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

Research Units Department

AERES report on unit:

Institut des Neurosciences Cellulaires & Intégratives
INCI

Under the supervision of the following institutions and research bodies:

Université de Strasbourg
CNRS

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et de l'enseignement supérieur

Research Units Department

President of AERES

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Unit

Name of unit:	Institut des Neurosciences Cellulaires et Intégratives
Acronym of unit:	INCI
Label requested:	UPR
Present no.:	UPR 3212
Name of Director (2009-2012):	Ms Marie-France BADER
Name of project leader (2013-2017):	Ms Marie-France BADER

Members of the committee of experts

Chair:	Mr Jean-Philippe PIN, Montpellier
Experts:	Mr Thierry GALLI, Paris
	Mr Mark HANKINS, Oxford, United Kingdom
	Mr Michael HASTINGS, Cambridge, United Kingdom
	Ms Mayumi KIMURA, Munich, Germany
	Mr Régis LAMBERT, Paris (CNU representative)
	Mr Bertrand LAMBOLEZ, Paris (CoNRS representative)
	Mr Jacopo MELDOLESI, Milan, Italy
	Mr William SCHWARTZ, Worcester, USA
	Mr Andrew TODD, Glasgow, United Kingdom
	Mr Luis VILLANUEVA, Paris

Representatives present during the visit

Scientific Delegate representing AERES:

Ms Thérèse JAY

Representatives of the unit's supervising institutions and bodies:

Ms Evelyne JOUVIN-MARCHE, INSB du CNRS

Mr Eric WESTHOF, Université de Strasbourg

Report

1 • Introduction

Date and conduct of visit:

The visit took place within the INCI building, during two full days, from 9am to 6pm, 9-10 February 2012. After a general introduction by the AERES representative and the chairman, a 30mn general presentation of the unit by the former and future director was given in the presence of most of the personnel of the unit, followed by 15 min discussion. Each group leader presented the past activities and projects for 20 min followed by 15 min discussion in front of the director, the team members and the AERES committee members . The director and team members left the room 5 min before the end to allow a "private" discussion between the AERES committee members and each group leader. The committee was split into three groups each having one hour discussion with i) the students and post-doctoral fellows, ii) the researchers with permanent position, excluding the team leaders, and iii) the technicians and engineer staff. Half an hour exchange with the representatives of the research organization (CNRS), the University of Strasbourg and the hospital (CHU) took place the second day, before the final closed door meeting. The visit was conducted in the absence of Prof Hankins who has not been able to reach Strasbourg on due time, but sent his remarks and questions to the chair of the committee.

History and geographical location of the unit, and overall description of its field and activities:

The INCI is located in a CNRS building, originally occupied by the "Centre de Neurochimie", within the main campus of the University of Strasbourg, close to the faculty of chemistry, the Institute of Molecular and Cellular Biology (IBMC), and the Biology platform and the Physiology building. The INCI originates from the fusion of 3 research units: UPR2356 (Neurotransmission and Neuroendocrine secretion), UMR7518 (Neurobiology of Rhythms) and UMR7519 (Cellular and Integrative Neurophysiology), and was recognized as an independent CNRS unit (Unité Propre de Recherche) in 2005. These three laboratories became three relatively independent departments in the new INCI unit, and efforts have been done since then to improve the scientific exchanges between the departments. The present director was named in 2008, and initiated the fusion of the administrative staff, as part of her goal to better organize the group of teams as a single research unit. Today, the teams that are part of the pain axis are not located in the actual INCI building, but in another building close by. A 3rd floor of the actual INCI building is being renovated, and will soon be allocated to these teams, then offering an optimal situation for better scientific and technical exchanges. A specific space will also be built within the hospital to accommodate the clinical studies on sleep and mood disorders (CIRCSom).

The building also hosts a research service unit, dedicated to the management of the building and infrastructure. It also includes a service unit called "Chronobiotron" corresponding to an animal facility well equipped to control the night and day rhythm, and the raising of different rodent animals (rat and mice) including *Arvicanthis* a diurnal rodent that represents an important model to study the biological rhythms of diurnal mammals, making this unit unique in Europe for such studies.

At the scientific level, the three main research axes correspond to the main topic covered by the original units. The first axis covered basic programs aimed at identifying some molecular determinant involved in the release exocytotic process and in endocytosis, and the regulatory mechanisms of synaptic transmission. These programs have gained a large visibility in France, with a strong involvement in the scientific club "exocytose-endocytose" on one hand, and strong connection with the Ecole Normale Supérieure in Paris for the development of optogenetic tools. The second axis is dedicated to the understanding of the molecular and cellular mechanisms involved in pain, covering basic studies of the network organization in the spinal cord, the development of new apparatus for the analysis of pain in freely moving animals, up to the clinic, making INCI one of the main laboratories in France dedicated to pain studies. The third axis is devoted to the study of the neurobiology of rhythms, going from molecular to clinical studies, through animal experiments taking advantage of the chronobiotron facility, making this axis unique in France and in Europe.

Management team:

The Director is responsible for taking the main decisions regarding the organization, and strategic orientation of the research unit. She also represents the Institute locally, within the University, nationally at the CNRS, and internationally.

INCI research activity is based on well delimited and fully independent research teams. The management is organized around 1) a steering committee composed of the group leaders and headed by the director, that takes the main decisions, and discuss the strategic and scientific orientations of the institute, and 2) a Council composed of 10 elected personnel representing the various categories of personnel (researchers, technicians and engineers, students and post-docs), plus 3 person nominated in which the organizational points are being discussed and validated. In addition, three committees are specifically dedicated to the Health and safety (6 persons involved), training, and technical development. There is no external board.

The management is supported by an administrative staff composed of a Human resource person and three secretaries in charge of the budget, external contracts and mission for the various teams of the Institute.

Unit workforce:

As illustrated below, the workforce is composed of 59 researchers/professors, and 23.5 technicians, then illustrating a ratio of 1 technician for 2 permanent staff researcher/professor, not including the personnel of the two service units (Building/infrastructure and Chronobiotron). Of note, aside from the administrative staff, each technicians and engineers are affected in a specific research team.

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	14	16	15
N2: EPST or EPIC researchers	31	29	28
N3: Other professors and researchers	5	4	3
N4: Engineers, technicians and administrative staff *on a permanent position	26.5	23.5	
N5: Engineers, technicians and administrative staff * on a non-permanent position	5		
N6: Postdoctoral students having spent at least 12 months in the unit	20		
N7: Doctoral students	42		
N8: PhD defended	45		
N9: Number of Habilitations to Direct Research (HDR) defended	5		
N10: People habilitated to direct research or similar	32	32	
TOTAL N1 to N7	**143.5**	**72.5**	**46**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

2 • Assessment of the unit

Overall opinion on the unit:

INCI is the result of an important reorganization of the neuroscience community within the central campus of the University of Strasbourg. Following the fusion in 2005, the initial three research units now correspond to three main research axes: "Communication and network", "Pain" and "Neurobiology of rhythms". Important contributions were made in each of these fields, with the pain and rhythm axes being quite unique, and leading the field in France. INCI is involved in a number of local, national and European networks. The general quality of the science is good, with original findings in all three axes, though the international impact should be improved. INCI has important industrial outputs, including strong collaboration with the biotech and pharmaceutical industries and the creation of a start-up company. Important translational programs with clinical research have been implemented and open new opportunities. INCI is strongly involved in teaching, and training of graduate students. However, a limited number of post-graduate researchers are being trained in the institute. This is due to the limited number of external main grants and competition with nearby Germany and Switzerland. Although most teams have been able to raise external supports, there is still a limited number of major funding from the French and European agencies able to support salaries for engineers and post-graduate researchers. The expertise of the research teams covers a number of commonly used techniques including molecular and cell biology, electrophysiology, morphological studies, and animal experimentation. New approaches are being developed including those dedicated to pain and rhythm studies, optogenetics, and clinical studies, but efforts to further implement new state of the art technologies should be encouraged. INCI has attracted new leaders in all three main axes, offering new opportunities for the near future. The new director has clearly oriented INCI towards a new dynamics, and succeeded in creating a very good atmosphere in the institute, without any clear separation between the axes. This must be pursued with the support and strong involvement of the group leaders and technical staff who must amplify this movement.

Strengths and opportunities:

The fusion of the three units, and the actual dynamics put forward by the new director represents certainly a major achievement of the past period, and offers new possibilities for scientific exchange and attractiveness. Although the teams from one axis (pain) are still located in a different building, this should be solved soon since a new floor is being renovated before the end of this year, then offering the best possible environment for perfect exchanges between all scientific axes.

The director, and one team leader have important responsabilities at the CNRS head quarter in Paris, making INCI very well informed of the evolution of this structure and any new strategic orientation in health science in France.

Two of the three main axes (pain and rhythm) are quite unique in France, with original and dedicated environment (new methods to measure and quantify pain, chronobiotron, the *Arvicanthis* model as examples), and are then expected, especially because of their direct interconnection with the first more basic axis "Communication and Networks", to attract numerous collaborations, students and post-docs, as well as new group leaders.

The expertise covers a large number of technical skills, from molecular and cellular biology to new animal experimentation, through state of the art electrophysiological and optogenetic techniques. Of note, the Chronobiotron facility located in the same building offers an excellent opportunity to develop pre-clinical studies. Such an environment is optimal to perform high quality programs ranging from molecular to behavioral studies.

Most research teams have dedicated technicians or engineers, allowing the follow up of the team expertise, and the technical training of students and post-docs.

All teams have access to a large laboratory space, then not preventing their development, and not limiting the hiring of new non-permanent staff, including master students, graduate students, post-doctoral fellows, technicians or engineers.

Three new young group leaders have been hired at the beginning of the ongoing period, and brought new dimension in all three axes of INCI. Each of them succeeded in raising a number of grants, and developing new and innovative approaches (optogenetic, translational and clinical studies). Also two new researchers (CR), two assistant professors (MCU) and 5 technicians/engineers got a permanent position at INCI, thereby allowing the reinforcement of the teams with new expertise and training capabilities.

INCI is part of a number of local (IFR neuroscience), national and international networks in the neuroscience field, including "Neurex" (the director of Neurex being a member of INCI) that interconnects most neuroscience laboratories in Alsace, and the neighboring area in Germany and Switzerland, including the pharmaceutical and Biotech companies working in this field. This is also associated with a "master network" within the same area. INCI is also strongly involved in a network with emerging countries from the Mediterranean area. All these well-established connections offer a number of opportunities for efficient collaborations, and for attracting motivated students.

INCI has established good connections with the industry, with important contracts with a pharmaceutical company, a number of patents, and the creation of a new start up company. Such connections offer the possibility to further develop INCI expertise, through fee for service contracts, but should also help getting national support for translational research with industry, such as those from the dedicated programs from the "Fond Unique Interministériel (FUI)" or the ANR.

Weaknesses and risks:

The scientific production is of good quality, but still does not reach the expected level for such a large institute, according to the expertise on site, the possibilities to go from the molecule to the animal, and the national leadership in their field. Most papers were published in journals with a medium-low impact in the field. Too few papers in the top "General" or "Neuroscience" journals have been published within the last 4 years.

Related to the above weakness, many teams are carrying out too many projects, many being descriptive and with limited ambition.

The number of productive collaborations between the INCI teams remains limited (31 articles involving at least 2 teams, representing about 10% of the total number of publications)

Although a number of external contracts have been raised, the number of grants enabling the hiring of post-docs and engineers remains primarily limited to national fundings (ANR). The same is true with specific post-doctoral fellowships, such that few post-doctoral fellows are currently being trained in the INCI.

The INCI as a whole appears to have limited ambitions, as illustrated by its absence in applications to the "Investissement d'Avenir" program: no application was part of a labex, equipex, or national infrastructure. This will then limit the development of the INCI, as well as opportunities to reinforce its technological competitiveness, and attractiveness.

The INCI technological expertise is large, but deals mostly with commonly-used techniques. Very few state of the art recently developed approaches are being set up (but note the development of optogenetic tools), and/or used at INCI, even though these would certainly bring much to many ongoing and future projects (genomic, deep-sequencing, proteomic analysis, new high definition microscopy, biophysics, the development of viruses as vectors, the systematic and high content analyses, as examples). This is related with the absence of organization of the technical and engineer staff towards clear technological developments, and the establishment of designated facilities.

Although in a highly competitive university, with top laboratories around, the number of close collaborations with the other laboratories in Strasbourg appears limited.

The development of clinical projects is hampered by the slow process of finishing the CIRCsom facility.

Recommendations:

To improve the impact of the publications, the director and group leaders are encouraged to limit the number of ongoing projects in some teams, and stimulate internal scientific discussions to select more ambitious projects that take advantage of the multidisciplinary expertise of the Institute. The development and use of state to the art technologies will also help reaching better demonstrations, and will have higher impact in the field.

Higher impact publications will certainly help raising more funds, and then attract highly motivated students and additional post-docs able to bring new expertise in the INCI.

Much can be expected with collaborations with physics, chemistry and mathematic laboratories, as well as with other laboratories in biology (IBMC, IGBMC, school of pharmacy, ESBS) from the University of Strasbourg. Such collaboration should be reinforced and encouraged.

Efforts should be pursued to attract new group leaders, able to bring novel expertise, animal models and/or technical skills. International open calls should be organized and new leaders selected and encouraged to apply to the "atip-avenir" or starting ERC grants. This would be possible if INCI establishes clear and strong relationships with the other Institutes in Strasbourg, then allowing the new leaders to implement their projects based on the technological facilities available in the neighbor laboratories. Such a possibility should be discussed with all team leaders, offering them the possibility to liberate enough space to welcome two or three new teams within the next period.

To help the steering committee of INCI to select new group leaders, it will be valuable to identify a few external experts (at least one per axis) that could act as an advisory board. Such a board will also be useful to help with internal decisions regarding the renewal of the unit, the reorganization of the teams, and to propose solutions for less productive teams and teams lacking external support to carry out their research.

The group leaders should be encouraged to apply to competitive grants, and participate to programs like the "Investissement d'Avenir" in the future and also contribute to new projects developed within the Idex.

A general discussion should be engaged with the technical staff to delineate the contour of some technical facilities of interest to a number of programs, and in which, not only the best practice and state of the art techniques will be used, but also technological development will be conducted based on constant litterature survey. Such an organization will give equal access to these technologies to all teams, and will help attract new group leaders even though it will be difficult to guarantee them to have a dedicated permanent technical staff. To guarantee the involvement of all technicians in scientific programs, they can be proposed to equilibrate their activities into that of the facility, and that of a program conducted by one of the INCI team.

3 • Detailed assessments

Assessment of scientific quality and production:

The INCI research programs cover three main axes: one corresponding to more basic science (Communication and network) while the two others are more oriented towards translational research with clinical implications ("Pain" and "Neurobiology of rhythms"). Although originating from three independent laboratories, the creation of INCI facilitated interconnections between these axis, with common interests in all three axes in cell signaling, synaptic transmission and neuron-glia interaction. The detailed analysis of synaptic activities, synaptic networks and release processes of the first axis, has direct implications on the understanding of the neuronal network involved in "pain". The interaction between these two axes also involves the development of optogenetic approaches. The first and second axes have common interest in neuroendocrine cells and membrane trafficking, while the second and third axes are both oriented towards behavioral and clinical studies. Accordingly, not only INCI represents a major research center in pain and biological rhythms research in France, but it offers a very good environment for the development of projects going from the molecular and cellular processes to the behavior and the clinic. Such interactions lead to 31 publications involving more than 2 teams, only 3 of them involving teams participating in two different axes. This needs to be improved in the future.

The quality of the science is very good in all three main axes, with important findings and developments. Of note the important observation made on the role of lipids and small G proteins in the exocytotic process, the identification of a new form of synaptic plasticity, the development of new systems to measure and quantify pain, the identification of important determinants of the effect of antidepressant in neuropathic pain control, the role of kisspeptin in the control of seasonal rhythm. New activities directed towards translational research have been implemented both in the rhythm and pain axes. These must be encouraged and supported.

A total of 259 original scientific publications have been published since 2007, including those recently accepted and not included in the final report, representing a means of 1.8 scientific papers per researcher FTE with permanent position per year. The INCI members are the main authors (first or last authors or co-authors) of about half of these publications, while the other half is the result of join effort with external laboratories, indicating the expertise of the INCI teams is well recognized outside. Among the 29 researchers and 15 professors and lecturers with permanent position, three did not reach the threshold to be considered as "producers" according to the AERES requirements.

The mean general quality of the publications is very good, and superior to that of the French neuroscience community (means IF of 5.7 compared to 4.2). Most publications are in good to very good specialized journals, and a few (28, about 10%) are in the top journals of the discipline or in general journals: Biol Psy (x6), Blood, Curr Biol (x2), JCI (x2), Mol Psy, Mol Cell, Nat Genet (x2), Nat Med, Nat Neuro (x2), Neuron (x3), Plos Biol, PNAS (x6), from which 11 are issued from INCI as the major contributor.

Assessment of the unit's integration into its environment:

The INCI researchers are well considering protecting their research and are very active in the development of the economical world. INCI is very active within the Neurex network that involves academic laboratories working in Neuroscience in the Strasbourg, Freiburg and Basel areas, including some biotech and pharma industries. A number of collaborative efforts with industry, including several programs with Servier and LVMH, highlight the important relationship this institute has with the economical world. This is also illustrated by 9 patents and a start up company created in 2008 (Innovative Health Diagnostics – IHD). This company is still hosted at INCI, within renovated laboratories and offices dedicated as "Neuroincubator". For this achievement, INCI received the "Trophée INPI de l'Innovation".

INCI teams have been active is raising funds for their research, with external fundings representing 70% of the total income, not including salaries of the permanent personnel. External funding comes mostly from the ANR (14 projects funded, for a total of 2600 K€), collaborative programs with the industry (1600 K€ mostly from Servier and LVMH), private foundations (740 K€ from ARC, Retina France, FRM, La Ligue contre le Cancer) and other national programs (559 K€). Of note, very few supports have been obtained from the European Commission. Although important, such external funds should be increased with the aim to attract more post-doctoral fellows. Large differences in raising funds can be noticed between the 9 teams of INCI. Although some will be well supported for the coming years, a few have very limited funds (see the detailled comments, teams by teams), and this will have to be taken very seriously to allow these teams to generate enough good quality preliminary results to be able to raise funds in the near future.

Assessment of the research unit's reputation and drawing power:

INCI members have been invited to give presentations in various meetings, 164 of which where at international conferences, including the most prestigious ones like Gordon Research conferences (6) and Keystone symposia (1). This represents a very good success relative to what can be found in other French laboratories. When adding the invitation for seminars in universities abroad, this indicator nicely illustrates the international visibility of INCI members.

INCI members received national (CNRS bronze medal (team 2)) and local prices, including 4 from the Alsace comittee of the Fondation pour la Recherche Médicale (2 for team 1, and 2 for team 4 members).

This international visibility is also well illustrated by the number of international collaborations with a number of countries including the USA, Canada, Argentina, Marocco for those outside europe. Most of these collaboraions led to common publications, including most of those published in top international journals (Nat Neurosci, Neuron, Mol Psychiatry, PNAS, Curr Biol, JCI, Blood, Nat Genet). Among these collaboration one can note the very effective ones with Switzerland and Italy (Team 2), Canada (Team 3), USA (Team 5).

The INCI is very active in participating in national and international research networks. Of note, INCI members have important responsibilities in networks like: Neurex that links most neuroscience research teams and biotech companies in Alsace, and the neighbouring German and Swiss area; the Neuromed program of the 7th PCRD that includes 26 partners from 7 Mediterranean countries. INCI is also a member of the ENI-NET European network, in which only 3 French cities participate (Strasbourg, Paris and Bordeaux). Two Associated European Laboratories (LEA) have been established and supported by the CNRS, together with a Max Planck Institute in Germany, and a with a Dutch laboratory, both in the rhythm axis. Surprisingly, the INCI leaders have not been involved in any program of the "Investissement d'avenir", despite insistence from the University of Strasbourg.

INCI has been quite successful in recruiting new researchers and lecturers (two CR CNRS and two lecturers at the University of Strasbourg), and has been very active in supporting its personnel to get promoted : five researchers get promoted Director of Research (1) or CR1 (4), 5 promotions among the professors have been obtained, and 11 technicians got promoted to a higher level. Also, 4 CRs (3 CNRS and one INSERM) have joined the Institute coming from other laboratories, demonstrating the attractiveness of INCI. Most importantly, INCI has been able to attract young team leaders just before the evaluated period, bringing in a new dynamics and opening new possibilities. Five new technicians have been recruited.

INCI has trained many graduate students who defended their PhD (45), and 35 are actually preparing their thesis, 25% of which are coming from abroad, mostly from European, North African and South American countries. However, a few post-doctoral researchers joined the INCI, only 8 being present on January 1st 2011.

Assessment of the unit's governance and life:

The Director is a biochemist, well recognized in the endocytosis-exocytosis field. She has made original achievements in demonstrating the involvement of G proteins in these processes. She took a number of important responsibilities over the last 5 years, including the chair of an evaluation section at the CNRS, the section 25 dedicated to physiology. She is also an editor at the Journal of Biological Chemistry, demonstrating her clear international reputation. She is the author of more than 100 publications with a mean citation per article of more than 40 (200 citations a year since 1992), again illustrating her leadership in the field. Her strong involvement in taking national and international responsibilities is very well received, and is important to bring this laboratory to its best scientific level.

The research organization is based on the full independence of 9 research teams, each headed by one group leader or two co-leaders. In addition, technological facilities have been set up, one dedicated to microscopies, the Chronobiotron and the CIRCSom (Centre International de Recherche en ChronoSomnologie). The first two facilities are well organized, and appear as independent units dedicated to facilitate the access to state of the art technologies of main interest to most research teams of the INCI. The third facility will be installed in a new environment that will be finished in a year or so, within the Strasbourg hospital. Group leaders are also involved in the strategic and scientific decision at INCI, all being part of the steering committee. Such an organization appears optimal to facilitate exchanges between the 3 main axis, and due to the limited number of teams in this institute. The decision are also based on the 4 advisory committees, the council of the INCI, the INCI health and safety committee, the INCI training committee, and the technician committee.

Overall the researchers and faculty expressed positive comments on the life at INCI, and feel that they have a positive and active intellectual life. They represent a group of ~50 mixed age people, with global sex parity. Half of them have the habilitation to direct research and they said to be directing their own project and signing as last author the work of the students they mentor. They expressed concerns about the replacement of retiring technicians and engineers, and the lack of funding in certain areas. They criticized the bureaucracy associated with leading a group as argument not to move to or have dropped a group leader position. They explained the lack of postdoctoral fellows by the low salaries in France in comparison with Germany and Switzerland and the lack of specific funding. They also mentioned that lab meetings and journal clubs are in English or French depending on the attendance. They were concerned about the criteria the visiting committee used to evaluate their teams and asked whether or not the committee would assess in comparison with the 2008 report. They would welcome open calls to host new junior groups and bring new concepts and ideas.

The INCI did not take advantage of an external committee to help and get advisory inputs on its internal strategic decisions. Although this may not appear necessary as long as the Institute is not facing critical issues, this will be very helpful when considering the reorganization of the teams, reorientation of scientific projects to tackle the most important issues of the field, and for the recruitment of new teams. Such a board, in association with the steering committee should be beneficial in limiting the number of on going projects in some teams, and stimulate them to develop more risky and ambitious projects. It seems that this aspect has to be improved, and should be part of the ambition to improve the general quality of the publications.

Although a technician (ITA) committee has been set up, it does not appear to function properly. The 45 min discussion with the ITA was very open and lively, with contribution from almost all ITAs present. The general impression was that ITAs are satisfied with working conditions and were committed to INCI's success, and were strongly supportive of INCI's project. Most ITAs in INCI are permanent staff, mainly from CNRS, except 7 having temporary position. All ITAs have a yearly formal interview with their direct supervisor. ITAs employed by University of Strasbourg bitterly complained about their bonuses and career advancement as compared to those of their CNRS colleagues. This point was addressed during the interview of the committee with the University representative who clarified the question of bonuses but admitted that issues of career advancement were still unresolved. ITAs are encouraged by the INCI board and team leaders to attend vocational training courses and INCI conferences/meetings. The majority of technical staff works in research teams, under supervision of a PI and in relation to other team members including post-docs and students. However, not every teams have dedicated technician personnel, especially the newly created teams. It is noteworthy that technical staff is in general reluctant to being enrolled in technical platforms in the future, but were receptive when it was mentionned that such facilities are a necessity due to the necessity to follow new technology development, and that not every teams will be able to develop for its own programs all required techniques and equipment. Most are involved in collective tasks, with 6 of them being responsible for implementation of health and safety rules (ACMO). Relevant contributions of ITAs are acknowledged by authorship in publications of most, but not all INCI teams. The committee recommends that equal authorship opportunities are given to ITA in all teams of INCI, and that a clear organization of the technician and engineers expertise allowing a perfect access to the techniques to every research programs within INCI. Such an organization should strongly favor technical development, especially regarding those techniques missing at INCI (biophysics, genomic, proteomic), then improving resaerch projects.

INCI has an up-todate web site, and dedicated intranet allowing the diffusion of key information both outside and within INCI. A booklet presenting the institute has been printed. INCI members have access to external seminars given by external invited speakers (28 since 2009, representing one seminar a month), with half given by researchers from abroad. The number of external seminars could be increased to offer more possibilities for collaborations and for stimulating new programs and approaches within INCI. Team meetings are also organized in most teams, many being in english due to the presence of foreign students and post-docs.

The personnel from INCI is highly involved in structuring the neuroscience research community at the national and local level. In addition to the director being the president of a CNRS commission, one team leader took important responsabilities at the CNRS central headquarter, to participitate in the structuring of the french neuroscience community. INCI members are also in charge of the structuring of the local neuroscience community (Institut Fédératif de Recherche), local (Neurex), european (ENI-NET) and international (Neuromed) networks. Professors within INCI plays important role in structuring the neuroscience training and teaching at the university, and created a club and electrophysiology school, one of the first of such initiative in France. A network initiative for master and graduate students in neuroscience has also been initiated (Docto-Neuro), with the aim to stimulate scientific and cultural exchanges between graduate students. This is unique in France and represents an excellent initiative.

INCI researchers are very active in a number of national scientific organisations, such as the Endocytose-Exocytose Club, the French “Sleep research and medicine” society, the national network for pain research, the Society for Neuroendocrinology, the European Biological Rhythms Society. INCI researchers organized in the Strasbourg area a number of meetings for these societies, with a total of 6 national or european meetings, in addition to the 6 Neurex workshops all within the INCI research axes. This is really a major achievement of INCI members.

Assessment of the strategy and 5-year project:

The INCI scientific projects will be conducted by the 9 individual teams, and take profit of the already established expertise of the institute in molecular biology, biochemistry, electrophysiology, animal physiology and behavior, towards the three main axes: "Communication and networks", "Pain" and "Neurobiology of Rhythm". Most projects correspond to the continuation of ongoing programs, for which the teams have demonstrated experience to reach their goals. Team 2 and Team 3 have made major efforts to reorient and concentrate their project towards new orientations, and based on excellent international and national collaboration involving the development of innovative optogenetic approaches. The important development of clinical translational programs initiated by 3 teams within the last period is likely to expand, with dedicated clinical space. This represents an important new prospect for INCI, and should be encouraged. Strong collaborative programs with industry are also going on and major efforts are being made to keep and expend these collaborations.

Very few strong collaborative projects between the teams have been clearly identified; this must be encouraged, with positive actions from the steering committee (financial support for example). For some teams, many sub-projects are being proposed, then limiting the ambition of the program. As already indicated, in those cases, priorities should be better defined, with a major effort of most team members put forward to bring the science quality to its best level, combining various approaches and techniques, many being available within the institute. The INCI teams are also encouraged to make a better use of the most innovative approaches recently developed including biophysical approaches, more systematic analysis such as those based on genomic or proteomic approaches (although not yet implemented in the INCI, such technologies are available in the Strasbourg area), the use of viral vectors, shRNA technologies, the development and use of biosensors, the development and use of transgenic animals.

To perform their projects, the teams have access to enough space (arround 250 m2 per team), allowing them to hire enough graduate students and post-docs, as well as to install the necessary equipment. All teams put in common part of their budget to buy common equipments. Most teams have raised enough funds to conduct their project at least for the first few years of the next period, but some appear not to have any external support, or very few. It will be necessary to define a strategy to help these teams to conduct their preliminary experiments requested for grant applications to be successful.

Assessment of the unit's involvement in training:

One third of the INCI researchers have Professor (PR) or Assistant Professor positions at the University of Strasbourg, all with heavy teaching duties in various disciplines all related to neuroscience, from molecular and cellular neurobiology to neurophysiology, making INCI a key player in neuroscience teaching and training in Strasbourg. Most notably, INCI professors are strongly involved in the teaching organization, one being the Dean of the Faculty of Life Science, one being the main coordinator of the entire physiology teaching program, another one being in charge of the master "Vie et Santé-Spécialité Neuroscience", one is in charge of the joined master in neuroscience between the Universities of Strasbourg, Freiburg and Basel. Five INCI members are elected members of the Faculty Council, while eight are members of the faculty teaching committee.

Forty five graduate students defended their PhD over the 4 years period. This is impressive regarding the number of researchers with the HDR (32). Among these, 32 are still working in science (24 are post-doctoral fellows, 6 are working in industry, and 2 got a CNRS position). Most thesis have been prepared within the 3 years funding limit, with a few extensions not exceeding 6 months. It seems likely that this time limit effectively prevents students from tackling cutting edge, but risky projects. While most completed a master program before their PhD thesis work, this was usually 6 months in duration and enabled them only to gain experience in laboratory methods.

The 35 doctoral students and 10 postdocs, representing the largest single group under INCI human resources, appear largely satisfied with their work at INCI. There are opportunities for inter-team interactions, including a well-attended institute-wide student seminar series, some joint laboratory meetings, and the DoctoNeuro program. There is no standing student committee to inform and advise INCI leadership on trainee issues.

75% of the doctoral students are French, who appear frustrated by post PhD funding mechanisms and stable career prospects. While most of them indicated that ultimately they wished to become team leaders or the equivalent, they likened their chances of achieving this outcome to a "lottery" over which they had no control. Moreover, most seemed to have little idea about how to strategically increase their chances of success.

Team 1: Intracellular membrane trafficking in the nervous system

Team leader: Mr Stéphane GASMAN & Mr Nicolas VITALE

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	7	7	7
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	5	4	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	6		
N8: PhD defended	5		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	6	6	
TOTAL N1 to N7	**21**	**12**	**8**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

• Detailed assessments

Assessment of scientific quality and production:

Team 1 proceeds from the fusion of two teams. The first team comprised 7 staff scientists, with strong expertise in cell biology, and focused on the molecular and cellular mechanisms of secretion in chromaffin cells. The second team comprised only one staff scientist, with strong expertise in mouse models of Prion diseases, and worked on the molecular and cellular mechanisms of neuronal degeneration. The team has a well known position in the role of actin cytoskeleton and lipids in secretory mechanisms, and the Prion protein in neurodegeneration.

The team published 49 articles overall among which, one article in PNAS and several articles in more specialized journals: J Immunol, J Cell Sci, JBC (2), Traffic (2), Dev Neurobiol (2), Cell Mol Neurobiol (3), IEEE TPAMI, BBA, Biol Cell, Eur J Neurosci, Neurosci, Autophagy and several reviews including Ann NY Acad Sci , as first or last authors. The scientific production is of very high quality but the impact could be improved.

Assessment of the research team's integration into its environment:

The team has obtained a reasonable level of external funding (1037k€), particularly from ANR and Alsace Biovalley. International funding is very limited (30k€). 46% of funding was disease-oriented (Prion diseases and cancer). The Alsace Biovalley project may lead to valorisation. Several staff scientists teach, mainly at master level. Overall, the team could increase its involvement in projects within INCI and at regional level.

Assessment of the research team's reputation and drawing power:

Several researchers from Team 1 obtained prizes and were invited to many (39) international events including International Symposium of Chromaffin Cell Biology, and International Society for Neurochemistry meeting. Only two postdocs were recruited, and both ended at the beginning of the evaluation period. There was no postdoc after 2008. Three staff scientists have been or are members of prestigious Editorial Boards: J Biol Chem, Curr Chemical Biol, Frontiers in Endocrinol.

Assessment of the strategy and 5-year project:

The fusion of the teams generates new opportunities such as the development of projects in mutant mice. 7 main objectives are listed which appear mainly as continuation of current research and range from the role of actin and phosphatidic acid in fusion, endo-exocytosis coupling, to membrane trafficking in mental retardation, AIDS, Prion and Alzheimer diseases, and cancer. While the team has a strong manpower with 8 staff scientists and 4 staff technicians, and a well recognized expertise in their field, focusing on fewer questions would allow going more in-depth and may lead to higher impact publications. The focus should be on the role of lipids and biophysical and dynamics approaches need to be implemented to produce major contributions and remain competitive. Furthermore, the team needs to consider their working hypothesis in a more open way.

Conclusion:

Overall opinion on the team: Team 1 proceeds from the fusion of two teams. The team has a well-known position in the role of actin cytoskeleton and lipids in secretory mechanisms, and the Prion protein in neurodegeneration.

Strengths and opportunities: The fusion of the teams generates new opportunities such as the development of projects in mutant mice.

Weaknesses and risks: The team has had too few postdoctoral fellows and the ratio students+postdoc/permanent scientists & technicians is too low.

Recommendations: While the team has a strong manpower with 8 staff scientists and 4 staff technicians, and a well recognized expertise in their field, focusing on fewer questions and combining complementary available expertise would allow going more in-depth and may lead to higher impact publications. The focus should be on the role of lipids and biophysical and dynamics approaches need to be implemented to produce major contributions and remain competitive. The project on Alzheimer should be second priority for instance. The team needs to work on improving impact and attractiveness. The scientific production is of very high quality but the impact could be improved. The team has obtained a reasonable level of external funding but could increase its involvement in projects within INCI and at regional level.

Team 2: Physiology of neural networks

Team leader: Mr Philippe ISOPE & Mr Bernard POULAIN

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	7	6	6
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	1	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	4		
N8: PhD defended	6		
N9: Number of Habilitations to Direct Research (HDR) defended	2		
N10: People habilitated to direct research or similar	7	5	
TOTAL N1 to N7	**15**	**7**	**6**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

• Detailed assessments

Assessment of scientific quality and production:

The team's main studies concern synaptic transmission, plasticity and integration in diverse models and brain structures. It has made very important and original contributions to this field during the last term by identifying a novel mechanism of Long Term Potentiation (PNAS 2008, Nat Neurosci 2009), a novel form of synaptic plasticity (Low Frequency Depression, J Neurosci 2010), synaptic defects caused by mental retardation alleles (PNAS 2007, Curr Biology 2010) and mechanisms that permit high-frequency synaptic transmission (J Neurosci 2012). The team also continued its highly regarded contribution to the field of bacterial neurotoxins. Finally, 2 patents were issued from team's research on Alzheimer disease diagnosis, which led to the creation by a team member of an award-wining start-up hosted at INCI.

Team members published 30 articles over the period, among which 18 from studies led by the team (including several in high profile journals: such as PNAS (x2), Nat Neurosci, J Neurosci (x3)) and 12 in collaboration with major input from the team (including Curr Biology, Neuron (x2), J Neurosci, J Cell Sci). The team also published 9 reviews, as well as 2 patents exploited by the start-up mentioned above.

Assessment of the research team's integration into its environment:

The team's integration is outstanding on several grounds. The team leader is involved in local and national research administration at the highest level (e.g. scientific director of CNRS research in Neuroscience/Cognition). Another team member's work led to patenting and successful creation of a Start-Up. Several team members have collaborative contracts with industrial partners and numerous informal partnerships with leaders of medical research in France. The team is part of the European network ENI-NET and Neurex.

The team obtained grants, industrial funding and fellowships from national and international sources (notably 3 ANR contracts) for a total amount of 1.44 M€ since 2006 and secured funding till end of 2013.

Assessment of the team's reputation and drawing power:

Team members gave 19 invited conferences in international meetings over the last period. A team member was awarded the CNRS Bronze Medal prize and recently obtained a very competitive position in Bordeaux. The team attracted the proposed co-director of the future team, as well as 3 post-docs and 8 PhD students. The team is part of the European network ENI-NET and Neurex. Collaborations with excellent foreign laboratories have resulted in outstanding output (Nat Neurosci, PNAS), in which the group clearly shares leadership for publications.

Assessment of the strategy and 5-year project:

The excellent project is primarily focused on cerebellar physiology, taking advantage of the team's established expertise and excellent collaborative network in the field, and of optogenetics tools recently developed by the future co-director of the team. The most ambitious parts address a major question in neuroscience: how do synaptic organization, plasticity and network input/output function relate to the functional organization in cerebellar modules? The project design minimizes overall risk-taking by continuing very original studies on synaptic mechanisms at the parallel fiber-Purkinje cell synapse and pursuing research on bacterial toxins. The division of research aims between PIs and other staff members is clear and sound, based on each member's competence.

Conclusion:

Overall opinion on the team: This excellent team achieved an outstanding production over the last period in a variety of basic and translational research topics and proposes a recentered and well-designed project with a high impact potential on cerebellar synaptic transmission, plasticity and organisation in functional modules.

Strengths and opportunities: the team's highly regarded expertise in synaptic plasticity and cerebellar physiology, an excellent collaborative network, the development of cutting edge optogenetic tools (as part of an on going network with other laboratories in Paris) and a good financial support.

Threats: the reduction of team's size in the near future, which is likely to be overcome. Indeed, the project has been carefully re-sized and funding is currently available for postdoc recruitment, with a high probability of obtaining further funding as the project and its applications develop.

Recommendation: give a high priority to the most ambitious and original parts of the project dealing with synaptic plasticity and the input/output physiology of functional modules.

Team 3: Nociceptive signaling in the spinal cord

Team leader: Mr Rémy SCHLICHTER

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	4	3	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	1.5	1.5	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	0		
N7: Doctoral students	3		
N8: PhD defended	3		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**9.5**	**5.5**	**3**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

• Detailed assessments

Assessment of scientific quality and production:

Work of this relatively small team (currently 4 permanent scientific staff) has covered a range of topics, centered around synaptic transmission in the spinal dorsal horn, in particular co-transmission by GABA and glycine, and neuromodulation (by steroids and neuropeptides). They have also provided evidence for target-derived factors in axonal growth in co-cultured primary afferents and keratinocytes, and have investigated cholinergic interneurons in the spinal dorsal horn. In addition, they have contributed to the work of two other INCI teams on pain mechanisms. One criticism of this team (recognized in their self-assessment) is the limited number of publications (9 papers from direct work or with a major collaboration, the best being published in a very good neuroscience specialized journal: Journal of Neuroscience; 11 papers with a minor contribution). Although this meets the "scientific production criterion" (1 "A rank" publication/team member/contract period), it is considerably lower than that of the other teams. There are significant mitigating factors: (1) much of the electrophysiological and anatomical work is extremely labour-intensive, (2) the papers are generally of high quality, describing carefully-performed work with adequate controls, and most contain a large amount of data, (3) the self-assessment states that much of the work is either recently submitted or in preparation. In addition, two members of the team are at an early stage of their independent careers, when it is unreasonable to expect high publication rates. A related concern is the productivity of two team members, neither of whom is a first/last author on papers during the review period. As stated above, the work is of high quality, and has important implications for our understanding of nociceptive processing at the spinal level.

Assessment of the research team's integration into its environment:

The team leader has a large teaching load, substantial administrative responsibilities within the University, and has contributed to outreach activities, while teaching/administrative duties of other group members are moderate or light. Overall, this therefore represents a relatively modest contribution to the local environment. The team does not have any contracts with commercial companies, but this is not unreasonable, considering the "basic" nature of the work that they perform (electrophysiological studies of synaptic transmission, neuroanatomy). They have a relatively low level of external funding (~€330k since 2007): mainly an ANR grant to the team leader that finished in 2010, with a number of smaller grants to one of the younger staff members.

Assessment of the team's reputation and drawing power:

The team leader has recently been promoted to the highest professor position, and is the only member of the team to have contributed to conferences (3 national) or given seminars (2 national/2 international). He has a good reputation in the field of dorsal horn electrophysiology, although with a relatively small number of citations for someone of his seniority (total ~1300; H index 19). The team has not recruited any post-doc, and has had a limited number (5) of PhD students, one from overseas. They have active international collaborations with groups in Canada, and a number of other collaborations that provide animals/materials. They have some collaboration with other INCI teams.

Assessment of the strategy and 5-year project:

The 5 year project focuses on two dorsal horn topics: (1) the role of cholinergic interneurons, and (2) modulation of GABAergic neurotransmission. The first of these, representing an extension of work already carried out by one of the team members, aims to characterize a small but distinctive and important population of inhibitory interneurons. The justification for working on these cells is partly the known role of cholinergic transmission in pain modulation, and also that they appear to form a homogeneous population. This aspect of the proposed work is highly ambitious, involving paired recording from synaptically coupled neurons, optogenetics and a recently described method that allows in vivo recording from GFP neurons. Since many of these techniques are new to this group, there is a concern that some intended outcomes may not be achieved. However, the project is very well designed, the necessary animals and equipment are available (meaning that the project does not necessarily require significant external funding), and the study will extend the collaboration with an expert laboratory, providing reassurance that these technically difficult experiments are feasible. The second topic extends the current work of the team leader and colleagues on modulation of GABAergic transmission, and includes techniques that are currently in use in this laboratory, as well as some that will be more challenging (optogenetics, paired recordings). Overall, the project is highly original and combines techniques already available in the lab (which are therefore "safe") with higher risk approaches which (if they work) will yield very important data. Both topics will involve some work on pain models, thus increasing their translational significance.

Conclusion:

Overall opinion of the team: The team is undoubtedly among the weakest in the Institute based on "measurable" outcomes (publications, funding, numbers of PhD students and post-docs). However, the team leader has a respectable track record and the two younger team members show considerable potential. Between them, they have made significant contributions in the field of dorsal horn physiology.

Strengths and opportunities: Despite the limited number of papers, the quality of their published work is high, and the team leader has previously published in Nature Neuroscience and has several papers in the Journal of Neuroscience. Although the two younger members of the team are yet to prove themselves, one of them has managed to obtain several small grants and both have a substantial paper, either recently published or under review. Both therefore show considerable promise. The team has an impressive range of techniques and is addressing important issues in somatosensory neuroscience. The specific collaboration with the expert Canadian laboratory should be of great benefit.

Weaknesses and risks: As stated above, the team has a relatively low number of publications and restricted funding. However, they have the necessary facilities (equipment, mouse lines etc.) to enable them to carry out the proposed project, so this is not likely to be a significant risk.

Recommendations: The team leader has an extremely high teaching/administrative load, and should be encouraged to try and reduce this. There is already some collaboration with the two other "pain" teams, and this should be strengthened. It will be very important for the team, particularly its younger members, to continue applying for external grant funding, concentrating their effort in generating the preliminary data requested to obtain a large enough grant that could cover the salary for a post-doctoral fellow. The team should maintain and strengthen its on going Canadian collaboration.

Team 4: Molecular determinants of pain

Team leader: Mr Pierrick POISBEAU

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	3	4	4
N2: EPST or EPIC researchers	1	1	1
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	3	3	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	3		
N8: PhD defended	6		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	**14**	**8**	**5**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

• Detailed assessments

Assessment of scientific quality and production:

The work of this team has been based on two major areas: (1) the development of improved measures for pain in animal models, and (2) CNS mechanisms that control pain. Work on the first area has led to development of valuable new approaches to assess symptoms and signs of chronic pain, as well as the use of endogenous morphine as a marker for neuropathology. Work on the second area has provided important information concerning the modulation of synaptic transmission and functional circuits in spinal nociceptive pathways (e.g. the role of GlyRα3 and nicotinic β2 subunits, oxytocin, neurosteroids and endogenous morphine). Among other things, this has led to the identification of neurosteroids as potential therapeutic targets for pain treatment, and the development of a telemetric device for monitoring heart rate that may be of particular value in measuring the frequency of episodes of spontaneous pain. The work of this team is original and highly relevant to our understanding of pain mechanisms.

It has resulted in ~17 papers on which members of the team are first and/or last authors, with most being published in reputable international journals (mean impact factor ~4). There are a further 7 papers to which the team has made a major contribution, and 2 involving a minor contribution. The 3 PIs who have been in the team prior to 2011 have all contributed to these publications. Their work generated several patents (4 derived from their work on alkaloids and one on the use of a stimulator of neurosteroid production for treatment of neuropathic pain).

Assessment of the research team's integration into its environment:

Two members of the team have high teaching loads, while the team leader has several other administrative duties at national level and has contributed to the organization of two symposia (one international). The team therefore makes a significant contribution to the local environment. Their long-standing links with commercial companies and with hospitals mean that they are well placed to investigate and exploit the therapeutic potential of their basic science findings. Their work during the review period has led to the filing of a number of patents (as described above). They have obtained a reasonable level (~€600k) of external funding since 2007, with each of the established PIs making a contribution.

Assessment of the team's reputation and drawing power:

Two members of the team have been awarded prizes, and these two have contributed to several symposia (6 national, 2 international) and given seminars in France (8 during the review period), and abroad (6). They have been successful in recruiting three established scientists, which is important in allowing them to maintain a critical mass. They have recruited two foreign post-doctoral RAs (one for 3 years and one for 6 months), and there has been a steady throughput of PhD students (between 3 and 4 being present at any time, which is comparable to the numbers in other teams), two of whom have been from abroad. They have a wide range of collaborations – both national and international, with the latter involving mainly European labs, and these have resulted in several publications.

Assessment of the strategy and 5-year project:

The team's 5 year project covers 3 topics: (1) the role of steroids in pain, (2) further studies of endogenous morphine, particularly in relation to chronic pain and schizophrenia, and (3) the involvement of VIP and related peptides in normal and pathological pain. Each of these represents an extension of the team's current work, but the work will also involve the expertise of their recently appointed colleagues. The work plan addresses important issues in pain research, such as the mechanism of anti-nociceptive effect of neurosteroids, the possibility of manipulating endogenous morphine to treat pain, and studies of the role of VIP in knock-out mice. Some of the proposed studies will have potential difficulties of interpretation. For example differences in spinal nociception between rat strains may not be entirely due to differences in glucocorticoid levels. In addition, in their single-cell studies of the dorsal horn the great diversity among interneuron populations may complicate data interpretation: they should therefore be encouraged to try to characterize the cell types that have been recorded from. However, overall, this represents a highly original plan, which should be feasible given the expertise of the team members.

Conclusion:

Overall opinion of the team: The team is close to the average level within INCI in terms of research publications, funding and numbers of PhD students and postdoctoral RAs. Team members have made significant contributions in the pain field, including development of methods/devices for pain monitoring in animals and the identification of potential new analgesics.

Strengths and opportunities: The leader has a very good track record. A major strength of the team is their "multidisciplinarity", with expertise extending from the molecular level, through electrophysiology to behaviour. They also have strong links with pharmaceutical companies. The "age profile" of the team is advantageous. Their recent recruitments will further strengthen the team.

Weaknesses and risks: In their self-analysis, the team notes the lack of technical support, but this appears to be similar to the situation for other teams in INCI. No other significant weaknesses or risks are apparent.

Recommendations: There are clear opportunities for collaboration with the other pain teams in INCI. These links should be strengthened, as they will be to the mutual benefit of all those involved. For example, collaboration will allow members of team 3 to take advantage of the expertise of team 4 in in vivo electrophysiology, while team 5 will benefit from using the pain models from team 4 in their studies on mechanisms underlying co-morbidity of depression, stress and chronic pain.

Team 5: Anatomo-functional approach of chronic pain and its treatments

Team leader: Mr Michel BARROT

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	2	3	3
N2: EPST or EPIC researchers	3	3	3
N3: Other professors and researchers	1	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	2	2	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	4		
N8: PhD defended	3		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	4	6	
TOTAL N1 to N7	**15**	**8**	**6**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

• Detailed assessments

Assessment of scientific quality and production:

This is a well-recognized international group in the field of neuropathic pain and central mechanisms of pain processing. Their contributions on these particular topics have been very sound. The team has produced original and impacting results in the field of pharmacology of pain systems and pain-relieving drugs, using a wide number of techniques and animal models ranging from molecular and cellular biology, immuno-histochemistry, transgenic mice, to behavioral pain models in rodents and clinical assessment in patients. Novel, translational insights on pain pharmacology concerns both the results obtained directly within the team's laboratory (analgesic mechanisms and neuroanatomical site of action mediated by ¤-adrenergic and opioid-dependent action of antidepressants) as well as those worked up in collaboration with clinical teams in Strasbourg Hospitals. Very recently, the group developed a new rodent model which allows the study of the interactions between anxiety, depression disorders and neurophatic pain mechanisms, showing that mice developed in a different time-related frame, anxiety and depression-like behaviors. Finally, by combining tract-tracing anatomical studies and pharmacological in vivo studies, they showed that a sub-region of the ventral tegmental area is a link for tonic inhibitory control of dopamine cells via GABAA receptors, and could be a major target by which morphine increases dopamine cells activities. As a whole, these studies, in addition to other transversal projects where the group acts as collaborator, and the associated international patent to both the leader and other fellow members, are progressively positioning this young team as an internationally respected research group.

The group has a good publication track, with 38 papers in international peer-reviewed journals between 2007 and 2011 (almost half with IF>5, including varied, most highly ranked journals such as PNAS, Biol Psychiatry, Ann Neurol and Nature Neurosci). The citation index of the leader (H=30) corresponds to an excellent recording track in the field of neuroscience at this carrer level. Interestingly, despite the low number of full-time researchers, the team members are first or last authors in 74% of papers of the team, suggesting that they were leading the research in a majority of cases. It should be emphasised that such impressive scientific output was obtained despite the fact that this is a young team, with a restricted number of full-time team members (only 3 full-time researchers, added to 3 Professors which have a huge amount of teaching hours/year).

Assessment of the research team's integration into its environment:

The team has developed academic and research links with universities in France and abroad (Strasbourg, Bordeaux, Germany, USA, Greece, Turkey). These partnerships are stable, of good quality, and have given rise to joint publications in good – to very good Journals, to which the team appears to have represented an added value. It is clear that the role of the team in the collaborations and published papers is absolutely relevant. Recruitment of scientists, PhDs and post-docs originates both from local and abroad levels. Support from the local university and regional council is very strong.

Assessment of the team's reputation and drawing power:

The team has shown ability to successfully apply for competitive funding, and to participate to scientific and industrial clusters. Local and national attractiveness as estimated by external funding is important, with more than 1.5 M€ obtained in 2004-2011 of which around 60% was from external non-institutional sources. Attractiveness and scientific impact estimated by invitations to international events is however still limited (8 invitations in the past 4-year period). As a whole, the group has honoured 22 invitations to lecture in congresses and symposia. They collaborate with a number of national and international laboratories in the field, as well as with frequent interactions with industrial partners.

Assessment of the strategy and 5-year project:

The team will carry on, on one hand, with translational work focused on the search for novel treatments of neuropathic pain, on the basis of a number of lines currently explored. They will continue with the development of research activities (behavioral and molecular pharmacology combined with clinical studies) with the aim to elucidate the mechanisms and discover novel pharmacological targets of neuropathic pain. On the other hand, the group will develop transversal projects recently started, especially aimed to create a relevant model of neuropathic pain-induced mood disorders. This second axis considers, as stated by the team, "the anatomo-functional basis of long-term affective consequences of chronic pain". This appears highly ambitious, as it includes virtually all types of clinical pain with the exception of inflammatory pain. The team's proposal covers clear translational research (i.e. from animal models up to the clinics) to develop preclinical models that are relevant for human pain. This notion has granted meaningful results obtained by the team in recent years, e.g. with the discovery of analgesic mechanisms and neuroanatomical site of action mediated by b-adrenergic and opioid-dependent action of antidepressants.

This work will be pursued by a multi-center epidemiological study and a PHRC-funded study on the effects of terbutaline (b-mimetic drug) on neuropathic, post-thoracotomy pain patients. The team leader and his colleagues - well aware of the limits of current pain models- are determined to pursue this line of research, through the analyses of time-related, maladaptative neuronal changes at the origin of chronic pain. This aspect although crucial in the field of pain is poorly developed. However, the team conclusions are based only on data obtained in a single model of neuropathic pain.

Conclusion:

Overall opinion of the team: The team is an active and attractive group with strong leadership, excellent scientific output, good track and high potentialities in preclinical and clinical pain pharmacology. The leader has important visibility and publication track record.

Strengths and opportunities:

- The team masters a wide range of techniques, from cellular and molecular biology to immuno-histochemistry, behavioral studies and clinical trials.
- The team has a strong experience with animal models of neuropathic pain and knowledge of their current insufficiencies.
- The team has the opportunity to work in close interaction with other teams within the same Institute and to benefit from a wider spectrum of clinically-founded hypotheses.
- The research might have a strong translational impact.

Weaknesses and risks:

The main weaknesses are:

- Behavioral studies based mainly on a single experimental model of neuropathic pain and subjective measures of behavioral reactions, which reduces the universal aim of this ambitious project (elucidate the mechanisms of neuropathic pain and related mood-induced disorders). As stated by the team leader during the on-site evaluation, this issue has already been taken into account. The team is currently testing two other models of experimental neuropathy;
- The temptation to follow existing, not entirely original research lines on 'neuroanatomical basis of pain and mood interactions', which could limit the likelihood of paramount discoveries;
- A too restrictive collaboration in projects with teams 3 and 4 which could limit the visibility and international impact of all "pain groups" within the INCI.

Recommendations: Caution with the behavioral models that are used, as some of those explored in the past may not be universal or completely applicable to humans –thus explaining divergent results relative to clinical work. The development of new models proposed by the team may be a better option for that. Include other measures of pain perception in both humans and animals (in vivo brain electrophysiological responses and imaging) to assess the effects of drugs. Take advantage of the skills of teams 3 and 4 to develop collaboration on other pain models aimed at tagging the progressive, maladaptive processes that turn from central sensitization to chronic pain states. This may provide important insights into the origins of co-morbidities in neuropathic pain patients. Efforts to integrate in more transversal projects permanent full-time researchers from the different pain groups within the INCI, should be highly rewarding for everybody.

Team 6: Rhythms, life and death in the retina

Team leader: Mr David HICKS & Mr Frank W. PFRIEGER

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	2	2	1
N2: EPST or EPIC researchers	4	4	4
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	4	3	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	5		
N7: Doctoral students	7		
N8: PhD defended	8		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	**22**	**9**	**5**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

• Detailed assessments

Assessment of scientific quality and production:

Team 6 proceeds from the fusion of two teams with two PIs. Work in the first team is noted for their contribution to understanding retinal degeneration and associated aspects of normal retinal function, including disc shedding and phagocytosis. He is well established in the vision field (ARVO Fellow), and more recently he has developed his interest in circadian clocks in the retina with a view to elucidating their adaptive function and contribution to pathology. It is a truism that laboratory (nocturnal) rodents are a poor but nevertheless widely used model for human (diurnal) retinal biology. This team has put considerable effort into developing diurnally active rodent models, especially Arvicanthis in parallel to similar initiatives by other groups across INCI. These animals will be very useful for in vivo transgenic manipulations (e.g. viral and plasmid therapies) and also for in vitro analyses exploiting whole mount and layer specific cultures. This should allow for the discrimination between cell-autonomous and circuit-dependent properties of photoreceptor and other cell types, in the contexts of degeneration, circadian timing and their interactions (see below).

Separately, the second team has been successful in developing new mouse models for conditional control over astroglial and other cellular functions notably through the generation of a botulinum neurotoxin conditionally expressing transgenic mouse ('iBot'). Using this new model, the second team obtained data supporting the idea that glial volume regulation involves a secretory mechanism, but not that glial cells influence retinal function by SNARE-dependent substance release. Additionally, provision of the transgenic mice develop by the second team to other groups worldwide (>15) will further be a significant production. Continuation of previous projects further established the importance of cholesterol secretion by astrocytes and the idea that the requirement of glial signals for synapse development varies with the type of neuron and the type of synaptic connection. The team also has a patent on experimental models of age-related macular degeneration.

The current "h-indices" are 21 and 18 for the two PIs. The papers of the first PI appear mainly in specialist journals, especially those for which the PI is part of the editorial board. The second co-PI publishes more scarcely but was able in the past to publish in very high profile journals (Science). Significantly the second co-PI obtained a major high profile publication (Neuron) just accepted.

Overall, the team has published 22 papers (plus 7 collaboratively with other groups) that stands as an average productivity for a team of this size.

Assessment of the research team's integration into its environment:

There has also been a welcome level of grant funding from both public and private sources and one patent established. The team is well embedded in its local and national context, including a series of collaborations within INCI (circadian biology, genetic modification of mice, development and exploitation of Arvicanthis). The team contributes to teaching and Masters organisation and has a good level of PhD students.

Assessment of the team's reputation and drawing power:

Fellowship of ARVO is, by definition, a mark of recognition within the research community, as is membership of the EU-sponsored project ENI-NET and the distribution of mutant mice to several laboratories. The national and international recognition of the team are somewhat limited in terms of collaboration, which is principally French and German. The links to the USA involve the Salk and Moorehouse (Atlanta, GA) institutes, and a reasonable series of Invited lectures (23) and conferences including Gordon Research Conference provide good evidence of extra-mural recognition but also room for improvement. The second PI has a strong international recognition from past work on cholesterol secretion. Recruitment has been acceptable with both post-doc and graduate student arrivals and one significant addition of CR1.

Assessment of the strategy and 5-year project:

The new project is intended to benefit from the combined strengths in physiology and genetic manipulation brought by the two groups. Whilst recognizing the positive drivers to this initiative, it is patently evident that a greater likelihood of success will arise from co-direction of the team by the two PIs. Moreover, physical contiguity between the groups is an obvious pre-requisite for effective launch of the new team.

As for project details, exploiting Arvicanthis as a model diurnal organism is extremely promising. Also, analysing circadian function by bioluminescence rhythms in retinal explants will facilitate a considerable step forward in elucidating clock properties, not least developmental control of the clock, as noted. An important issue to be

addressed is which reporter genes are best to use and why. Moreover, opportunities exist in generating viral vectors to deliver clock reporters and to manipulate the retinal clock(s) in cell-specific manners, in vivo. Considerable effort will be applied to discovering the role of the circadian clock in retinal function, with a focus on shedding and phagocytosis. This is well worn ground in terms of a phenomenon, so a critical question is what distinct advantage and new development does the team have to hand to make it confident that significant progress over mechanism might be gained. There is a nexus of clocks in retinal neurons, clocks in retinal glia, local melatonin rhythms and pineal-dependent melatonin rhythms. This provides opportunities to unravel causative processes, but brings the risk of difficulties in being able to isolate individual functions experimentally. Nevertheless, it is worth having a go.

Identification of the factors that regulate the development of intrinsically photoreceptive retinal ganglion cells (iPRGC) may also reveal novel properties. This is an important and unexploited area, and constitutes an approach that will allow the group to establish a particular and definitive contribution to ipRGC biology. The challenges of testing in vivo novel findings made in vitro are not, however, to be underestimated and the program may make early progress and then get bogged down in definitive in vivo tests. That is no reason not to embark on the work simply recognition of potential risk. Significantly, the iBot mice may be especially useful for in vivo studies in this regard. The former second team should continue its strategy of publishing few high profile articles.

The theme of retinal degeneration will exploit Arvicanthis as well as genetically modified mice. This component offers appreciable translational promise, although the mutation (NPC) models a rare genetic disease in humans and so one might ask to what extent, and how, will these findings in a rare condition inform a wider understanding of retinal function and pathology. The team has the opportunity here to make a significant contribution.

Conclusion:

Overall opinion of the team: One former team has an acceptable productivity, the second team has a high visible profile and a project that offers significant potential.

Strengths and opportunities: The team has a sound understanding of retinal neurobiology on a diurnal rodent model offering genetic manipulation, thus with a translational potential. There is a good professional relationship between senior members.

Weaknesses and risks: Governance of the group through clear co-direction must he handled carefully to ensure effective operation and growth. One of the founder team publishes currently in journals with low impact factors – it needs to focus on quality output to enhance profile.

Recommendations: Co-direction and physical proximity are required conditions to facilitate success.

Team 7: Regulation of circadian clocks

Team leader: Mr Etienne CHALLET

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	2	2	2
N2: EPST or EPIC researchers	3	3	3
N3: Other professors and researchers	0	1	1
N4: Engineers, technicians and administrative staff * on a permanent position	2	2	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	8		
N8: PhD defended	6		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	**18**	**8**	**6**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

• Detailed assessments

Assessment of scientific quality and production:

Work in this team is perhaps best known in the circadian clocks field on food entrainment (FE), and in particular its genetic basis in relation to the known circadian pacemaker based upon Period gene expression. The location and neurochemical identity of the FE oscillator (FEO) is unknown, although it is clearly independent of the archetypal circadian clock the suprachiasmatic nucleus (SCN). In the previous 4 years, the principal notable finding from this group has been the implication of the cerebellum in FE. A central issue to this area of work is whether the FEO resides in the brain or in peripheral metabolically relevant organs (e.g. liver). Consistent with this theme, a second line of research of the group has been to characterise peripheral feedback action onto the SCN. This has involved putative indirect 5HT-mediated actions of glucocorticoids as well as indirect and direct actions of metabolic hormones and arousal state (including reward). This component of the work lacks the insight and "bigger picture" coherence of the FEO work. A major strategic development, shared by other teams, is the application of Arvicanthis as a diurnal rodent, the basic circadian properties of which have been mapped out. Finally the team has examined the interplay between daily and seasonal (photoperiodic) time. The group has contributed more widely by the development of the ChronoBiotron as a strategic facility and by facilitating the development of Arvicanthis as a research model for other groups.

Overall the team has made an uneven contribution to understanding, and at times has focused more on extensive analysis of phenotypes rather than seeking to elucidate underlying mechanisms. The broad range of topics considered has not helped – this relatively small group is spread rather thinly, and is clearly dependent upon external collaborations to sustain its expertise. The committee does not sense that there is an underpinning, conceptually coherent view to the extensive past program – rather it is matter of fact and report, and is slightly piecemeal, addressing topics of rather limited interest to a general audience and often re-discovering what was already known.

Nevertheless, the publication list is long (34 from the group plus 9 as secondary collaborations) - a sign of great energy, but the journals are at best solid – there are few papers in leading journals (one in J Neurosci). Of the two principal researchers, the "h-index" of one (team leader) is 20 from 79 A-ranked publications (ca 25% ratio), whereas the real bulk of publications comes from a more senior principal with a notable "h-index" of 47, albeit accrued from over 400 publications (ratio ca. 10%). The team might be re-assured that concentration on higher quality at the cost of producing less quantity would not prejudice their reputation and impact.

Assessment of the research team's integration into its environment:

The team is very well integrated into its local environment with a series of collaborative enterprises. Moreover, it has made maximum use of its facilities and expertise to obtain significant grant income from private as well as public sources. In particular, its association with pharmaceutical companies is well established and ongoing. It contributes significantly to under-graduate teaching and post-graduate training and is a catalyst for many meetings, symposia etc.

Assessment of the team's reputation and drawing power:

The national and international recognition of the team is in large part inherited from the longstanding contributions of prior team leaders. This carries a very strong European and Mediterranean aspect, which has carried through in terms of recognition and participation of this team. Of particular note, the team has no particular profile in USA, even though this is the principal leading forum for modern (post-genomic) as opposed to historical (formal analysis) chronobiology. In comparative terms, the team leader has a profile comparable as someone who features in the wider context but does not/ or rarely leads from the front. Nevertheless, an acceptable profile is evident from an extensive series (45) of conference invitations, including Gordon Research Conference and Keystone but this has yet to translate into significant activity on the editorial boards of better journals. The team has consistently attracted a good number of post-graduate students, some of whom have made further contributions to the field.

Assessment of the strategy and 5-year project:

The main strength of the team is its ability to conduct extensive in vivo analyses combined with brain chemistry and anatomy. This is augmented by excellent external grant support from pharmaceutical companies and other sources. The proposed work does, alas, suffer from significant weaknesses. It contains an extended and uncoordinated range of topics, and anticipates moving into areas where many large laboratories already have extensive experience and reputation – not least reward mechanisms, inter-neuronal signaling in the SCN and clock-metabolic interplay. Moreover, there is little sense that the work is informed by "post-genomic" developments and it lacks any consistent and coherent conceptual underpinning. The risk is that they will not be the first to reach important conclusions regarding underlying mechanisms, no matter how adept they may be at describing a phenotype.

The sense given is that leadership needs to be enhanced, with a single vision for future progress. Currently it lacks the necessary sharp focus: the project has too many individual elements, each of them of interest but not feasible ensemble. To be executed to internationally competitive standards, each of these would require multiple techniques applied in a coordinated manner and with a rigorous intellectual appraisal of its wider context and relevance. This ambitious project, as currently formulated, risks being beyond the capacity of this (or any other) team. Put another way, the landscape of the circadian field has now changed. Therefore, should this team adopt a "business as usual" approach, i.e. deploy its resources in multiple areas simultaneously (which might have been arguably acceptable in the past) it will not find it easy to take the lead in any particular area.

Conclusion:

Overall opinion of the team: The team is energetic in publication, training of post-graduate students and maintaining a profile focused on Europe and Mediterranean but not competitive with principal groups in USA and northern Europe. Considerable elements of output are at best iterative and sometimes derivative.

Strengths and opportunities:

- The team has strength in whole animal work and comparative chronobiology and physiology
- The team is well connected with pharmaceutical companies.

Weaknesses and risks:

- Projects are too widely spread across different areas leading to insufficient focus on topics (e.g. FEO) where the group may be competitive
- Despite some work with genetically modified mice and Arvicanthis, the studies are not particularly informed by “post-genomic” developments.
- The leadership of the team leader regarding all proposed projects is not clear.

Recommendations: The team is strongly urged to terminate the seasonal, photoperiodic part of their portfolio (which anyway overlaps with that of team 8) and concentrate on their “core business” of FEO. To achieve a competitive edge here, they will need to invest heavily in new technology within their own group rather than persisting with techniques they have used historically. The leadership position of the team leader on the entire research programs must be improved and recognized by the entire team.

Team 8: Melatonin and seasonal rhythms

Team leader: Ms Valérie SIMONNEAUX

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	2	2	2
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	1	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	4	3	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	5		
N8: PhD defended	8		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	**17**	**7**	**4**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

• Detailed assessments

Assessment of scientific quality and production:

For many years, members of this team have focused on investigating the pineal hormone melatonin and its role as a key circadian clock output; several studies from 2007 - 2011 continued to contribute to this theme, including characterization of clock gene expression in rodent pineal gland, identification of possible molecular substrates for melatonin's feedback (synchronizing) effect on the suprachiasmatic nucleus, and description of melatonin's action on the TSH system in the pars tuberalis. Much of this effort consisted of reliable, in some cases predictable and incremental, progress that built on the initial discoveries of this team and of others, with resulting publications generally appearing in solid specialty journals.

Then, in 2006, the laboratory reported that the protein kisspeptin (Kp) mediates photoperiodic control of reproduction in hamsters (published in Current Biology), providing the impetus for further detailed analyses of the regulation and neuroanatomy of Kp and related peptides from 2007 - 2011. Although to some the link between Kp and seasonal reproduction might have seemed obvious, the team rightly deserves credit for this important advance, and their follow-up publications have appeared regularly in well-regarded neuroscience, neuroendocrinology, and endocrinology journals.

The team published a total of 43 peer-reviewed original investigations and reviews, of which 30 came from direct work of the team; one of these, on hibernation in the hamster, appeared in Proc Natl Acad Sci USA. The team leader's "h-index" is 26, with 21 average citations/item and a total of 1825 citations (without self-citations); notably, her citations/year have risen progressively over the last five years, from 110 - 120 to > 250 in 2011. These data are comparable to others, perhaps just a little junior than she, in seasonal or behavioural neuroendocrinology.

Assessment of the research team's integration into its environment:

Total team funding from 2007 - 2011 was € 1,145,000, from a mixture of sources, the largest of which was Servier (€ 270,000). Other than the Servier funds and a Région Alsace grant for hamster breeding, the other sources have expired or will expire this year.

Assessment of the team's reputation and drawing power:

There is no question that the team's international recognition and reputation have been boosted by their recent focus on kisspeptin, RF-amide related peptide, and diodinase 2 as putative intermediates between photoperiodic melatonin production and seasonal reproductive patterns. The team leader has given 16 invited international presentations since 2007, including some at highly selective conferences (Gordon and FASEB research conferences), and she has served as an editorialist for the journal Endocrinology. The team's visibility also has been enhanced by productive collaborations with prominent circadian- and neuro-biologists from Netherlands, Denmark Germany. Not yet achieved is service on prominent journal editorial boards.

Of course, another measure of a laboratory's overall impact is on the training, career development, and eventual productivity of its trainees. Twelve former PhD students over the 2007 - 2011 time period are listed, and nearly all are said to still remain in science.

Assessment of the strategy and 5-year project:

The proposed 5-year plan is tripartite, ambitious, and introduces the team to new paradigms (maternal programming and pubertal development) as well as powerful tools utilizing molecular genetics, mass spectrometry, bioinformatics, and the delivery of interfering RNAs. Thus, the first project seeks to delineate the role of the tanycyte in seasonal reproduction, culminating in experiments that will selectively impair median eminence tanycyte Dio2 using cre-lox recombinant technology. The second project aims to analyze mechanisms by which RF-amides control reproductive activity, investigating receptor pharmacology and the RF-amide system in female mice (including those with mutations of circadian clock genes) as well as in photoperiod-dependent pubertal development in hamsters. Finally, the third project seeks to determine cellular and molecular sites of melatonin action in brain, proposing state-of-the-art peptidomic, pharmacologic, and reporter knock-in strategies.

This is a meritorious proposal, moving the team in the welcome direction of tackling deeper mechanistic questions rather than (or at least in addition to) accumulating archival data that – while effectively "dotting the i's and crossing the t's" – do not make the kinds of pioneering leaps that ultimately define the cutting edge of the field. The risks here are not only obviously technical but also logistical. Almost every project includes a key collaborator outside INCI. While complementary collaborations are certainly to be encouraged (and even necessary when involving the

laboratory in new approaches), the team leader will need to be aware that overall team progress might be vulnerable to events outside the team's control if a large part of the project portfolio depends on outside expertise. While the project already has obvious translational significance in animal husbandry, the team leader is also proposing to explore additional medical and social applications of her research through a collaborative study of rotating shift work nurses in Colmar. The likely success of this project is not at all clear, but it does have the advantage of taking the team in directions that might ultimately lead to interesting new collaborations (e.g., with team 9).

Conclusion:

Overall opinion of the team: This is a very solid and productive team.

Strengths and opportunities:

Strengths include

- the evolution of the team project to a more mechanistic analysis of a defined neural system with clear behavioral and endocrinological outputs,
- the application of the team leader's experience and expertise in seasonal physiology to the project, including potentially very informative phenomena (e.g., the effect of prenatal maternal photoperiod on offspring pubertal development),
- the exploitation of new methods and approaches for this laboratory.

Weaknesses and risks:

Weaknesses include

- past research goals that have been somewhat diffuse, precluding the kind of concentrated attention and momentum that could lead to more high impact discoveries,
- a grant portfolio that is expiring. A calculated risk of the proposed 5-year project is an over-reliance on outside collaborators, exposing team progress to events outside of its control.

Recommendations: By focusing effort and resources on a critical and deep understanding of the RF-amide system, the team may improve its international impact in the field and the placement of its papers in higher impact journals.

Team 9: Light, rhythms, sleep homeostasis and neuropsychiatry

Team leader: Mr Patrice BOURGIN

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	0	0	0
N3: Other professors and researchers	3	3	2
N4: Engineers, technicians and administrative staff * on a permanent position	0	0	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	0		
N7: Doctoral students	2		
N8: PhD defended	0		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**7**	**4**	**3**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

• Detailed assessments

Assessment of scientific quality and production:

As a new group which has been founded during the last 4 years, the establishment of the team and their research quality meet quite satisfaction with the level of internationally renowned institutes. The team leader has made a sensational finding on the role of melanopsin on sleep homeostasis and tries to expand his research line on the related subjects after his relocation to Strasbourg. So far, considerably many publications (reviewed articles in total as a team; 33) are archived in spite of the extremely low number of personnel (1 scientist, 2 physicians, 2 PhD students at the beginning) and successfully released to high-impact journals (e.g., Molecular Psychiatry, Plos Biology, Nature Medicine), while most of those studies might have been performed still back in Stanford or San Diego. Although it is very good to continue a strong collaboration with former colleagues, the originality of this Strasbourg team is yet invisible. It is expected that the work based there in collaboration within the institute and the local university/hospitals develop to be internationally notable. Regarding their animal studies, the research by this team has been conducted with higher standards than average. However, human studies may need more attention to focus on a specific aim in general to further facilitate translational studies besides light therapy applied to restless legs syndrome (RLS) or Parkinson's disease (PD).

Assessment of the research team's integration into its environment:

It has been a good movement that this sleep research team launched in synergy with other 'Rhythm' teams in the INCI and also will establish the sleep clinic in "International Research Center for ChronoSomnology (CIRCSom)" around 2013-2014. For the regional contribution, it was an excellent decision to accommodate such a sleep center for locals, however considering a huge load of the team leader it is still a question if both basic animal research and clinical human studies can be headed by one person. Based on the written report, it is not very clear how many solid staff members this team consists of, and who does what exactly. During the site visit, this personnel issue became a bit clear; one well-trained engineer and one PhD student are in charge of animal experiments. But still the team leader will be occupied with grant application and writing papers, although grant funding is very successful in the current situation as compared with other teams.

Assessment of the team's reputation and drawing power:

The team members are considerably active for organizing local meetings and being invited to scientific societies. Considering this new research ensemble, it is not really appropriate to judge on this matter at this moment. They will certainly gain their reputation and research impact and power in the next few years. Regarding the recruitment of students, still from Stanford is the majority. This is also a matter of time until the team will be renowned in the European communities.

Assessment of the strategy and 5-year project:

Most of projects planned for the near future would be feasible for this team. As a part of the Rhythm research section, it is understandable to focus on a topic of light effects on sleep regulation. However, a study of lesioning the SCN, for example, does not sound novel depending on which methods were used. An innovative way to shut off the neural signaling or gene expression would be interesting. Most of mouse studies using Opn4-/- (melanopsin deficient mice) are encouraged, however regarding the project on non-circadian effects of light if the Opn4-/- mice do not clearly show anxiety-related or depression-like behavior, pursuing the study would become difficult. They should also consider alternative animal models for this project. Further, the effects of light on non-REM and REM sleep need to be differentiated, since previous animal models of depression exhibit unique changes in sleep, especially REM sleep. Compared with their mouse projects, the research plan using Arvicanthis ansorgei (as a diurnal rodent) has a lower priority, which can be also conducted by other Rhythm research teams (e.g., Master or PhD students of Team 7). Clinically-driven projects with patients are more concerned. If the light therapy can be applicable to Restless Leg Syndrome (RLS) or Parkinson Disease (PD), it has a high originality. However, if the mechanism of light therapy is to boost the dopaminergic tone, how does it work with PD patients who have a complete lack of those neurons? Does this therapy evoke an augmentation in RLS patients who are under medication? Moreover, the projects including autism and fragile X syndrome require a lot of research efforts of this team, thus expanding human projects without increasing the number of personnel would be challengeable but risky.

Conclusion:

Overall opinion of the team: The team leader is a world-leading scientist in the field. Considering their previous contribution to sleep research and their recent discovery on melanopsin, the proposed experiments must have been conducted properly and have gained insights into direct non-circadian effects of light on sleep homeostasis. The activity of this team is very welcome and promising, and their international visibility should grow in the next five years.

Strengths and opportunities: Further, the new establishment of sleep research team is very exciting to the society, especially if the light therapy becomes effective to certain populations of patients, and research results can be preciously shared with publicities. This can be achieved only by a unique setting such as their Sleep Clinic (CIRCSom) attaching with the INCI unit and will facilitate translational research not only within the team but also across the other teams.

Weaknesses and risks: The policy of their research goal is very high. Maybe their target is too global, as neuropsychiatric disorders are heterogeneous. Targeting plural disease models would be of risk. Further, mouse models of depression-like or other affective conditions are tricky to work with and require considerable expertise and intense utilisation i.e. maybe a drain on resources. Part of the project rely on the finalization of the CIRCSom facility, not yet available.

Recommendations: Beside light therapy, no other particular translational outcome, e.g. drug development, are proposed except for melatonin application to autism patients. How do melanopsin studies proceed to finally cure sleep or rhythm disorders? Are there mutations or variants in Opn4 in depression or insomnia? These might be interesting questions that could be addressed by this team. Another concern is that same personnel are in charge of several projects. The team should recruit more personnel in the near future, since the work load is very heavy for this relatively small team. Probably, it is better to assign a sub-leader for each project when the team expands with assistant professors and post-docs. The opening of the CIRCSom facilty must be urged, since this is necessary for the realization of this invaluable translational program.

4 • Grading

Once the visits for the 2011-2012 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

Overall assessment of the unit [Institut des Neurosciences Cellulaires et Intégratives]:

Unité dont la production, le rayonnement, l'organisation, l'animation et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A**	**A**	**A**

Overall assessment of the team [Intracellular membrane trafficking in the nervous system]:

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A**	**-**	**A**

Overall assessment of the team [Physiology of neural networks]:

Équipe dont la production et le projet sont excellents. Le rayonnement est très bon.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A+	**A**	**-**	**A+**

Overall assessment of the team [Nociceptive signaling in the spinal cord]:

Équipe dont la production et le rayonnement sont bons mais pourraient être améliorés. Le projet est excellent.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
B	**B**	**-**	**A+**

Overall assessment of the team [Molecular determinants of pain]:

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A**	**-**	**A**

Overall assessment of the team [Anatomo-functional approach of chronic pain and i ts treatments]:

Équipe dont la production et le projet sont excellents. Le rayonnement est très bon.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A+	**A**	**-**	**A+**

Overall assessment of the team [Rhythms, life and death in the retina]:

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A**	**-**	**A**

Overall assessment of the team [Regulation of circadian clocks]:

Équipe dont la production et le rayonnement sont très bons. Le projet est bon mais pourrait être amélioré.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A**	**-**	**B**

Overall assessment of the team [Melatonin and seasonal rhythms]:

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	**A**	**-**	**A**

Overall assessment of the team [Light, rhythms, sleep homeostasis and neuropsychiatry]:

Équipe dont la production est excellente. Le rayonnement et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A+	**A**	**-**	**A**

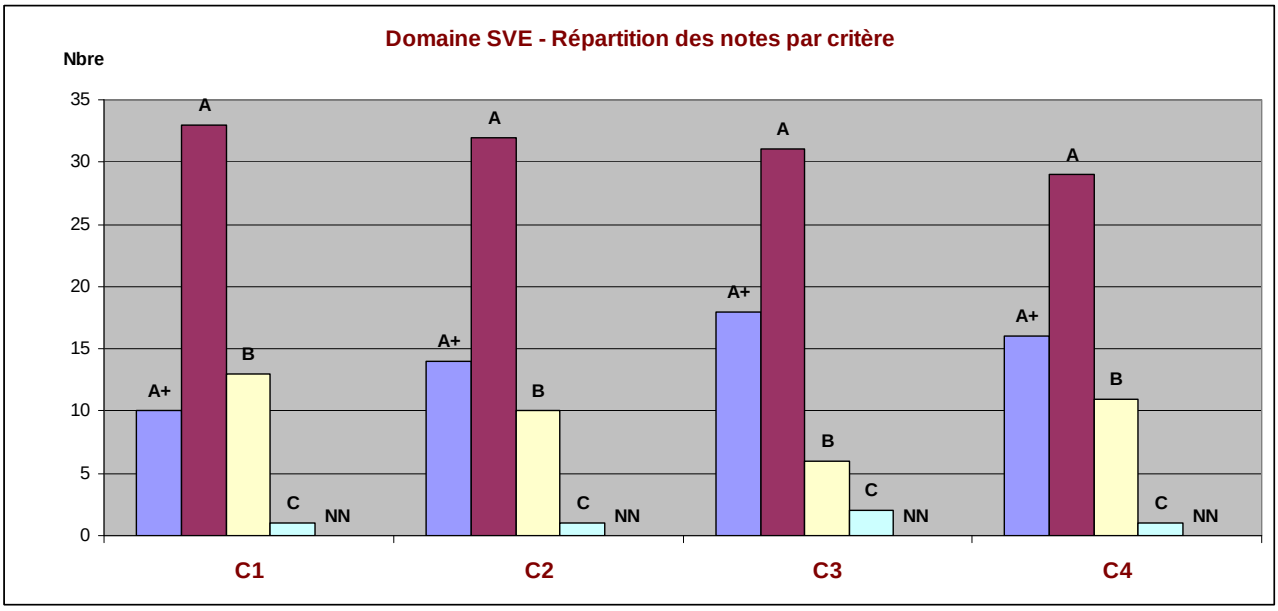
5 • Statistics per field: SVE au 10/05/2012

Notes

Critères	C1	C2	C3	C4
	Scientific quality and production	Reputation and drawing power, integration into the environment	Laboratory life and governance	Strategy and scientific project
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Scientific quality and production	Reputation and drawing power, integration into the environment	Laboratory life and governance	Strategy and scientific project
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-



6 • Supervising bodies' general comments

UNIVERSITÉ DE STRASBOURG

Monsieur Pierre GLAUDES
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Agence d'évaluation de la recherche et de
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20 rue Vivienne
75002 PARIS

Alain BERETZ
Président

Strasbourg, le 27 avril 2012

Objet : Rapport d'évaluation de l'UPR 3212 « Institut des neurosciences cellulaires et intégratives » (réf. S2PUR130004546-RT)
Réf. : AB/EW/N° 2012-209

Affaire suivie par
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Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation de l'unité propre de recherche « Institut des neurosciences cellulaires et intégratives » (INCI – UPR 3212) dirigée par Madame Marie-France Bader.

Vous trouverez ci-joint les réponses de la directrice de l'unité de recherche concernant les erreurs factuelles et les remarques et appréciations du comité d'experts.

Je n'ai pas de remarque particulière à ajouter au nom de l'Université.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments distingués.

Alain BERETZ

P.J. :

- **Une première partie corrigeant les erreurs factuelles**
- **Une seconde partie comprenant les observations de portée générale**

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Rapport d'évaluation de l'INCI par l'AERES: Observations de portée générale

From a general point of view, we agree with the recommendations made by the AERES committee. We accept the challenge of taking better advantage of the multi-disciplinary expertise present in the Institute, in order to promote ambitious projects in areas in which we are competitive. Except for one team, for which we were surprised and even shocked by some of the comments, we align ourselves with the assessments of individual teams and the need to re-focus certain projects.

Regarding Team 7, INCI wishes to underline the many positive aspects of their work during recent years and its current and planned involvement in cutting-edge research of wide interest and value to important public health issues. The team has a solid publications track record by international scales, with numerous invitations to prestigious conferences and participation in international collaborations. In particular the team was at the origin of two funded European networks. The team leader, Dr. Etienne Challet has a strong reputation in his field of research, and the team has recruited recently two new members. The AERES report indicated a certain number of weaknesses in the programme, notably an excessive number of scientific projects in relation to the team members. The team accepts these remarks, and has decided to streamline the proposed research axes – a first major axis devoted to interactions between feeding/reward and brain rhythmicity, and a second focused on neural mechanisms underlying diurnality.

However, the Institute finds that the evaluation for team 7 has been written in a deliberately aggressive, unfair and non-academic style, which emphasizes negative points and has completely overlooked the positive aspects cited above.

Marie-France Bader
Directrice de l'INCI