects focusing on glutamate transporters at type I hair cell calycial synapses are highly topical and of potential clinical relevance

There is no completely transpearent policy although many of the projects are proposed as collaborative with leading groups involved in vestibular function. For example, the project to study endolymph homeostasis depends on funding from the Swiss government; the project to study vestibular neurotransmission depends on collaboration with groups in Chicago or in Kansas. The success of the Biotech company, Sensorion, also is a prerequisite for at least one of the postdoctoral fellows for the evaluation of the neuropharmacology.

The organotypic culture of the vestibular endo-organ uses an original preparation. The project to investigate the factors which determine the plasticity of the functional restoration of the vestibular synapse need specific hypotheses to be developed and only then can a definitive strategy be developed. If there are indeed vestibular stem cells - and this would be a big coup – then many different and integrated strategies need to be put in place to exploit them. The review therefore found the stem cell project interesting and cutting edge Once the stem cells have been identified, however, it is important that some functional assays are carried out.

- Conclusion

— Summary

This is a new grouping of researchers with specific expertise in the vestibular system. This is a team with virtually unique expertise, well focussed on the physiology and with considerable potential. The future projects cover important basic research topics on endolymph composition homeostasis, vestibular hair cell neurotransmission and its possible plasticity; and the identification of stem cells to regenerate hair cells in the vestibular system (and maybe the cochlea). There is a strong translational component as a spin off company, Sensorion, has been created to test a novel compound (SR1001 covered by a European patent) in animal models of vestibular deficits as a preliminary to clinical trials. The nature of the compound means that there is likely to be a short time to market.

— Strengths and opportunities

There is a clear demand for treatments to treat vertigo. The Team leader is a high profile player in a small field. Two new compounds (SR1001 and SR2001) have been identified and patented for use against vestibular deficits. The project may also develop model systems to explore the the therapeuric value of the compounds. The team has a unique opportunity to develop further an in vitro assay system for drugs targeted to the vestibular system. The expertise to identify vestibular system stem cells is a unique resource.

— Weaknesses and threats

Much of the funding is not yet in place for personnel. It may also depend on the success of the spin off company, Sensorion to generate income. The strategies also need to be firmed up more. Although there are clearly unique systems to explore the vestibular system in this team, there is likely to be severe competition to study vestibular transmission from at least two laboratories in the US alone (e.g. from laboraties in Chicago, and in Charlottesville).

The plans to develop whole animal models and testing proceedures for vestibular deficits is made the responsibility of the spin off company Sensorion. Such animal models are important. Clarity of the ownership of the data should not limit any publications in high impact journals

The organotypic culture proposed for the study of endolymph ionic homeostasis is not a strong project without a definite plan, a problem exacerbated by the weak publication record of the researcher in charge. The review suggests that it be combined with genetic mouse models.

— Recommendations

This is an important team in, internationally, a small field. For that reason the reviewers thought had great potential. However, there need be mechanisms to encourage publication and the dissemination of the basic science before the clinical application takes over. Thus there needs to strategic thinking about the effort and resource devoted to each subproject by the team without depending, excessively, on external collaborations. The review suggests that, in view of the clinical importance of the vestibular system deficits, the team could explore in the longer term ways to build local expertise in the clinical assessment of vestibular function, for example by collaboration with a group working on human movement disorders.

Team 4: Peripheral nerve injury and regeneration

Team leader: Mrs Frédérique SCAMPS

- Appreciation on the results

This is a new and rather small team which has emerged from previous team 4 (which was headed by J. Valmier, who remains a team member). This team focuses to a large degree on ion transport in primary sensory neurons and its relation to peripheral nerve regeneration and neuropathic pain, whereas the new team of Carroll, which has also emerged from former team 4, focuses on the developmental biology of sensory cell specification.

The team is interested in the changes in sensory nerves after injury, with a particular focus on changes in ion channels and intracellular ion concentrations that occur after nerve injury and during nerve regeneration. They have discovered that the intracellular chloride concentration is increased in sensory neurons after injury and have provided evidence that phosphorylation of the cotransporter NKCC1 is responsible for that increase. They have further shown an upregulation of a Ca-activated chloride current which has been tentatively attributed to bestrophin 1. They are also studying effects of the KCl cotransporter KCC3 using a KO mouse provided by others and have investigated Ca-channels in sensory neurons. Their hypothesis is that the increase in intracellular neurons during regeneration leads to a depolarization through Cl efflux via Cl-channels, in turn activating voltage-sensitive Ca-channels that activate cellular programs by increasing intracellular Ca-concentration. This is solid, mostly electrophysiological work that has been published in several papers in neuroscience journals, with two articles in the Journal of Neuroscience.

From 2005-2009, members of the team have published 30 articles in peer-reviewed journals, excluding reviews. These publications include collaborations in which one or more members of the present team is a co-author, some of which have been published in excellent journals like Neuron and EMBO J. There are ten publications in the same period in which team members are the senior (last) authors, including the two papers in the J. of Neuroscience mentioned above (with the actual team leader being corresponding author). Three Ph.D. students have defended their theses from 2005-9 in the core research area (ion homeostasis in regenerating neurons) of the newly formed group.

- 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 been invited to give 5 external seminars within France, but not abroad, from 2005-9. Two members of the team organized an INSERM workshop on pain in Montpellier (2006) and the French Neurosciences Association Congress (2007).

The new team has attracted two clinicians to join, and it has had 4 postdocs from 2005-9, some of which came from abroad. They have been funded by different French sources (ministry, ATER, AFM). In addition, they have attracted several Ph.D. students who have published up to two papers as first authors.

Team members have obtained external funding from various French sources (AFM, FRM, INSERM transfert etc), which includes money for salaries, large equipment and consumables. The total sum was 695 k€ for the period 2005-9.

The group is collaborating internationally, in particular with groups in the US. However, some of the collaborations seem to be limited to getting access to knock-out mice generated in those laboratories, or to antibodies and clones. The fields of peripheral nerve regeneration and neuropathic pain are internationally very competitive and the group does not appear to collaborate or interact significantly with other groups in France, Europe or elsewhere in these areas.

- Appreciation on the strategy, management and life of the team

Most members of the team are involved in teaching neurobiology at the Université Montpellier II, with one of the members being heavily involved (directing a Master program).

- Appreciation on the project

Two major projects build on the team's previous work on chloride regulation in sensory neurons. First, they would like to generate (in an already funded project) a conditional bestrophin1 KO mouse that expresses a GFP fusion protein, with the aim of determining the subcellular localization of the presumed bestrophin1 chloride channel (with the risk of changing expression or localization by the fusion). They will also try to disrupt bestrophin conditionally to avoid compensatory upregulation of another bestrophin isoform which they have observed in their previous study. This is a long-term and risky project.

Another project will test the hypothesis that chloride channels play a role in the mechanosensitivity of somatosensory neurons and whether this, in turn, plays a role in regeneration. These studies may also take a couple of years and will almost certainly lead to publishable results. Of course, a positive outcome is not guaranteed, and a role of mechanosensitive Cl channels in regeneration may be very difficult to prove, even if they do exist.

The third major project aims at identifying changes in miRNAs during degeneration/regeneration. This is a feasible project that might yield very interesting and original, maybe even cutting edge results, but it might be difficult to compete internationally and a broader approach than the one suggested might be more promising.

Finally, they would like to test (e.g. by antisense strategy) candidate molecules and genes identified in the above approaches in an in vivo regeneration approach with the participation of the neurosurgeons of the team. This project is certainly long-term and impossible to judge/to assess at this point. The suggested approach also would need a lot of controls to yield conclusive results.

- Conclusion

— Strengths and opportunities

The team has thorough expertise in electrophysiology and ion imaging techniques and has established itself as one of the several groups working on ion transport in regenerating neurons. It has published well on Cl (and Ca) homeostasis in these cells and it makes a lot of sense to continue in this direction. Irrespective of whether Cl has the hypothesized important role in regeneration, the proposed studies promise to yield interesting results on chloride homeostasis and the molecules involved. The screening for changes in miRNAs upon degeneration/regeneration may uncover new principles. The environment of the institute offers excellent opportunities for collaborations, in which the group may contribute its electrophysiological expertise.

— Weaknesses and threats

The group is facing the problem of which candidate molecule (e.g. channel or putative channel) to focus on. There is a certain risk of making wrong choices. For instance, the role of tweety or (to a lesser degree) bestrophins as Ca-activated Cl channels is somewhat controversial, and therefore the interpretation of their results may be difficult. The proposed bestrophin knock-in mouse is risky, and this risk is not compensated for by the promise of a real break-through. The hypothesis that chloride channels play an important role in mechanosensitivity and thereby influence sensory nerve regeneration, may be wrong and at least difficult to prove. The microRNA projects makes sense, but probably there will be a lot of competition in this area. It might also be more appropriate to take a broader approach than just looking at known miRNA candidates, as the team proposes. At this point, the integration, prospects and competitiveness of the translational projects that are planned together with the clinicians are difficult to predict. It would certainly be important to set up effective *in vivo* rodent models before attempting clinical studies. The lack of interaction with other groups working on peripheral mechanisms of neuropathic pain and peripheral nerve regeneration means that there is a danger of becoming isolated in these very competitive areas.

— Recommendations

We recommend that the group focuses on its original strength, i.e. electrophysiological characterization of neurons, combined with optical methods and basic molecular biology. The existing collaboration and interaction with team 5 (Carroll) should be continued and further strengthened. Although the splitting of the former common team makes sense both from a scientific/technical point of view and because it gives the new team leaders more visibility and scientific freedom, both teams can nicely complement each other. Team 5 will soon need electrophysiology to analyse their mouse models, while team 4 can profit from the expertise in molecular and developmental biology of team 5. The same arguments hold for the existing interactions with the Avenir team that also focuses on developmental biology of sensory neurons. For the translational aspects and the collaboration with neurosurgeons, the team lacks currently a good hypothesis on which to focus. It may also need more external expertise. The team should decide whether regeneration or pain is their primary focus for translation, identify a few key hypotheses and proposed mechanisms and collaborate with groups that have more background and expertise in these areas. The team leader is to be congratulated on her achievements to date and provided with financial support and encouragement to promote successful internal and external collaborations.

Team 5: Neural differentiation and connectivity in the somatosensory system

Team leader: Mr Patrick CARROLL

- Appreciation on the results

This team studies the developmental neurobiology of the somatosensory system. This is a newly-formed team with origins in Team 4 (previous Team 3). They have identified transcription factors expressed in particular populations of neurons and glia, and have used this information to study the role of these factors in neuronal and glial development within the somatosensory system. They have used a range of techniques to pursue these studies, including the generation of interesting transgenic mice.

Neuronal specification in primary sensory neurons and the spinal cord is an exciting field. This team is on the front lines with respect to neuronal specification in the somatosensory system and is publishing high quality work that will have significant impact in the field. Over the long term, this approach may lead to new strategies towards the treatment of peripheral sensory neuropathies, a significant clinical issue.

Team 5 consists of 5 researchers, 1 post-doctoral fellow, 1 PhD student, and 1 technician.

Since 2005, they have published 24 papers, including 13 peer-reviewed manuscripts in top journals (eg. J Neurosci, J Comp Neurol, BMC Neurosci, Stem Cells, Embo J and recently in Neuron) as well as 2 reviews, and a dozen papers outside the main field and/or in collaboration with others. The paper in Neuron in December 2009 was featured as a Preview in this top journal.

Since 2005, 5 students have completed PhD theses. Currently, there are 3 additional PhD students. Carroll has been an invited speaker 4 times since 2007.

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

This is a young team and as such has few invitations to international symposia and conferences. It is expected that, given the high quality of the research, there will be an increasing number of invitations. The researchers should be encouraged to accept such invitations.

This team has trained 2 post-docs since 2005. It does not appear that either were attracted from abroad. Another post-doc is currently being trained, and was first author on the recent Neuron paper. One former post-doc is now a researcher in the team.

The team has attracted 469,000 Euros in support since 2005. Of this, 120,000 is from the Partner University Fund and is supporting collaboration with the Goulding lab at the Salk Institute in the USA. The research of the team and that of the Goulding lab fits well with each other, and was an excellent partnership to pursue. The group has been recently funded by ANR.

The collaboration with the Goulding lab is relatively recent, but is a good demonstration of international collaboration. The team also collaborates with the Eychene team and the Valleix team in Paris, the Landgraf group in Cambridge, the Lewin group in Berlin, and the Darling group in Louisville. This demonstrates excellent national and international collaborations.

Concrete results are demonstrated by the excellent publication record.

- Appreciation on the strategy, management and life of the team

The project studying neuronal specification in the somatosensory system is cutting edge.

The team contributes to teaching in Arts and Science, Medical genetics, and Neuropsychology. The amount of teaching is not clear.

- Appreciation on the project

The team has now established itself in the field of somatosensory neuronal development. They use a variety of molecular biology tools, including the development of new transgenic mouse models, to study neuronal and glial specification in the somatosensory system, specifically dorsal root ganglia and the spinal cord.

They will study 2 main areas in the next four years:

1. The role of an anti-apoptotic transcription factor in the regulation of neuronal numbers during development.
2. Spinal circuitry involved in mechanoreceptor pathways identified by expression of MafA.

Understanding the development of the somatosensory system may lead to new treatment strategies for sensory peripheral neuropathies, both idiopathic and secondary.

For project 1, the team has identified a transcription factor, Zfh1, that is evolutionarily conserved. Zfh1 is involved in cell survival during development. There are 2 orthologous genes in the mammal (Zfhx1a and Zfhx1b); the team has created a transgenic mouse line for the conditional blocking of the function of these proteins. In part 1 of this project, the team will study the role of these proteins in neuronal survival, specifically in relation to the Jun-kinase pathway in cultured DRG neurons (Aim 1); the relationship of these proteins with neurotrophins (Aim 2); their interaction with small non-coding microRNAs (Aim 3); and whether these proteins are specific to subtypes of sensory and/or motor neurons (Aim 4). In the 2nd part, they will study the role of Zfx proteins in glial development. Thirdly, they will create a conditional Zfhx1a knockout mouse.

For project 2, the team will build on their demonstration of MafA expression in DRG neurons, spinal interneurons in dorsal and intermediate laminae, and motor neurons, and study the hypothesis that MafA labels neuronal circuits involved in transmitting and integrating tactile information. In Aim 1, the team will further develop transgenic tools by making a MafA-flipase mouse so that, in combination with cre recombinase expressing animals already made, the team can use a combinatorial approach to study and manipulate MafA-expressing sub-populations at different developmental stages. They have sought collaboration with the Goulding lab in California for these experiments, as the Goulding lab has developed a number of animals that can be used in combination with these for the manipulation of neuronal populations. In Aim 2, the team will study MafA expression in motor neurons. Using tracing techniques, they will see whether the various populations are synaptically connected.

The described experiments are very relevant and feasible within the time frame of four years. The results will be readily interpretable and meaningful. These are cutting edge projects.

- Conclusion

— Summary

This team proposes to use molecular biological tools to study neuronal and glial specification in the somatosensory system. The questions being asked are as cutting edge as the tools being used. The understanding of the development of the somatosensory system will lead to new approaches in the treatment of somatosensory disorders such as sensory neuropathies.

— Strengths and opportunities

- High quality science.
- Very focussed, logical project.
- The evo-devo approach is very strong.
- Cutting edge techniques.
- Development of national and international collaborations is excellent.

— Weaknesses and threats

- For the study of neuronal circuitry, the team may want to look at techniques involving viruses (eg pseudorabies virus, modified pseudorabies viruses developed at the Salk) for the tracing of neuronal pathways.

- The addition of electrophysiological techniques to bridge the gap from development to behaviour would be an asset. This would possibly best be done by hiring a researcher with expertise in electrophysiology, although could possibly be accomplished via collaboration (eg. with team 4). Ideally, this could involve the testing of reflex pathways following genetic manipulation, study of the electrophysiological properties of the identified neurons, study of connectivity as well as the use of intracellular labelling for morphological and connectivity studies. Collaboration with Team 4 may be advisable for this electrophysiological expertise.
- To maintain high visibility in this competitive field, the team should consider organising an international research meeting in Montpellier.
- Project 1 appears to be under-funded.

— Recommendations

The team should be encouraged to stick to their well-defined projects. They should be encouraged to seek additional funding for project 1. Consideration should be given to adding an electrophysiologist (with expertise in patch clamping) to the team and collaborating with Team 4.

This project merits continued support. The team has published high quality work in top journals, and the approach described is likely to result in continued high impact research.

Team 6: Plasticity of the central nervous system, stem cells and glial tumors

Team leader: Mr Hugues DUFFAU

- ### Appreciation on the results

This team was recently created for implementing research focused on the central nervous system and developing new approaches for the treatment of low grade gliomas. The three principal investigators come from different disciplines and they complement each other. The team had little time to produce concrete results but preliminary ideas and proposed projects are interesting. The Team is heading for a high risk but high rewarding strategy in the medium and long term. Other secondary outcomes may shed light into the mechanisms of tumour proliferation, brain mapping, and plasticity.

The activity of the Team 06 spans from basic molecular science to translational medicine in the field of neurooncology. The lines of research are extremely original and of high quality. The head of the team is a recognised scientist in the field of intraoperative brain mapping. The results of their studies are now shifting towards a combined neurosurgical and chemiotherapy approach to neurosurgical patients with low grade gliomas.

A total of 146 papers (16.2 per person) have been published in the last 5 years by the members of the unit with an overall h-index of 38 (4.2 per person). Total citations is 1,255 (139 per person) with a total average citation index of 47.1 (5.2 per person). The overall output in terms of papers is impressive, especially if one considers that for some members of the team the clinical and teaching workload is extremly high. However the h-index and the average citation index indicate that the impact of the publications can be improved. Most of the members do not provide information about their attendance to international conferences as invited speakers and it is therefore difficult to understand their ability to disseminate their work.

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

Very little information is provided regarding the awards obtained by the members of the staff. Except for the Head of the Unit, invitations and participations to international conferences are very rare.

This information is not available. An indirect exstimate from the names of the co-authors, it seems that the unit is able to attract only visiting surgeons for short periods of time.

Team members have obtained external funding from various sources, which includes money for salaries, equipment and consumables.

There is little evidence of an intense international collaborative effort except for the team leader.

- ## Appreciation on the strategy, management and life of the team

Most members of the team are heavily involved in teaching at the Université Montpellier II. The distribution of the teaching time appears uneven.

- ## Appreciation on the project

The project of the team is based on two main lines. First, developing new molecules for the treatment of low grade gliomas. This project seems well advanced and ready to be tested in clinical trials. This is relevant and feasible. The second project concerns the exploratory analysis of the role of stem cells in brain plasticity and neuroproliferation. This second project is not well defined and difficult to understand its relevance in the short term.

- ## Conclusion :

— Summary

The Unit is composed of 9 members heavily committed to clinical activity and teaching. The clinical research programme aims to study low grade gliomas in a comprehensive approach, including identifying molecular biology markers for response, developing clinical prognostic indexes, applying stem cells-based therapy.

— Strengths and opportunities

The project is focused and detailed. Research questions are well laid down spanning from molecular biology to diagnosis and therapy. The head of the unit is internationally recognised for his scientific work and achievements. The team has throurough expertise in the field of neurooncology and is highly driven. The link with external partnerships is positive.

— Weaknesses and threats

The prognosis of patients with low grade gliomas is unfortunately still very poor due to the lack of effective treatments. Treatments have been developed for decades without major breakthrough. The Team is well aware that they are competing with pharmaceutical industries and other groups in the world that are trying to develop similar approaches. The project, if successful, could lead to immensily important results. But the chances are against a successful outcome. The stem cell approach is the weakest part of the project. The Team seems to have not clear how to stimulate native stem cells that could restore function of damaged pathways. In the adult brain the creation of new long range tracts is impossible and they should reformulate the overall concept of subcortical plasticity. Finally the demand from the rest of the department for collaborative projects linking peripheral organs and the brain could distract them from their main scientific goals.

— Recommendations

The group will need to consolidate internal cohesion in order to achieve fruitful interdisciplinary spirit. This will require to potentiate neuroimaging mapping and possibly appointing a cognitive neuroscientist with functional imaging expertise. The stem cells research is of interest to elucidate possible molecular mechanisms but at the moment has little potential for becoming truly translational in the short or medium term. The Team should start recruiting PhD and Postdoc fellows dedicated to research as it is evident that the teaching and clinical commitment of the principal investigators is quite onerous.

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

Nom de l'équipe : NEURAL DIFFERENTIATION AND CONNECTIVITY IN THE SOMATOSENSORY SYSTEM

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

Nom de l'équipe : PATHOPHYSIOLOGY AND THERAPY OF VESTIBULAR DEFECTS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	B	A

Nom de l'équipe : PLASTICITY OF THE CENTRAL NERVOUS SYSTEM, STEM CELLS AND GLIAL TUMORS

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

Nom de l'équipe : GENETICS AND THERAPIES OF RETINAL AND OPTIC NERVE BLINDNESS

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

Nom de l'équipe : DEAFNESS, TINNITUS AND THERAPIES

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

Nom de l'équipe : PERIPHERAL NERVE INJURY AND REGENERATION

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	A

Administration Droit Economie Gestion Médecine Odontologie Pharmacie Sports

Université Montpellier 1

Montpellier, le 12 mars 2010

Le Président
Ph A/ NG
Départ n° 2010 - 85

Monsieur Pierre GLORIEUX
Directeur de la section des unités
de recherche
Agence d'Evaluation de la Recherche et de
l'Enseignement Supérieur (AERES)
20, rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je m'associe aux remerciements formulés par l'ensemble de la direction de l'unité de recherche **«Institut des Neurosciences de Montpellier, U583 : Physiopathologie et thérapie des déficits sensoriels et moteurs»** pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise.

Vous trouverez ci-joint les réponses du Directeur de l'unité auxquelles le Vice Président du Conseil Scientifique et moi-même n'avons aucune remarque particulière à rajouter.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.

Philippe AUGE

5, boulevard Henri IV – CS 19044 – 34967 Montpellier cedex 2 – Tel : 04.67.41.74.00 Fax : 04 67 41 74 56

Unité de Recherche 583

Physiopathologie et Thérapie Des Déficits Sensoriels et Moteurs

Directeur Christian Hamel

- **Equipe 01 :** *Christian Hamel* - ***04 99 63 60 10***
  Génétique et thérapie des cécités rétiniennes
- **Equipe 02 :** *Jean-Luc Puel* - ***04 99 63 60 09***
  Physiopathologie et thérapie de l'oreille interne
- **Equipe 03 :** *Jean Valmier* - ***04 99 63 60 07***
  Neurobiologie moléculaire et cellulaire du système somato-sensoriel
- **Equipe 04 :** *Alain Privat* - ***04 99 63 60 06***
  Physiologie et approches thérapeutiques des pathologies médullaires
- **Equipe 05 :** *Jean-Ph. Hugnot* - ***04 99 63 60 08***
  Cellules précurseurs neurales

Agence d'évaluation de la recherche et
de l'enseignement supérieur
20 rue Vivienne
75002 PARIS.

Montpellier, le 11 mars 2010

Objet :
Observations sur le rapport d'évaluation
« Sensory pathology, neuroplasticity and therapy »

Madam, Sir,

Please find enclosed our response on the evaluation report of our project entitled "Sensory pathology, neuroplasticity and therapy"

Be sure, we appreciate the scientific expertise of the evaluation committee, and that their evaluation will strengthen our research project.

Sincerely yours

Jean-Luc Puel
Head of the Research Unit

Commentaries for the research unit

After a brief presentation of the past activity, the AERES referees underline the impressive output of the unit in term of publications: 245 papers with IF>1 (mean IF 5.5) since 2005 (67 of them with impact factors >7 and 14 with IF > 10). The reviewers acknowledge the excellence of the groups (with international visibility and good funding), the emergence of new teams and the synergy of the topics, the excellence of the technical platforms, the strong interactions with the clinical departments and start-ups; and the excellent public and educational dissemination.

General comments

The AERES committee draws attention to weaknesses and threats, which we would like to discuss point by point in the following response.

- Many groups extend research to stem cells and gene therapy, often without being internationally competitive.

In fact, 3 groups are involved in stem cells research (team 01, 03 and 06), and 2 groups (team 01 and 02) in gene therapy. Stem cells are studied under various aspects: In team 6, stem cells are characterized as tumoral stem cells to explore their involvement in the glioma pathophysiology and to find new molecules and innovating therapies against these cells. In team 1, stem cells (iPS) will be used as a tool to develop cellular model of gene therapy. Only in team 3, are stem cells being studied as a therapeutic tool to replace vestibular hair cells. However, as the reviewer stated into the AERES appreciation of team 3 "The review therefore found the stem cell project interesting and cutting edge". Despite the fact that human resources working on stem cells are rather small, the teams produced more than 6 papers in international journals with IF>7 (Stem cells, Embo) papers since 2005, which is very competitive. As regards iPS, our institute is located in the same campus as the new "Institut Régional of Therapy" which is currently developing iPS technology, which is an unique and timely opportunity to integrate this cutting-edge advance in our field of research.

Gene therapy is mainly developed in team 1, and to a lesser extent in team 2. To that goal, team 1 has recruited a senior investigator, Vasiliki Kalatzis, who comes from an internationally renowned laboratory in this field (E Kremer, IGMM, Montpellier). We would like to stress that Vasiliki Kalatzis is the authors of (28 papers, 11 of them with an IF> 7) in the field of genetic and gene therapy. Besides, 4 people are also working on that topic in team 1 (2 engineers, 1 post doctoral fellow, 1 PhD student). Gene therapy projects are based on clear rationale for well defined genetic diseases, such as inherited optic neuropathies with loss of function, or retinal dystrophies (retinitis punctata albescens) for which there is already many supportive data.

Our goal is to favor the growing of this core group specialized in gene therapy towards a full team. To reach this goal, we will focus our annual "Call for New Teams" on the recruitment of new researchers in the field of gene therapy.

- Pertinence to integrate a team working on human glioma.

First of all, this thematic is not new since Jean-Philippe Hugnot (MCU, UM2) and Norbert Bakalara (PR, ENSCM) started this project 3 years ago, as evidenced by Pr Bakalara's patent on the antiproliferative effect of phostines against the C6 glioblastoma cell line (PCT Int. Appl. (2009), WO 2009004096 CNRS and l'INSERM since July 7, 2008). One patent from Jean-Philippe Hugnot which is currently written on the elimination of cancer stem cells by their forced differentiation into neurons. Publications on this topic will be submitted soon.

Growing interest in gliomas led Jean-Philippe Hugnot and Norbert Bakalara to look for collaborations with clinicians and scientists in brain tumors. They met Hugues Duffau, who is an internationally renowned researcher and clinician in gliomas (h-index = 30). Pr Duffau is also heading the neurosurgery department of the neurological hospital Gui de Chauliac on the Saint Eloi campus where the Institute of Neuroscience (INM) is located. He was recently awarded by the "victoire de la médecine 2009", one of the most important French medicine distinctions.

Gathering the competences of these 3 researchers in the same Institute provides an elegant, unique and original multidisciplinary research program centered on glioma. Hugues Duffau is internationally recognized for his work on neuroplasticity following low grade glioma resection with cutting-edge brain imaging combined with intra-operative electro-stimulation mapping in awaked patients. Integration of his research topic in the INM constitutes a starting point to explore further the cellular and molecular mechanisms of brain plasticity in relation with the sense organs and glioma, which is very likely to be a unique international situation. Jean-Philippe Hugnot explores the differentiation pathway of normal and glioma stem cell which has led him to find innovating therapy based on forced neuronal differentiation. Jean-Philippe Hugnot investigates the tumoral process leading to gliomagenesis, and Norbert Bakalara develops, in collaboration with the spin-off BétaInnov, therapies using oxysterol and phostin agents. The group also benefits of the expertise of Alain Bonafé (head of the neuroradiology department), a senior researcher (Jan de Weille, CR1 CNRS), 2 associate professors (Christine Fabre, UM2 and Catherine Gozé, UM1), and they attracted a senior researcher from CNRS (Bernard Rothhut, CR1 CNRS), 2 postdoc and 4 PhD. . It is noteworthy that these projects are well funded by several national funding agencies (INCA, ANR), charities (AFM, ARTC, La Ligue, ARC, Gefluc, FdF) and industrial grants (Beta Innov).

We would like to emphasize the impact that team 06 will have on our research from peripheral nervous system to CNS. Indeed, team 02 already had close collaborations with team 06 regarding central auditory deficits using dichotic tests in patients with gliomas located in the temporal area, but having a normal audiogram. As stated in the review of team 02, “what the team has to do eventually is to extend their peripheral model work to incorporate more central aspects” to take into account the central component of the tinnitus disorder. This is now achieved by using functional brain imaging (fMRI) in collaboration with Alain Bonafé (Team 06). Therefore, instead of detracting our attention from the sensory systems, we are convinced that the interactions with team 06 will considerably widen our possibilities to study the central integration of the sensory organ signals. Therefore, we are now discussing the integration of Andreas Kleinschmidt (INSERM U562, NeuroSpin, Saclay, Paris) a specialist of perception and of Anne-Lise Giraud (INSERM U960, ENS, Paris) working on the basic mechanisms of speech perception to reinforce the topic on Neuroplasticity.

- No broad discussion within the Institute of future common research directions

The steering committee is in charge of the future common research directions under the supervision of the external scientific advisory board. However, we agree that it would be a good idea from the point of motivation, cohesion and collaboration within the institute to integrate all the researchers in the discussions of future research directions. To foster the discussions about scientific directions within the institute, we plan to organize in September an annual 2-day brainstorming outside the laboratory to favor the emergence of collaborative or new projects.

- PhD and Postdoc are not represented in comparison to permanent staff.

We noted that the PhD students and Postdocs feel poorly represented. This most probably arise from a lack of discussions between the PhD students and Postdocs with the overall staff members of the INM, despite the representation of PhD/Postdoc into the laboratory council, which takes place every month. In accordance with the AERES recommendations, we plan to organize a journal-club lunch -get together- every week with all the PhD students and Postdoc. The Journal club should be in line with the topic interest of the speaker. A staff member (most probably a researcher, Guy Lenaers) will be in charge to initiate and organize the journal-club. To improve the involvement of PhD students and Postdoc in the decision-making for the Unit, the PhD students and Postdoc council will meet accordingly to a regular schedule. This should help to get feedback into the laboratory council. Internal seminars will from now on be presented in English by the PhDs and Postdocs. Moreover, the teams will be strongly encouraged to send PhD students and Postdocs to internationals meetings. This will be incorporated into the PhD-team leaders “ethical contract” at the beginning of the PhD.

- International PhD and Postdoc

We are aware that the number of foreign PhD students and Postdocs is relatively low. Therefore, we will pay particular attention to the hiring of international candidates. To this aim, we will encourage Erasmus students doing a training or Master at the INM to pursue their PhD within the INM. We will also try to adapt our Master program (Audiology, Neurosciences, Health/Chemical) to international Masters by providing English lessons.

Specific comments

- Awards are not extraordinary and few team leaders have been invited to international conferences and symposia.

We agree that we need to increase our visibility. However, we would like to stress that 3 of the 6 leaders are well recognized in their field of competences, accordingly to their h-index (Christian Hamel: 24; Hugues Duffau: 30, Jean-Luc Puel: 32) and their invited conferences in international meetings or symposia (Jean-Luc Puel: 33; Hugues Duffau: 66; Christian Hamel: 7 since 2005). We also believe that the emergence of the new teams (teams 03; 04 and 05) will contribute to a better identification of their respective team leaders from the international scientific community. Finally as stated by AERES appreciation: "*The Unit has been able to recruit several promising young investigators trained in excellent laboratories*", we strongly believe that the young investigators, who should take more responsibilities and become independent in the next few years, will contribute to excellence at the INM institute.

- The recruitment of foreign scientists needs to be increased.

The AERES reviewer is right; we need to increase the number of foreign fellow. While we have a significant number of foreign PhDs [Lima Maldonado (Brazil), JIA Huan (China), Yong Tang (China), Smati Ibtihel (Tunisie)], we now focus our recruitment on foreign postdoc (Gaston Sendin, Argentina) and senior scientist [Simone DiGiovani (Tubingen University)]. In addition to the call for new team, we are quite active in announcement process through international meetings.

- Researchers may soon emerge as new group leaders.

We totally agree with the recommendation of the AERES committee. The emergence of the new teams reflects our goal to promote the development of independent researcher with their own profile. We would like to stress that some of the investigators compete for their own grants (for example, Guy Lenaers, E-RARE grant; Benjamin Delprat, Chercheur d'Avenir), whereas others are part of the steering committee (for example, Régis Nouvian). The Unit also encourages the young investigators to obtain their HDR, needed to have officially PhD student. No doubt that new independent researchers will arise from the largest teams in the next couple of years

- Technician's policy for promotions.

Up to now, technician's promotions are not dependent on whether they are working on a team project or in a core service but rather, we try to promote all the technicians. Since core services often needs high expertise, it is mandatory that they are under the responsibility of qualified technical staff. Of course, the choice for a technician to supervise services comes from a common decision between the technicians and the steering committee. However, we agree with the AERES committee that we really do need more competence regarding animal facility. We are currently asking for a CNRS partnership in order to get qualified technicians for genotyping in the animal facility. We are also aware that the university has employed one of our key staff on a 10-month contract/year for the past 8 years. We really do try to "push" the university policy in order to get a permanent contract.

Commentaries for team 01

Christian Hamel

General comments

- Gene therapy

During the last years we focused our activities on pathophysiological studies (OPA1, FATP1). Switching progressively towards therapeutic approaches is critical. We therefore put a strong emphasis on therapeutic studies by recruiting in 2009 Dr Vasiliki Kalatzis (CR1) who is experienced in gene therapy to oversee this work. In addition, 1 post doctoral fellow, 1 PhD student and 2 technicians strengthen the project and we plan to add more. Our project is based on a realistic analysis of the clinical constraints and of the international competition in the field.

We chose to treat dominant optic atrophy and Wolfram syndrome as i) we have the relevant animal models, ii) we have extensively studied the pathophysiology, and iii) therapeutic trials have never been done for these conditions.

Similarly, we want to develop a gene therapy approach for retinal pigment epithelium (RPE) dystrophies such as retinitis punctata albescens and choroideremia. In these cases, the animal models either do not exist or do not accurately reproduce the human disease. Therefore, our approach consists of generating disease-specific iPS cell lines that will be differentiated into RPE cells. To do so, we will collaborate with the neighbouring IRB institute in which several iPS cell lines were already generated. The goal is then to validate the therapeutic gene of interest using these newly differentiated RPE cells, not the optimal vector to use, since the vectors for targeting the retina have already been validated by animal preclinical and human clinical studies worldwide. We are fully aware of the caveats of this project, however, its potential must be considered in an international context: should our preclinical approach be successful, our results will complement those obtained by other groups on (incomplete) animal models, and should be sufficient to begin clinical trials. Needless to say, this endpoint is only possible because human trials have already been successful for other genes expressed in the RPE and leading to a RPE dystrophy.

- Developing a platform to produce the vectors of interests in situ

This is not a priority as we do not have the direct interest or the competence necessary to develop our own vectors, especially as there are several specialised vector production platforms in France (for example, the Laboratory of Gene Therapy, Nantes, and the AFM, Evry). It is of better value to benefit from the services of these platforms and concentrate our efforts on validating the gene therapy strategy in vitro and in vivo.

- It would be nice to promote the visibility of some members who will also enhance the general visibility of the team

The senior investigators of the team firmly want to keep close relationships with each other to assure efficient progress of their projects (sharing materials, expertise, clinical investigations and resources). Subjects are well defined for each senior investigator so that their expertise is well visible and recognized outside the laboratory.

Commentaries for team 02

Jean-Luc Puel

We are really grateful to the AERES committee for their evaluation that will strengthen our research project. The AERES referees point out that the team is a clustering of high quality packages with a good to excellent quality of publications. Moreover, the AERES committee acknowledges that the team 02, with the original and highly significant results obtained over the past 4 years. The team can be considered among the top 10 in the world of the hearing field. Finally, AERES reviewers underline that the new recruits to the established team ensure an infusion of new techniques, age structure and make the team highly competitive.

As a fair evaluation, the AERES referees raise some concerns that we would like to answer point by point.

General comments

- AERES Reviewer comment

"The most annoying and clinically manifest forms of tinnitus to the patients are to be those that arise past the stage where local drug application in the middle ear/cochlea can do anything about it. This assertion has however never been tested. Thus the peripheral model explored here is mainly geared (rightfully) to the prevention and early intervention aspects of hearing loss and tinnitus."

- Team leader answer

The reviewer is right. It has been proposed, but never proved, that the presence of tinnitus for years (20 or 30 years) may induce durably cortical plasticity leading to central tinnitus. If true, local drug application in the middle ear/cochlea may not be efficient to treat "old" tinnitus. Actually, the only clinical study where anti-NMDA was applied onto the round window membrane in human is a compassionate use trial in which the tinnitus began less than one year before treatment (Wenzel et al., Eur Arch. Otorhinolaryngol. 2009 Oct 22). In this project (see page 5 in the project document), we propose to probe the efficiency of NMDA blockers in animals experiencing recent versus long-term tinnitus. Although conditioned avoidance response is a powerful method to demonstrate that animals experienced tinnitus, this procedure does not permit to probe "old" tinnitus because the motor response disappears after one week. Consequently, we proposed to use the behavioral model based on gap detection reflex procedures developed by Turner et al. (Behav. Neurosci., 2006, 120:188-195) to measure tinnitus during long periods of time. The Turner's model is based on the ubiquitous property of the startle reflex to be reduced in magnitude by a preceding silent gap in an otherwise continuous acoustic background. When the silent gap is presented in the background sound just before (100ms) a startle stimulus, the response to the startle stimulus is reduced. When the animal experiences tinnitus qualitatively similar in frequency to the background sound, the silent gap is filled with animal tinnitus, and the startle response can occur. This procedure has been successfully used to evaluate tinnitus after salicylate treatment and acoustic trauma.

- AERES Reviewer comment

"The perfusion salicylate model is technically elegant and beautiful, but in humans salicylate (in the form of aspirin) is applied systemically. In contrast, it is known that this drug also affects the central nervous system GABAergic activity (as does noise-induced hearing loss)."

- Team leader answer

In our experiments, salicylate is applied systemically (Guitton et al., J. Neurosci. 2003, 23, 3944-3952; Eur. J. of Neurosci. 2005, 22: 2675-2678). We agree that drug- and noise-induced hearing loss affect the central nervous system, especially the GABAergic activity. However, local application of NMDA blockers into the cochlea prevents the occurrence of tinnitus in animal receiving systemic application of salicylate. This suggests that salicylate-induced tinnitus originates from the periphery, and that they are mediated by cochlear NMDA receptors.

- AERES Reviewer comment

"What the team has to do eventually is to extend their peripheral model work to incorporate more central aspects; this is not in the current set of proposals but that may need to wait until the next research program."

- Team leader answer

We totally agree. We need to extend our work to incorporate more central aspects of tinnitus. This can be done through collaborations with external research teams working of this topic. This is needed to track basic mechanisms of tinnitus, but also to evaluate the efficiency of local treatment. That's why it is very important

to have an INM team working on the central nervous system, especially on the physiological aspect of the neuroplasticity, which is the basement of the long-term tinnitus.

- AERES Reviewer comment

"International recruitment is not strong and few international links make the team more fragile than need be. This information was not clearly available. It is clear that one CNRS position in the team has been recruited from Germany, and a student has also been recruited from a francophone country, but on the whole the group is composed stably from local expertise. Attention needs to be paid to maintaining and strengthening national and international collaborations."

- Team leader answer

We agree that the information was not clearly enough explained. Despite the fact that our research relies somehow on local expertise, we would like to point up we recruited researchers from abroad (Jing Wang, China) or after postdoctoral training in non-francophone foreign country [Jérôme Bourien (USA), Jérôme Ruel (Australia) and Régis Nouvian (Germany)]. Please find below the brief history of the young researchers who joined the team since 2005:

1. Régis Nouvian did his PhD in Montpellier between 1999-2002, thereafter he joined the lab of Tobias Moser (Göttingen, Germany) for his post-doc and he was recruited through a CNRS position in 2008.
2. Benjamin Delprat did his PhD in Montpellier between 1998-2001, thereafter he successively joined the labs of Christine Petit (Paris, France) and Käthi Geering (Lausanne, Swizerland) before being recruited through an INSERM position in 2007.
3. Jing Wang is basically a MD coming from China. She did her PhD in Montpellier between 1999-2002 and did her postdoc in a biotech company Auris Medical. She was thereafter recruited through an INSERM position in 2006.
4. Jérôme Ruel did his PhD in Montpellier between 1998-2001 and did his postdoc in the lab of Donald Robertson (Perth, Australia) and was appointed as assistant professor in 2007.
5. Jérôme Bourien did his PhD in Rennes (France) between 1999 and 2002 and he thereafter did his postdoc in José Principe lab (Gainesville, FA, Florida, USA) and was appointed as assistant professor in 2005 and integrated the unit in 2006.

Following the recommendation of the AERES committee, we will favor the hiring of postdoctoral fellow from abroad. As an example, Gaston Sendin (Argentina) will join our team as a postdoc in 2010 to implement patch-clamp technique with hair bundle deflection. Accordingly to the AERES recommendation, we will pay attention to our international links, but we are convinced that the young investigators recruitment will boost our international collaborations within the next couple of years.

- AERES Reviewer comment

"The projects also depend on the success of several ANR funding applications over the next year. The younger researchers in the team need to emerge in the near future with appropriate responsibility being allocated."

- Team leader answer

It is true that the DFNA25 project relies on ANR grant submission. Since ANR grants are quite competitive, we need to supply robust preliminary data in order to be funded. Therefore, preliminary data with the phenotype investigation of the DFNA25 knock-in mouse, which should be available in June 2010, would ensure an ANR grant. Moreover, we encourage our young researchers to compete for "young investigator ANR" once they will get preliminary data on their own projects. Accordingly to the AERES comments, there is no doubt that the promising young researchers will succeed into their research plan as well as their funding. Logical future for them is to become independent researcher with their own profile.

Specific comments

- AERES Reviewer comment

"The translational aspects are promising but the reviewers wonder about the practicality of the promontory testing of spontaneous activity in humans, as impedance between the electrode and promontory, leaking impedances through epithelium moisture levels etc cannot very well control. All of these assumptions still assume that chronic tinnitus is a peripheral phenomenon, which is advocated by Team 2 but a view not widely held outside this Team."

- Team leader answer

That's right; the impedance between the electrode and promontory might be a problem. If this is the case, we can place the electrode onto the round window membrane in anaesthetized patients. Remember that this test will be only performed in candidate patients to receive a totally implantable drug delivery device. In any case, cochlear implant device will be upgraded with this test to monitor the functional properties (spontaneous activity, synchronization, adaptation) of spiral ganglion neurons in patients.

- AERES Reviewer comment

"It would be important to compare salicylate-induced changes to noise-induced changes with respect to spontaneous auditory nerve fiber activity."

- Team leader answer

Totally agree. Experiments are in process.

Commentaries for team 03

Christian Chabbert

Specific comments

- Number of papers per group member, 3, is quite low:

As stated in the presentation, four papers that should reach high impact factors have been delayed in 2009 for one year, due to the deposit of the 3 patents. These papers will be published in 2010. To be noted: Pr A Zine is co-author in 2009 in a PloS One paper focused on the vestibule innervation (Katayama K, Zine A, et al. Disorganized innervation and neuronal loss in the inner ear of Slitrk6-deficient mice. PLoS One. 2009 Nov 11;4(11):e7786).

- There is no completely transparent policy although many of the projects are proposed as collaborative with leading groups involved in vestibular function.

We want to emphasize that fact that our team is the leading team in each of the collaborations cited. Moreover, the project to study vestibular neurotransmission do not depends on collaboration with groups in Chicago or in Kansas. The project to study endolymph indeed depends on funding from the Swiss government, but additional funding applications will be done in 2010.

- The use stem cells to regenerate damaged cells

The project to use stem cells to regenerate damaged cells (hair cells, neurons, secreting cells) is based first, on the acknowledged demonstration that stem cells are present in the vestibular endorgans (Li et al. Nat Med. 2003 Oct;9(10):1293-9 Pluripotent stem cells from the adult mouse inner ear), and second by previous investigations from our team showing that utricle stem cells, harvested and selected from young rodents are able to form into microsheres and to integrate damaged sensory organs (non published yet). We therefore agree with the reviewer that this project (that is developed in collaboration with Dr Heller lab – Sandford University / the founder of vestibular stem cells – Nat Med 2003) is cutting edge. The functional assays already developed in our team will undoubtedly promote a fast development of the project.

- The need to develop strong collaboration and partnership with the ENT clinic

As suggested by the reviewer, in view of the clinical importance of the vestibular deficits, the team is already developing a strong collaboration and partnership with the ENT clinic of Hopital Gui de Chauliac, through the expertise of Dr F Venail. Recent pilot clinical test indeed demonstrate a protective property of a compound upon vestibular neuritis (vestibule damage) in human. Dr Venail shares one of our patents on that application.

Commentaries for team 04

Frédérique Scamps

Specific comments to recommendations

- The existing collaboration and interaction with team 5 (Carroll) should be continued and further strengthened

I am totally aware of the scientific plus-value to collaborate with team 5 and team Avenir. In addition to classical patch-clamp, the team is presently developing the mechanostimulation in vitro and the recordings of the H-reflex in vivo for proprioception analysis to complement our in vivo expertise in sensory-motor testings. I am convinced that these electrophysiological tools will lead to fruitful collaborations between our teams.

- For the translational aspects and the collaboration with neurosurgeons, the team lacks currently a good hypothesis on which to focus. The team should decide whether regeneration or pain is their primary focus for translation, identify a few key hypotheses and proposed mechanisms and collaborate with groups that have more background and expertise in these areas

Role of chloride homeostasis in nerve regeneration is the main focus of the team. As clearly stated, pain belongs to the debilitating symptoms that do occur following lack or partial nerve regeneration. Thus improving nerve regrowth is aimed to prevent pain occurrence and motor dysfunction, which does not mean that we are working on pain.

Presently we have firmly established a collaboration with Pr. Jean Coudane's team (2 staff researchers, 1 engineer and 2 master students are involved in the project), expert in biomaterial engineering (Institut Charles Gehart: Institut de Chimie Moléculaire et des Matériaux de Montpellier), to propose new regeneration chambers able to fulfill several criteria such biocompatibility, biodegradability, flexibility. We are also currently working on "drug" delivery with these materials. Regeneration chambers are tested in vivo on mice and rats with surgeons (1 master/year) from Hôpital Lapeyronie at Montpellier (pre-clinical studies, not clinical) and an invited professor from Brazil (J. Braga-silva, surgeon who is doing clinical research on this topic) with whom we are developing long term collaboration (phD student from Brazil). Patents are expected to be produced.

Which "drug" and when to deliver to efficiently improve nerve regeneration is the most difficult task. It is established that only one molecule will never be efficient. Recent studies on miRNA have demonstrated that one miRNA is able to control several processes and its delivery at promixal part of injured nerve induces efficient inhibition. It is this new strategy associated with a permissive environment that we plan to address for both nerve regeneration and basic science. Among the 600 miRNA identified to date in mice, we decided to quantitatively analyze 22 miRNAs according to 1) their chloride homeostasis (NKCC1, Best1, TMEM16) interaction, 2) neuronal expression, 3) injury relation, 4) growth status and 5) receptors involved in regeneration. Our first results are promising concerning candidate selection. I agree that focusing on 4 % of total population remains risky. To screen all miRNA remains an exciting challenge that however needs to ask for complementary financial support.

- The team leader is to be congratulated on her achievements to date and provided with financial support and encouragement to promote successful internal and external collaborations.

No comment

Commentaries for team 05

Patrick Carroll

We thank the committee for their helpful evaluation of our projects. Our responses to the specific critiques and recommendations of the committee are given below.

Specific comments

- AERES Reviewer comment

"The team contributes to teaching in Arts and Science, Medical genetics, and Neuropsychology. The amount of teaching is not clear."

- Team leader answer

Two members of my team, Agnes Fichard-Carroll and Ilana Mechaly are lecturers at the University and give a total of 400 hours of teaching a year to students from undergraduate level up to the second year of Master degree. Moreover, Agnès Fichard is responsible for 4 lecture modules and co-head of "Master 2 professionalising research and Development in Neuropsychology". Patrick Carroll also gives 3h of teaching on "Development of the peripheral nervous system" at Master2 level

Weakness

- AERES Reviewer comment

"*For the study of neuronal circuitry, the team may want to look at techniques involving viruses (eg pseudorabies virus, modified pseudorabies viruses developed at the Salk) for the tracing of neuronal pathways.*"

- Team leader answer

We are aware, through our collaboration with the Goulding group at the Salk Institute, of the newly-developed mouse models using pseudorabies virus for neuronal tracing developed by the Calloway group, and we are well-placed to get access to some of these models that have not been published yet.

- AERES Reviewer comment

"*The addition of electrophysiological techniques to bridge the gap from development to behaviour would be an asset. This would possibly best be done by hiring a researcher with expertise in electrophysiology, although could possibly be accomplished via collaboration (eg. with team 4). Ideally, this could involve the testing of reflex pathways following genetic manipulation, study of the electrophysiological properties of the identified neurons, study of connectivity as well as the use of intracellular labelling for morphological and connectivity studies. Collaboration with Team 4 may be advisable for this electrophysiological expertise.*"

- Team leader answer

We strongly agree with the committee that we need to acquire/develop competence in physiological assays including electrophysiology in order to exploit our models to the full. Our collaborators in the Goulding group possess recognized expertise in physiological assays such as fictive locomotion for the study of spinal circuit function (Zhang et al. 2008 Neuron) which opens the possibility of importing this type of technology or carrying it out in collaboration. In addition, in the group we are actively working on the development of an ex-vivo assay of cutaneous afferent stimulus-response properties in an isolated nerve skin preparation developed by G. Lewin (Berlin). A Ph.D student (S. Grimal) has spent several weeks learning this technique in the Lewin lab and we have set up the system in our lab in Montpellier. We are also considering trying to hire a competent scientist, either by mutation of permanent post or as a post-doc, with expertise in physiology to strengthen this side of the project. Otherwise, various teams in the INM, and especially Team 04, have expertise in physiological assays in sensory systems that will allow fruitful collaboration. In addition, we have recently received several offers to collaborate on certain aspects of this project from groups in France. These different possibilities are presently under careful consideration.

- AERES Reviewer comment

"To maintain high visibility in this competitive field, the team should consider organising an international research meeting in Montpellier."

- Team leader answer

To increase the groups visibility, and possibly to get involved in a European research project, we plan to organize and international meeting on Sensory neuron development and Spinal Circuitry in the coming year. Several internationally recognized scientists have aleady given verbal commitment to participate including G. Lewin (Berlin), P. Ernfors (Sweden) and M. Goulding (USA).

- AERES Reviewer comment

"Project 1 appears to be under-funded."

- Team leader answer

We intend to seek funding for this project in partnership with a clinical research group (S. Valleix, Hôpital Cochin, Paris) who showed that human mutations in Zeb1 are involved in corneal dystrophy. The endothelial cells affected in the disease are neural crest derived. Our aim here would be to create a conditional knockout mouse model at the Zeb1 locus in order to circumvent problems of early lethality in the classic knockout model.

Recommendations

- AERES Reviewer comment

The team should be encouraged to stick to their well-defined projects. They should be encouraged to seek additional funding for project 1. Consideration should be given to adding an electrophysiologist (with expertise in patch clamping) to the team and collaborating with Team 4.

- Team leader answer

See reply above

- AERES Reviewer comment

"This project merits continued support. The team has published high quality work in top journals, and the approach described is likely to result in continued high impact research."

- Team leader answer

No comment

Commentaries for team 06

Hugues Duffau

General comments

First of all, we are aware that we would like to build a new Team, much more dedicated to the study of the central nervous system, in an Institute renowned in the field of peripheral nervous system. However, our goal is clearly to interact with the other teams in order to better understand the central integration of the sensory organ signals. In this state of mind, we have begun a work about central auditory deficit in patients who underwent awake surgery for a low-grade glioma in the left dominant hemisphere, with preservation of language function (in collaboration with team 2). We will also study the neural basis of vestibular processing using intraoperative electrical mapping, in line with previous works already performed and published by our team (in collaboration with team 3). As a consequence, our team will be rapidly integrated in the INM, by providing additional data not accessible using the methods more classically by the other teams of the Institute.

Furthermore, it will be not difficult to "disseminate our work", as written by the reviewers. Indeed, we are already internationally recognized both in the field of brain mapping and plasticity as well as in the field of (low-grade) glioma – as evidenced by more than 160 articles and more than 60 international invited lectures given since 2005. Our previous works have allowed a dramatic improvement of the prognosis of low-grade glioma, which is no more "unfortunately still very poor due to the lack of effective treatment" (as claimed by the reviewers). Indeed, it is now well admitted worldwide that the early surgical resection of low-grade gliomas enables to increase the overall survival beyond 10 years, as we have demonstrated. This is the reason why the quality of life and then the knowledge of mechanisms of brain plasticity should be improved, both at a macroscopical scale (using intraoperative electrical mapping combined to pre- and post-surgical functional imaging) and at ultrastructural scale (explaining the need to study the possible role of stem cells in cerebral reorganization and the necessity to develop animal models). Even if we are aware that international competition is important in the field of glioma, as well as in the field of brain plasticity, we would like to insist on the fact that very few teams in the world are presently able to study both simultaneously.

Indeed, with regard to the feasibility of the project, we have strong relationships between a university hospital and the INM within the same place. In the hospital, we have a unique international recruitment of patients with low-grade gliomas in the department of neurosurgery. All patients can benefit from an extensive neuropsychological assessment performed before, during and after surgery, thanks to Sylvie Moritz-Gasser, who have more than 10 years of experience in the field of cognitive neurosciences, and who is now PhD in our Unit. All patients can also benefit from functional neuroimaging (functional MRI and diffusion tensor imaging), once again before and after surgical resection (which is quite unusual in the literature), thanks to the strong collaboration with the department of neuroradiology of Pr Alain Bonafé – who is helped by a neuroradiologist specifically involved in this field and who is now PhD in our Unit: Dr Nicolas Manjeot, as well as by an engineer specialized in the analysis of signal: Emmanuel Lebars. In addition, in the INM, Jean-Philippe Hugnot investigates the tumoral process leading to gliomagenesis, and Norbert Bakalara develops, in collaboration with the spin-off BétaInnov, therapies using oxysterol and phostin agents. Taken together, this complementary and multimodal expertise gives us a unique opportunity to develop a translational research, since we have to insist on the fact that it is very rare in the world to associate so many experiences in the same Institute.

Finally, we would like to emphasize our perfect awareness of the limitations of our study, especially with regard to the subcortical plasticity. We are very surprised to read that the referees think that we would like to restore the white matter pathways by using stem cells, since we were the first to review the literature about the impossibility to induce subcortical reconnection and thus about the absolute necessity to detect and preserve the white matter tracts intraoperatively (see for instance Duffau, Neuroscience Research 2009). Our aim is to better understand the mechanisms of cortical plasticity induced by the unique model in the human brain of slow-growing low-grade glioma, an extensive research we begun many years ago, internationally recognized both by researchers and physicians, and surprisingly not detailed by the reviewers in their comments.

Specific comments

- Comments on the new drugs development section of our project

The development of our new molecules is not dedicated in a first step of selection against low grade glioma. The molecules are firstly selected against high grade glioma. Once we will have established primary cultures of low grade glioma and characterized them we will go through a screening against low grade glioma.

We do not develop similar approach to pharmaceutical industries which mainly develop products such as alkylant agents, anti-mitotic agents, kinase inhibitors or immunotherapies. The target product profile of our compounds is designed to interact with new target(s) with an original mechanism of action. That's the reason why, so far, we have a collaboration contract going on with the BetaInnov start up on the oxysterol projet and why our phostine project interests big industrial pharmaceutical industries. We actually are with the "the canceropole grand sud-ouest" in discussion with big pharma (MATWIN program) to have the phostine project develop in association with one of these industries.

Because we were asking for a patent on phostine and because these projects are new (two years of existence) we did not yet communicate to international meetings.

- Comments on the stem cells section of our project

First, Jean-Philippe Hugnot holds an INSERM "contrat d'interface" for 4 years. His teaching duty is reduced to 50 hours so he can devote most of his time to research in this competitive stem cell field. This will give him more time to disseminate his work, to participate to international congress and to publish more high-profile papers.

As regard attractiveness, not only visiting surgeons are joining the team, but one full time CNRS researcher (B Rotthut) and one associated-professor (C Gozé) have now reinforced this topic. One new PhD student (K Gamal) who has just been granted a 3 year-fellowship by a charity will join the group in September 2010 and one young post doc with a very good record in the field of glioma (A Tchoghandjian) is applying to several calls to join us.

As for international collaborations, these were not mentioned as they were related to previous work. Jean-Philippe Hugnot spent a month in 2007 as an invited researcher at the Riken Institute in Tokyo (Pr Yoshiara) to study the role of NCAM2 in the self-renewal of mouse spinal cord stem cells. Results from this collaboration will be published this year. One collaboration with Canada (M Kmita) started last year to develop new methods to kill stem cells in the brain white matter so as to get insight of their role. More recently, JP Hugnot was invited in China in last December to set up a collaborative work with Pr Bian at the Chongqing Hospital (China) on glioma stem cells.

As regard dissemination, new results on forced differentiation of glioblastoma stem cells that will be submitted this spring in a high-profile journal could not be disseminate due to a patent which is being written.

The reviewers express concern about "the exploratory analysis of the role of stem cells in brain plasticity and neuroproliferation. This second project is not well defined and difficult to understand its relevance in the short term. The Team seems to have not clear how to stimulate native stem cells that could restore function of damaged pathways". In fact, while an exciting idea, the stimulation of endogenous stem cells for promoting brain plasticity was not mentioned as part of our project for the next 4 years. This may be a long-term development of our research, but so far so little is known on normal human stem cells that one cannot plan anything serious on this issue. This point must have been mis- or over-interpreted by the reviewers.

Our group is more devoted to studying stem cell differentiation and extending in the tumoral context, his previous work on the molecular mechanism of differentiation of normal stem cells which has led to 6 publications over the last 4 years (3 Stem cells, 1 EMBO, 1 JNR). This strategy has led us to generate innovating therapeutical approachs based on the forced differentiation (one patent, one high profile publication expected this year). We very strongly disagree with the reviewer's comment who considered "The stem cells research …. has little potential for becoming truly translational in the short or medium term" as differentiation-based therapies have led to effective treatments for leukemia and is pursued for glioblastoma by other groups (for instance the use of BMP proteins for glioblastoma, published in Nature. 2006 444(7120):761-5). Reviewers were not specialists in the stem cell and in glioma fields which likely explains this comment at odds with the tremendous dynamism of this research domain worldwide.

Besides stem cells, thanks to a national wide recruitment of patients by H Duffau, the group is developing a new topic on low grade glioma cells, which are not stem cells. A full time researcher (B Rothhut) and an associated-professor (C Gozé) are in charge of this project and several aspects are being explored, notably migration which is a major problem for these tumors. This may ultimately lead to the development of a mouse low grade model with associated brain plasticity as observed in man. This could constitute a starting point to study involvement of normal stem cell in glioma-associated brain plasticity but this is a remote goal, obviously not attained over the 4 years as clearly stated in the project.