Centre de génétique et de physiologie moléculaire et cellulaire Mouchiroud Guy

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Centre de Génétique Moléculaire et Cellulaire

From the

CNRS

Université Claude Bernard

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Research Unit

Name of the research unit : Centre de Génétique Moléculaire et cellulaire

Requested label : UMR

N° in the case of renewal : UMR 5534

Name of the director : M. Pierre COUBLE (past), M. Guy MOUCHIROUD (future)

Members of the review committee

Chairperson

M.Yacine GRABA, IBDML, CNRS Marseille

Other committee members

M. Christian COGNARD, Institut de Physiologie et de Biologie Cellulaires, Poitiers

Mrs. Britta EICKHOLT, MRC Centre for Developmental Neurobiology, London

M. Vincent GELI, IGC, Marseille

M. Norbert B. GHYSELINCK, IGBMC, Strasbourg

M. Christo GORIDIS, Ecole normale supérieure, Paris

M. Jose Luis JORCANO, Epithelial Biomedicine Division, CIEMAT, Madrid

Mrs Catherine SADZOT, Virology and Immunology Unit, Marseille

M. Michael SIEWEKE, CIML, Marseille

Mrs Florence SMADJA-JOFFE, Hôpital Saint-Louis, Paris

M. Shahragim TAJBAKHSH, Institut Pasteur, Paris

M. Denis THIEFFRY, TAGC - INSERM U928, Marseille

Committee members nomminated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS....)

M. Olivier OUDAR, CNU member

M. Lucas WALTZER, CoCNRS member

Observers

AERES scientific advisor

M. Pierre BEDOSSA

University or School representatives

M. Germain GILLET, University Lyon 1

Research Organization representatives

M. Bertrand DAIGNAN-FORNIER, CNRS

Report

1 • Introduction

- Date and execution of the visit

The site visit of the evaluation committee lasted two full days, starting and ending January 19th and 20th. The execution of the visit started with an audition of the present and future Directors, followed by a brief summary of the main scientific achievements and projects given by each group leader. Team activity evaluation was further refined by team visits, each by one of three distinct sub-committees. Conclusions were drawn in a final closed-door committee meeting. The committee also had meetings with staff representatives of the research unit (PhD students/postdocs; engineers, technicians and administrative assistants ; researchers with permanent positions) and local representatives of the University and the CNRS.

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

The Centre de Génétique Moléculaire et Cellulaire assembles about 130 people in 13 Research teams, and is located on the "Campus de la Doua". The research activities of the CGMC focus on basic processes in differentiation and development. They cover multiple scientific topics, ranging from virology, alterations of cellular functions, cell self renewal, and developmental mechanisms.

- Management team

The CGMC has been headed by Pierre Couble, assisted by an executive board composed of team leaders and an administrative staff composed of 4 persons.

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	13	18
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	22	22
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	11	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	24,4	24,4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	7	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	29	12
N7: Number of staff members with a HDR or a similar grade	23	25

2 • Overall appreciation on the research unit

- Overall opinion

The CGMC research unit, with a critical mass of 13 research teams, covers broad scientific topics that extend beyond basic research by developing several initiatives of translational research and research valorisation. Beyond this apparent heterogeneity lies, however, a community of concepts and technical approaches, including molecular and cellular genetics and integrative biology. Internal collaborations between teams crossing this scientific diversity have been developed, proving that this diversity provides an added value to the research unit. Yet, this diversity impacts negatively on the critical mass working on closely related scientific topics.

During the last four-year period, its size remained relatively constant, but the quality of published research papers increased when compared to the previous one. The committee however was unanimous that given the projects and the expertise of most groups, the scientific production should increase further in quality during the next four years period in order to remain competitive internationally. The Research unit has also a strong and positive commitment to teaching and administrative duties at the University Claude Bernard of Lyon (UCBL).

Overall, the CGMC is a solid well-organised research unit with a good critical mass, which produces good science, and plays fully its role in promoting valorisation and science teaching and training.

- Strengths and opportunities

The internal organisation of the CGMC provides a good environment that favours scientific research, a fact clearly acknowledged by all lab representatives met by the committee. The CGMC has developed a good level of scientific animation, with regular external and internal seminars, and journal clubs. Its role in assembling the curricula of students and teaching at the UCBL efficiently attracts PhD students, which recognize the CGMC as an excellent place for training. Based on this strong commitment, but also on the thematic positioning of the unit at the boundary between fundamental research and medical research, the CGMC is very strongly supported by UCBL.

The CGMC has been extremely successful in attracting financial support from various sources: French foundations (AFM, FRM, “La Ligue”, “l’ARC”), the region, national research agencies (ANR, INCA) and the European community. Another important strength is that, due to the prominent role played by its Director in establishing fruitful contacts with several local research units and to the strong support from the UCBL, the CGMC appear to act as a driving force for the necessary reorganisation of biological research in Lyon (geographical distribution of scientific topics often relate more to the history of the teams than to common scientific interests).

- Weaknesses and threats

It was generally felt that while producing good science, the CGMC needs to progressively improve its number of higher impact publications. Several groups have already the potential to publish in more prestigious journals. Improving their publication record would require, besides modifying the publication strategy, to develop more in depth analyses, and in some cases to use a different model system (for instance, primary cells rather than cell lines). A consequence of the modest number of highly visible publications for a majority of the team is that the research unit does not seem a very attractive place for post-doctoral scientists. In this context, the committee noted the absence of open calls for the recruitment of new teams. This hinders promoting the national and international visibility and recognition of the CGMC.

- Recommendations to the head of the research unit

In terms of scientific strategy, the committee has two general recommendations.

First, the unit needs to improve further the international visibility and attractiveness of the research unit. The quality of the science produced so far provides the basis for attaining a stronger international recognition. Keys to that aim are to favour publications in higher impact journals, even if that would result in an overall quantitative decrease in the number of publications, and to launch open competitive calls for the recruitment of new teams.

The second is to further promote translational research by fostering interactions with the clinics. The topics of several teams are appropriate in that regard and the long-term move towards the Charles Mérieux South Campus will certainly provide the opportunity to evolve in that direction.

While appreciating the effort invested in restructuring the unit, the committee expresses its doubts about the opportunity of two of the proposed changes. This regards first the creation of the team « Stress response to protein misfolding », which was at this point judged as premature. The second concern is about the co-direction of the team "Regulation networks in normal and pathological myeloid cells » by three scientists which appeared inappropriate. Finally, the committee considers that the research project of team « Epidermis, Stress and differentiation » needs serious focusing to be scientifically competitive.

- Data on the work produced :

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

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	35
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	11
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	35/40
A4: Number of HDR granted during the past 4 years	
A5: Number of PhD granted during the past 4 years A6: Any other relevant item in the field	22

3 • Specific comments on the research unit

- Appreciation on the results

Quantitatively, the research unit produced during the last four years about 150 publications, a number that remained constant when compared to the previous four-year period. A qualitative analysis shows that the overall quality of papers has increased, although the number of publications in journals of high visibility could be further improved. The committee felt that the ongoing projects and local expertise should encourage group leaders to be more ambitious in their publication strategy. On the research valorisation side, the CGMC has produced 5 patents, and 2 Biotech companies (one in incubation and one already created) have emerged from the research unit. The CGMC also largely contributes to research training, with an average of 30 PhD students in the lab, 22 having obtained their degree in the last four-year period. Overall, the activity of the CGMC has provided a solid contribution in terms of science production, valorisation, teaching and training.

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

The CGMC has a good national visibility. This is attested by its efficiency in raising funds from local and national foundations, in particular significant funds from l'Association Française contre les Myopathies (AFM), la Ligue contre le cancer and la Fondation pour la Recherche Médicale (FRM). It also efficiently attracted funds from the national research agencies ANR and Inca. Notably, most of the teams contributed to this overall success. It is also attested by the capacity to recruit junior as well as well recognised senior teams.

From an international perspective, many teams have ongoing international collaborations, and the overall level of European and international grants (7) is good. However, and in contrast to national funding, only two of the 12 teams proposed for the next four-year period are attracting the totality of these international funds. Notably, some teams that have a strong publication record do not contribute to attract international funding and networking. The relative limited international visibility of the lab may also explain the modest number of post-docs (be it national or international) in the research unit, and the absence of newly recruited teams that do not come from the local research tissue. A difficulty for attracting international post-docs may be the language barrier. More efforts should be made to have seminars and lab meetings in English, in order to provide a more welcoming atmosphere for international visitors.

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

The general organisation of the research unit relies on fully independent research teams, shared core facilities and administrative services. This organisation seems generally appropriate with regards to the needs, although ongoing projects may generate stronger needs for bio-computing in the near future. Discussion with lab representatives highlighted the quality of the governance. A few problems have been raised however, and improvements suggested with regards to human resources: sharing technicians between teams are in some instances problematic; Engineers and Technicians expressed the wish that the decisions on their promotions be made more transparent. The scientific animation is very good, with regular internal/external seminars and journal clubs. Adding a yearly-organised retreat may further improve scientific communication and interactions.

The action of the present Director has been extremely efficient in connecting the activity of the CGMC to the local research tissue. The CGMC is part of the IFR41 (Bioenvironment and Health), and entertains a privileged relationship with two other IFR in Lyon, IFR 62 Laennec on the East campus, and IFR 128 on the South campus (Charles Mérieux). It is also part of two local networks of Excellence, focused on Infectious diseases and Cancer.

The connection with UCBL is also excellent, with 13 Professors or Assistant Professors, heavily involved in teaching, designing curricula for students and leading of the graduate programme (Ecole Doctorale). The positive outcome of its strong involvement in management at UCBL is the attractiveness of CGMC for PhD students, but its drawback is the heavy teaching load for many permanent researchers. Finding solutions to alleviate the teaching load, especially for those that are group leaders, appears highly desirable.

- Appreciation on the project

The proposed project presents a profound reorganisation/evolution of team organisation, affecting half of the previously existing teams. The supporting rationale for this is multiple. First, it aims to reach a sufficient critical mass for new teams, which led to the fusion of three teams into one single entity « Regulation networks in normal and pathological myeloid cells ». While the fusion appears to be appropriate at first sight, the proposition that the team is co-headed by three scientists appears awkward. The committee invites the Director to re-evaluate this strategy with the concerned scientists, by examining for each of the previous group leaders his contribution to the fused team with regards to scientific leadership, financial support and manpower. Second, the new organisational chart aims at taking into account the evolution of existing teams, and led to the proposition of a change in the leadership of two teams. For the first team, « Muscle pathologies in C. elegans », this seems appropriate, while in the second case, that of « Stress response to protein misfolding », this is somewhat premature (see team report). Third, it aimed at recruiting novel projects in the research unit, namely "Functional genomics of nuclear receptors" and "Excitability and signalisation in normal and pathological muscle", which form the bases for two novel teams. The venue of the first team will reinforce bio-computing, that of the second will add a new facet (physiology) to the approach of normal and pathological muscle function already led by one of the CGMC team. Both are arguably good strategic choices, in particular with regards to long-term evolution (see below).

From a more general and long-term perspective, the CGMC and its present Director, together with ENS, Lyon, have launched the project of a new research centre, with a hosting capacity of about 20 teams. This research centre will be located on the East campus, in direct proximity to the Hospital, a location that suits the goal to promote the interface between basic and clinical research. The anticipated impact of the creation of this new research centre, for which building and funding have already been secured, is that it will result in increasing the critical mass of the research teams aimed at providing the knowledge upstream of clinical application. More generally, it will allow the increase in critical mass of teams tackling the same scientific issues. A good illustration of that is the muscle axis that already benefits from the addition to CGMC of a new team, which will further benefit from the joining of additional teams working on muscle development and pathologies in the context of this new centre. The committee feels that this long-term evolution embraces the wish to increase the scientific efficiency and ambition of most CGMC teams. To sustain dynamism, it would be important to recruit young group leaders on the international level where possible.

Team 1: Regulation Networks in Normal and Pathological myeloid Cells

Team leaders: M François MORLÉ, M Faouzi BAKLOUTI and M Guy MOUCHIROUD

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	7	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	2X0,5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.8 of the application file)	5	1
N7: Number of staff members with a HDR or a similar grade	5	4

Annexe: past staff-members in each group composing the Team 1 project

- Appreciation on the results

Team 1 focuses on normal and pathological haematopoietic differentiation. As this team results from fusing 3 research groups that share this interest, appreciation of past achievements was done on the basis of each research group. These groups are

1) Team "Transcription and Haematopoietic differentiation (3 full-time researchers including a recently recruited young researcher). The group has shown that the importance of Fli-1 transcription factor in erythroid differentiation is in part related to its role in regulating genes involved in ribosome biogenesis and oncogenic miRNA clusters encoding genes. It has also established the critical role of the transcription factor EKLF in the commitment decision of human bipotent erythro-megakaryocytic progenitors. This work has lead to 5 publications, some of which are in high impact journals (Blood), including collaborative publications (Molecular Cell, PNAS).

2) Team "mRNA Metabolism in Normal and Pathological Cell" (a single full-time researcher). This group studies the regulation of mRNA splicing of protein 4.1R (a major structural protein) during erythroid differentiation. It has shown that overexpression of PU.1 inhibits erythroid splicing of protein 4.1R exon 16 and that a positive feedback loop couples PI3K/AKT signalling to high expression of PU.1. This work has lead to 5 publications, with a recent publication in a good specialized journal (Oncogene).

3) Team "Signalling and Cell Renewal" (2 researchers). This group aims at deciphering differentiation signalling of M-CSF (macrophage-colony stimulating factor)-induced in monocytopoiesis and monocytic commitment. It has demonstrated that monocytic differentiation and commitment decision are tightly regulated by the duration of ERK1/2 activation, which is itself tuned by specific phosphatases (Dusp5). It has also initiated studies for identifying targets of Flt3-ITD mutation in progenitor cells (Fms-like tyrosine kinase 3 receptor/-internal tandem duplication) and for studying non-genomic signaling of androgen receptor in prostate epithelial cells. The work led to 12 publications in good specialized journals (Leukaemia, Oncogene...).

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

The 3 research groups have good national visibility, as attested by several national collaborations and numerous communications at national meetings. The international visibility and the number of post-doctoral fellows are modest. However, recent work provides a potential for improving international visibility, and the recent participation in high level international symposium (Cold Spring Harbor Symposium) is encouraging.

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

Gathering these 3 groups into a single one, as proposed, will clearly allow to synergizing their scientific competence. This is nicely illustrated by the combination of the expertise of the team "Transcription and Hematopoietic differentiation" on transcription factors and that of the team "Signalling and Cell Renewal" on signalling studies. Team "mRNA Metabolism in Normal and Pathological Cell" will provide expertise on RNA alternative splicing in the context of the scentific focus of the two first teams. The resulting team will assemble 5 permanent researchers, and 2 half-time engineers, thereby reaching the critical task-force size that is essential for developing competitive research and for being attractive. The size of the new team should help being more ambitious in terms of publications, and more successful in raising funds, which since 2006-2007, are modest.

- Appreciation on the project

The team presents 3 projects focused on (1) the oncogenic network activated in Friend erythroleukemia; (2) proliferation and differentiation control in normal erythropoiesis); (3) ERK signaling and regulations of transcription and splicing in granulo-monocytic lineages.

These projects are relevant. They address fundamental questions that will contribute to a better understanding of the leukemogenic processes. The team develops original approaches, shedding light on processes/molecules that received so far too little interest in hematopoiesis (ribosomes biogenesis, miRNA clusters, protein 4.1R alternative splicing and Dusp5 phosphatase). The technical approaches, using transfected cell lines and in primary hematopoietic cells, are appropriate, although the use of the latter should be reinforced.

- Conclusion

The teams to be fused into a single entity have made important and original contributions to the field of hematopoiesis, concerning questions of lineage choice, differentiation and regulatory events at the RNA level. In the past, the potential reach and impact of their interesting observations has sometimes been reduced by the limitation to cell line systems. The committee therefore particularly encourages new projects including primary cells and in vivo studies in mice (particularly using the conditional Fli-1 KO model generated) and the use of modern technologies (Chip-Seq gene regulation project). The committee is confident that with results from such systems the group could reasonably aim at publications even above the current level.

From a scientific point view, the fusion of three pre-existing teams is coherent. It should help attaining a critical mass and reaching a better international visibility. The committee however estimates that co-heading of the team by the three group leaders is not appropriate, as it leaves the issue of scientific lead of the team un-addressed. This issue needs to be properly addressed. If not, the team will not reach scientific coherence and synergism, and as such will not benefits from the expected positive reward of team fusion. The issue should be discussed by examining the contribution of each of the three teams in terms of scientific leadership (what are the leading scientific questions in the novel team), man power (how many scientists is each one bringing into the team), and financial support (how much of granting is each one contributing).

Annexe

	Past				**Future**
	Mouchiroud T1	**Morlé T2**	**Baklouti T3**	**Total**	
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	0	0	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3	1	7	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0	2	2	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	2 x0.5	1	3	2X0.5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0	0	0	0
N6: Number of Ph.D. students (Form 2.8 of the application file)	2	2	1	5	1
N7: Number of staff members with a HDR or a similar grade	2	2	1	5	4

Team 2: Molecular Bases of Self-Renewal and Alterations

Team leder: M. Olivier GANDRILLON

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0.5	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	0
N6: Number of Ph.D. students (Form 2.8 of the application file)	4	3
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

Focusing on the decision between self-renewal and differentiation, the research projects developed by this relatively young team combine experimental and computational approaches. The work led to 20 publications during the review period (2005-2009), most of them in specialised journals devoted to genomics, computational biology, mathematical biology, as well as one article published in EMBO Report in 2006. The team is thus very productive, although, higher impact factor journals could potentially be targeted.

The team leader has also co-authored a science popularisation book in French, entitled “Le hasard au coeur de la cellule: Probabilité, déterminisme, génétique” (2009). Furthermore, he is strongly involved in the organisation of symposia devoted to genomics and systems biology (annual editions of the Integrative Post-genomics days, and organisation of an interdisciplinary seminar series). These events attract a national audience to conferences by renown French and Foreign scientists.

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

As attested by several publications, this team is strongly engaged in collaborations with other teams at CGMC (in particular with the teams of F. Morlé and G. Mouchiroud), in other laboratories in Lyon (G. Beslon at PRISMa, INSA; J.-F. Boulicaut at LIRIS, INSA/UCBL, etc.), as well as elsewhere in France (Marc Seban, LaHC, St-Etienne, and Bruno Cremilleux, GREYC, Caen). The team was efficient in attracting PhD students, as well as a few postdocs, although mostly of regional or national origin. Furthermore it has been remarkably successful in raising funds (including ANR, ARC, Rhone-Alpes, regions, etc). It is currently taking part in a consortium application to the last FP7 call, still under evaluation. Finally, during the last four-year period, the team has hosted seven PhD students, most with neighbouring laboratories.

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

With still a relatively modest size, the cohesion of the team is apparently very good, with no sign of internal communication problem. External communication is dynamic, as the team is actively engaged in the development of collaborations at local, national and international levels. The team lists four projects in its research plans, although at least one of these projects is close to completion. With the current human resources, we encourage the team to focus on a few projects for the coming quadrienal, as proposed by the team itself. The team is active in teaching program at Licence and Master level.

- Appreciation on the project

The team presents four interdisciplinary projects (bio/info and bio/math) dealing with (1) gene expression (SAGE) data mining; (2) multi-scale dynamical modelling of normal and pathological hematopoiesis; (3) v-erbA induced changes in ribosomal biogenesis (using SAGE and 2D-DIGE); (4) Stochasticity of gene expression and measure gene expression at single cell level.

These projects address interesting questions and encompass original methodological developments. They largely rely on a powerful cellular system (T2E cells), enabling switching between proliferation/differentiation states. There is a clear synergy between the experimental and computational approaches, but this could be further increased. Synergy with other teams handling interesting experimental models could also be reinforced, in order to assemble the critical mass to publish in high impact journals.

- Conclusion

The team is dynamic, firmly embracing global experimental, computational and mathematical modelling approaches, yet focusing on definite biological questions. Its strength relies on mastering an original cellular system, and on a significant expertise in computational and mathematical biology, a cocktail necessary to develop top-level systems biology projects.

The size of the team remains modest in view of the envisioned projects.

Recommendations are to pursue the exploitation of the T2E cellular system and strengthen collaborations with other CGMC teams, in particular to address similar questions in the context of the developing organism.

Team 3: Epidermis Stress and Differentiation

Team leader: M. Jérôme LAMARTINE

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0,5*
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	1	1

The powerpoint information provided during the visit included an engineer which was not included in the original documentation.

- Appreciation on the results

One of the main problem in evaluating this project is that the team was formed relatively recently (2006). Only the PI had specific expertise in the proposed research. The two permanent scientists that joined the team in 2006 and 2008 have valuable experience in melanoma and epidermal dendritic cells, and in C. elegans molecular biology. They both have heavy teaching loads and had to adapt to work on skin as a new model system. As a consequence, the group as such has only 1 publication in a journal of moderate impact in 2009. All other publications (16 in the period 2005-2009) derive from previous work of team members in journal of good impact, supporting that the team has, in principle, the potential to carry out independent, good quality research

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

The PI has been an invited speaker at a national course. The team has presented oral or poster communications to three international and another three national congresses/meetings. The PI and a team member are each authors of book chapters. This indicates that the team pays attention to its visibility. At present, the team has recruited PhD students, but no postdocs. Two grants have been raised: a one-year EDF grant already expired and a three-years ANR grant running until 2011. Although the group has established collaborations with other teams, it does not participate to national, European or international networks. Publication of significant papers are central to the capacity of the team to obtain necessary grants in the next 1-2 years, to attract postdocs, and to reach a visibility giving access to established networks.

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

Not relevant

- Appreciation on the project

The proposed project is clearly interesting but too broad (three axes) and ambitious and in highly competitive topics, in particular axis 2. The committee considers difficult to make relevant contributions to the three axes in view of the current team characteristics (relatively small size and teaching load). It therefore feels that a careful re-examination of each of the three research axes is urgently required.

Axis 1 focuses on the role of Tetraspanins in epidermal function. Its main justification is based on limited previous experience of team members on the role of a tetraspanin in melanoma invasion. It has already been published by others that several members of this complex multi-gene family, comprising at least 33 members in humans, are expressed in human skin. The team is trying to identify additional expressed members. Although there is no doubt that the possible function(s) of these proteins could be relevant to skin physiology and pathology, in particular due to their known interaction with Integrins, the identification of other ligands, both intra- and extra-cellular, and its possible implication in disease is going to be a complex task. Although the field is not very crowded, what can be seen as an advantage, this part of the project can be considered as incipient, with only a few preliminary data.

Axis 2 proposes an interesting project in a very competitive field. Namely, they intend to study the role of the p63 pathway in the control of human inter-follicular epidermis proliferation and differentiation. They do not have preliminary data regarding genes upstream of p63 and they have the intention to use high throughput cell micro-arrays to study this issue. Downstream of p63, however, they have some interesting preliminary results leading them to concentrate on a p63-RUNX1-Wnt/ß-catenin pathway. p63 is probably considered nowadays as the most relevant gene in the control of epidermal development, proliferation and differentiation and therefore is being the research focus of the best skin molecular biology groups in the world. Other genes, such as Notch or IKK-α, are also regulated by p63 (a high number of genes, ranging from 100 to 1000, according to different authors are regulated by p63) and also play important roles in skin embryogenesis, proliferation and differentiation. Data and genetically manipulated animal models exist concerning all these molecules. Preliminary data of the group, so far unpublished, indicate that the situation in humans and in rodents could be different. In summary, this axis constitutes an ambitious and relevant project. It is probably the most attractive part of the proposed project, and some data on which they could build further have already been gathered. However the topic is hot, complex and highly competitive. The group clearly must focus their efforts in the next years if they are to make a significant contribution in the field. In particular, they should reconsider expending efforts in the analysis of the pathway upstream of p63, still not initiated, instead of using all the man power on the downstream part.

Axis 3 aims at using microRNAs as biomarkers for irradiation. This part of the project should be feasible if the preliminary data are correct. This would be particularly relevant at low/very low irradiation doses, where they should concentrate on. The second aspect of this project axis is to use microRNAs to change the sensitivity of epidermal cells to irradiation. Here, the technical complexity is largely under-estimated, and the project seems too ambitious at present to be considered as realistic. In summary, an important concern is the excessive division of the very limited team resources into three complex and ambitious research projects.

- Conclusion

This recently formed team is in the process of becoming fully established. The team proposes, in principle, interesting research plans, using state-of-the-art technologies and an interesting 3-D in vitro skin model, with a potential for medical applications (e.g. microRNAs as biomarkers of irradiation in cancer patients). The team members are young, enthusiastic, and have performed a remarkable work in their previous laboratories. Therefore, they deserve the opportunity to develop the proposed project provided that they take into consideration the need to carefully focus their objectives so that, without losing substantial interest, the project can be carried out in a competitive manner with the limited available resources. This holds particularly true as two team members have heavy teaching duties.

The recommendation of the committee is to allow the team to develop, provided that they take into consideration the need to carefully focus their objectives, a point that should be assessed within two years to ensure that it evolves properly.

Team 4 : Molecular Genetics of Herpes Simplex Virus Type 1

Team leader: M Alberto EPSTEIN

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2*	2*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1*	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	1
N7: Number of staff members with a HDR or a similar grade	2	2

* Bioviron

- Appreciation on the results

The team develops two activities in parallel: (1) Early interactions of HSV-1 with the host cells during the lytic cycle and (2) development and use of HSV-1 derived vectors for gene transfer and characterisation of the innate immune response activation by these vectors. The fundamental research on nucleolin is original and relevant to the study of HSV-1 biology. Imaging as well as proteomics approaches have allowed getting interesting information on the impact of HSV-1 infection on the nucleolar organisation and function. The applied research focuses on the development and improvement of HSV-1 derived vectors for gene transfer. This part of the team activity is very original and has generated many interactions with other groups especially from South America. An important part of the research is focused on a better understanding of the molecular mechanisms leading to a strong antiviral immune response induced by defective HSV-1 in fibroblasts. The team has shown that this antiviral response is independent of toll-like receptors and do not play a major role in the silencing of the transgenic expression observed in fibroblast. A better understanding of this silencing will help to further improve the vectors to reach higher transgene expression.

The group has a good scientific production: since 2005, it has published 18 papers (11 as first or last author) in good journals. These 18 publications include review articles published in excellent journals, increasing the visibility of the team. Two publications were in collaboration with another CMGC team. The majority of these publications are related to the amplicon technology developed by the team, while the fundamental research on nucleolin has lead to the publication of 5 papers (2 by the team, 3 linked to the past activity of one group member).

The group leader has been invited twice in international conferences, has published two books and has been the guest editor for another one. The group has made 7 oral communications at national or international workshops and their results have been presented as posters (18) at national or international meetings. Finally, the team leader has organized 2 meetings (4th meeting of the Société francophone de thérapie cellulaire et génique, France, 2005; Mid-rem HEVAR International conference, Urugay, 2008) and has been the general coordinator of 2 European research programs (FP6).

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

The group has developed an important network of collaborations, specially based on the amplicon technology and is involved in many international consortia. The work largely develops in collaboration with other teams, including a team form l'Ecole Normale Supérieure de Lyon (ENSL) and with one group from the Medical school of University of Buenos Aires (Argentina). The team leader has been invited to conferences and is frequently asked to write review articles or book chapter. He has attracted young scientist and trains PhD students in co-direction. The team leader with one of its former researcher has launched BIOVIRON, a biotech company exploiting the amplicon technology. This Biotech company is totaly independent (in particular concerning the budget) from the team, although keeping close interactions. The group has strong and continuous financial support from French sources (ARC, AFM). It is (or has been) involved in 4 networks in Europe, being the General Coordinator for 3 of them. It also has partnerships outside of Europe (Conicet, Ecos-Nord, Ecos-Sud) and has launched a LIA (CNRS International Associated Laboratory) that is financed by CNRS and Conicet (50/50).

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

The size of the group (2 full time researchers, 2 engineers, technicians, 2/3 PhD students), as well as the organization, are appropriate for the research activities proposed. The two permanent researchers work in synergy. The visibility is excellent and the network generated around the amplicon technology allows the validation and use of these vectors in different models.

- Appreciation on the project

Both the role of nucleolin and other nuclear proteins in the replication of HSV-1 and the characterisation of the silencing forces on HSV-1 amplicon vectors will be continued. The improvement of the vectors will be pursued in particular to decrease at the maximum the presence of bacterial sequences and to increase the production level while avoiding any contamination of the vectors stock. The collaboration with the Argentinean group (use of amplicon vectors to investigate neuro-plasticity and memory in rats) will be pursued as well as the use of vector in hepatocellular carcinomas (if financed).

Given the increasing importance of collaborative work, it is important that the group leader and associated scientists invest some effort in controlling more in depth the conclusions reached by their collaborators, especially concerning the specificity and efficiency of the observed effects.

- Conclusion

The team has a very strong expertise on nucleolin and HSV-1 based vectors. This offers the team the opportunity to have many collaborations. HSV-1 based vectors are a powerful tool that needs to be further improved, and at the same time assayed for their efficiency in different animal models. The team clearly follows both directions. It has a technical leadership and an excellent visibility leading to numerous collaborations in Europe as well as out of Europe, giving a real opportunity to validate the use of HSV-1 based vectors. The activity on the impact of nucleolin and other nucleolar proteins on HSV-1 replication constitutes an interesting issue that is novel and will improve the knowledge in the Herpes viruses fields. It is important to assess the vectors for their specificity and for their safety, an aspect that has been so far under-evaluated.

The team should keep the international collaborations ongoing and try to attract bright scientists.

Team 5: Virus and Centromere

Team leader : M Patrick LOMONTE

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	0
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The team has a long-standing interest and good expertise in the regulation of HSV1 latency. Notably, recent work from the team highlighted an as yet uncharacterised cellular response, the iCDR (for interphase centromere damage response), which is induced by ICPO during HSV1 genome reactivation as well as upon depletion of centromere components. These original results open a new field of investigation relevant to the study of HSV1 biology and more broadly, to the characterisation of (hetero) chromatin architecture maintenance. Moreover, the team has acquired a unique expertise in FISH technology to visualise the viral genome in situ. This still unpublished breakthrough will allow tackling important questions on HSV1 and should bring strong international recognition to the team in the field of herpes viruses.

The group published 6 papers since 2005, including one review and 1 collaborative paper. The main publication in Journal of Cell Biology underscores the general interest of their recent discovery, while the rest of their production is more specialised. Of note, seven other publications in good journals are linked to the past activity of one group member when he was abroad as a post-doctoral fellow.

The group has made 4 oral communications at international level workshops, notably 2 at the International Herpesvirus workshop (2009, 2008) and 1 at a CSHL symposium, has hosted 3 PhD students during the last four years, and one thesis was presented in 2007.

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

The group has attracted one bright scientist, recruited to the CNRS in 2005. Unfortunately, this scientist will join another Institute for the next contract. In addition, the group regularly attracts PhD students as well as post-doctoral fellows. The group leader has continuous and strong financial support from french national (ANR, INCa; as part of collaborative projects) or regional (FINOVI/RTRS Rhone Alpes) agencies and charities (ARC).

The past and present projects benefit from well-chosen national collaborations, and fit well with the activity of several other teams in the CGMC. The recently acquired unique expertise in FISH analysis of HSV genome will allow the group to develop international collaborations with leaders in the field.

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

This relatively small team has developed a sound scientific strategy, using state of the art modern approaches, relevant biological models, and genuine collaborations. The team leader appears to be very dynamic and capable of stimulating his colleagues.

The team has at present very limited involvement in teaching activities and in organising the research community.

- Appreciation on the project

The team has two main projects in line with their recent results: (1) understanding the role of centromeres in the epigenetic control of HSV1 latency/reactivation, (2) characterize the response to damaged centromeres and/or chromatin. Both projects are particularly interesting and the scientific strategy is sound. Given the small size of the group, the priority has clearly been set on the first project until further human resources are available.

- Conclusion

Team 5 has acquired a strong expertise on the epigenetic regulation of HSV biology and made significant scientific advances even though some have not been published yet. The team has developed a technological leadership (FISH to visualize HSV genome in situ) and opened a new field of investigation (iCDR). These two aspects constitute a true opportunity to reach international visibility and develop innovative projects. The size of the team at the moment is not sufficient to develop both projects in a competitive manner. The publication rate is currently not optimal to guarantee consistent funding.

The team should build on its expertise to foster a limited number of fruitful collaborations, and actively seek further human resources to develop the home-grown projects.

Team 6: Stress Response to Protein Misfolding

Team leader: Mrs Carole KRETZ

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	0
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

It is proposed that a novel group leader take over the heading of the team. This change is motivated by the imminent retirement of the present Group leader, and accompanied by a scientific refocusing on the role of NFkB signalling in stress-induced autophagy.

The team and its present group leader is well known in the field of heat shock induced stress response and the role of chaperon protein assisted protein folding. In the previous 4 years the team has build upon this reputation and published several reviews and about 15 articles in specialized journals. The proposed future group leader has developed in this environment where she has been associated with several publications as a co-author. Most relevant to her application to head the team in the future is the discovery that NFkB activity for the induction of autophagy and cell survival after heat shock. This work has recently been published in a good specialized journal (Autophagy).

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

See conclusion

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

See conclusion

- Appreciation on the project

The group leader is proposing to develop 3 main lines of research investigating (1) the nature of the stress signals activating NFkB, (2) the NFkB target genes activated by stress signals and (3) the relationship to sHSPs , protein quality control and degradation. The general presentation of these projects raised a number of issues that were addressed during the group visit.

The first pertains to the specificity of the signals activating NFkB and the downstream events that link it to autophagy. Additional data was mentioned, showing that not only heat shock or glycerol but also specific mutant proteins that induce aggregation could activate NFkB. These studies should be extended to determine which specific conditions of protein aggregation can activate NFkB. Similarly the proposed gene expression analysis in wild type and NFkB deficient cells should be focused on aggregation stress induced target genes (possibly comparing several mutant proteins) as these signals promise to be far more specific than general stress conditions such as heat shock and in addition provide interesting links to important diseases (Alzheimer, Huntington, Parkinson).

The second relates to the observation that protein aggregation induced activation of NFkB does not involve the classical activation pathway through phosphorylation and degradation of IkB. One interesting hypothesis is that NFkB is released from the inhibitory complex, possibly through unfolding and/or aggregation of Ikb, so that NFkB would act as a stress sensor for abnormal protein folding conditions. The committee considered this possibility as a promising perspective, where the team would have a chance to make a unique, important and original contribution to the field. The committee therefore strongly encourages the team to further pursue this line of investigation in detail. For example it should be investigated whether NFkB can still be induced by protein aggregation in the absence of the IKK1/2/Nemo complex, a clear prediction from this hypothesis.

- Conclusion

The proposal appears broad for a very small team and in particular part 3 lacks focus and a clear outline. It therefore appeared essential to the committee that the group focuses on questions where it has the chance to make a unique and original contribution to the field (see above).

Although the research proposed has significant promise, the committee felt that an independent team led by the proposed group leader would start under un-favourable conditions in a very competitive context. Both NFkB and autophagy are vast fields and the committee was concerned that a small team with only little experience in either domain need to identify its unique niche. In addition, neither independent funding nor the recruitment of new lab members, such as students, that could continue the work after the departure of the current PhD student could be secured for the moment. It thus appears somewhat premature for her to launch an independent research team in conditions where chances of success are reasonable.

The recommendation of the committee therefore is that the CGφMC provides the proposed group leader with the chance and means to further develop the promising elements of her research plan either in her current group if there is a possibility to temporally continue with the current leadership, or alternatively as a team in incubation under the "protection" of an existing group or that of the Director of CGφMC. During that period, the activity should focus on the most promising elements of the project (alternative activation and specific target genes of NFkB after protein aggregation stress) without diluting her efforts in more peripheral studies (part3: interaction with HSPs etc.). If successful, this strategy should lead to the publication of a second last author paper in a good journal, improving her visibility in the field, fundability and attractiveness for students. Together this should give her a much more solid foundation to launch her own group with good prospects of success in a few years.

Team 7: Epigenetics and zygote formation in Drosophila.

Team leader: M Benjamin LOPPIN

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

This team has recently evolved from a team co-headed by two group leaders. The scientific production, 14 publications over the last five years, covers work on gene expression in the silkworm and chromatin assembly and development in Drosophila. This report will focus on the second aspect only, which has become, with the increasing influence of the present group leader, the leading scientific question of the team.

This team has a unique expertise in the transmission of paternal DNA from sperm to the zygote. By using this model system of chromatin re-organisation, the team has made outstanding contributions in understanding the role of HIRA complex (and histone H3.3 deposition) in chromatin assembly during zygote formation in Drosophila. Particularly, they show that HIRA is only critically required for male pronucleus formation. The work identifies paternal chromatin assembly as the major role of HIRA. The model system and the approach to study HIRA and histone H3.3 deposition are original and place this group in a very good position in the field of chromatin assembly. This work led to 5 publications and 3 reviews since 2005, generally in high impact journals (Nature, Current Biology, Plos Genetics).

- Appreciation on the project

The objectives of the team for the next 4 years are clearly defined and rely on their expertise to manipulate their model. This includes the characterization of new gene products involved in the formation of male pronucleus that belong to the HIRA complex; the study of the role of the chromatin remodeller CHD1 in the nucleosome assembly mediated by HIRA; a genome wide genetic screens to search for maternal effects mutants affecting the formation of male pronucleus. All these projects are continuation of the ongoing research, are excellent and well-focused.

The team will also launch two novel projects aiming at understanding a genetic interaction between HIRA and the JAK-STAT signalling pathway and at characterizing a sperm chromosomal protein in paternal chromosome formation at fertilization. These are promising projects that perfectly match the expertise of the team. Although the team has an excellent collaboration with Biochemist, the committee felt that the question addressed could benefit from more investment in biochemical approaches.

- Conclusion

The expertise of this group is recognized internationally. Their experimental system underlines the importance of HIRA and histone H3.3 deposition in zygote formation in drosophila. This is probably the main role of HIRA. Their experimental model opens the way to dissect the mechanism by which HIRA operates and is regulated. Projects for the future are well-defined, and include a good balance of project continuation and novel projects fitting with the expertise of the team. This will certainly guarantee the efficiency for the next four-year period.

The quality of this team is demonstrated by the publication of major papers, the recognition by several prizes and awards, and the continuous support by competitive funding (ANR). Although the actual group leader has no major papers as last author, he had major contributions in the high impact publications of the group, and does seem to have all the qualities to lead the team.

Recommendations of the committee are to increase the size of the team, notably by attracting Post doctoral fellows and researcher with permanent position, a issue already partially addressed as the team is planning to recruit 1 post-doc and 1 assistant professor (MCU) in spring 2010, and strengthen the biochemistry whenever appropriate.

Team 8: Genetic control, development and ciliogenesis

Team leader: Mrs Bénédicte DURAND

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,5	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	2
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation of the results

The research of this group has its origin in past work of the team leader on the Rfx transcription factors. Following a lead from C. elegans, she has made the important discovery that one of the two Rfx genes in Drosophila and Rfx3 in the mouse control ciliogenesis, by investigating the corresponding loss of function mutants in both species. Rfx thus became the first transcriptional regulator known to be involved in the biogenesis of cilia, now widely recognized as organelles that are essential for a number of cellular processes and dysfunction of which causes a variety of human pathologies. In the last four years, the group has continued exploiting its expertise and animal models generated to advance both on the identification of genes involved in ciliogenesis and on the function of Rfx3. By comparative genomics, the group identified a number of Rfx targets many of which could be linked to the biogenesis and function of cilia and were experimentally validated as Rfx targets in Drosophila. A major result in the mouse was the findings that Rfx deficiency affects growth and function of motile cilia in a novel cell culture system. The mouse work was done in part in collaboration with a laboratory at Geneva University, which also led to a contribution to Rfx function in the endocrine pancreas. Still unpublished results concern Rfx function during lung development in mouse and in a set of central neurons in Drosophila. Among the 6 publications listed for the last review period, two involve only one team member and are on subjects completely outside the scope of the group's research activity. Three have group members as first and last authors. They convey solid work and interesting results, but lack perhaps the in-depth analysis required for publishing in journals of very high visibility.

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

While the team leader had an important contribution to the field of ciliogenesis, it only rarely was invited in international meetings (one invitation during the last review period). Still, the field is very competitive and the results obtained during the last four years did not have the same impact as the previous publications. The participation of the team members in a substantial number of international meetings should help to improve the visibility of the group in the near future. The team was able to secure competitive funding for the periods 2005-2008 and for 2009-2012, but should perhaps be more active in recruiting foreign post-docs. The team leader maintains a longstanding and successful collaboration with Walter Reith's laboratory in Geneva, whose main thrust is on the Rfx factors. In this collaboration, the team leader should make sure that due credit is given to her group and avoid the risk of dispersal.

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

This is a solid, well-organized team, whose senior members seem highly motivated and master their field of study very well. The wide range of technologies mastered by the group that range from bioinformatics to sophisticated cell biology is highly appreciated, as is the way the projects are thought out in face of fierce international competition. The expertise in both Drosophila and mouse genetics is another asset of the group. Apart from her position as group leader, the head of the team is heavily involved in teaching and organizing student curricula.

- Appreciation on the project.

Although the written report subsumes the different projects under the heading of ciliogenesis, the group asks in fact two different and only partially related questions: (i) how does Rfx3 and its target genes contribute to cilia assembly and function and (ii) what is the function of Rfx factors in organogenesis in general. Three main projects are led by the group. Concerning cilia assembly and function, the group relies on the candidate genes that popped up in its own screen and that conducted by Reith's group in Geneva, using as models both Drosophila and primary cultures of multi-ciliated ependymal cells. The group has already obtained interesting results in Drosophila on one such gene, but will refrain from moving into the mouse because of the competition from another laboratory. It will now focus on two other interesting candidates. On Rfx function, the group plans to conduct two projects. One concerns the function of Rfx3 in lung development in the mouse that may or may not be linked to defective ciliogenesis; the other one focuses on a set of Drosophila central neurons that are affected by Rfx deficiency without involving cilia. Both projects rely on substantial preliminary data and are well thought out and focused.

- Conclusion

This is a promising team operating in a highly competitive field. In appreciating its activity, it should be recognized that the team leader and one of the senior scientists have important teaching duties and that the team leader is heavily involved in the organisation of student curricula. The team leader has a solid reputation in her field. Still, this is based to a large extent on her previous work, and the group's publication record of the last 4 years is not entirely convincing. However, the results amassed during this time and the experimental models mastered by the team should allow the group to move now from an exploratory stage and descriptive analyses towards the in-depth investigation of selected topics. The parallel use of both Drosophila and mouse models is a great asset, as is the preponderance of in vivo work in both species. In the field of cilia assembly and function, the group should now concentrate on the one or two most promising candidates identified in the previous screens.

The projects for the next four-year period are clearly focused and well thought out and perfectly appropriate, both with respect to the group's expertise and the state of international competition.

With its 4 staff scientists, one post-doc and 2 Ph.D. students, the group has just the size necessary to successfully lead the proposed studies, which have solid funding until 2012. An effort should be made to attract and finance additional post-docs. Furthermore, a full-time technician or research assistant should be more efficient than the actual two half-time positions. There is a strong potential for further scientific development, and the prospects for the future look bright. The group should be encouraged to fully exploit its strengths to increase its visibility and the impact of its publications in a highly competitive field.

Team 9: Neurodevelopment and guidance cues

Team leader: Mrs Valerie Castellani

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This team uses different animal models and in vitro assay systems in order to investigate the developing connectivity of the nervous system. It exploits a series of exciting investigations into the role and molecular mechanisms of the Semaphorin family of axon guidance molecules, key regulators in a number of cellular processes controlling peripheral and central nervous system development. Recent work published by the team identified dual functions for one Semaphorin Class III member, Sema 3B, in regulating the positioning of the anterior commissure (published in 'Neuron') and detailed the signalling pathways downstream of the Sema 3A growth cone collapse (published in 'The EMBO journal'). Overall, the work in the last 5 years continued to unravel complex – sometimes surprising - functional relationship of different members of the Semaphorin, their cognate receptors and activated cellular responses during axon outgrowth and guidance, but also in synapse development and function.

The team leader strikes the evaluation committee as an engaged and very productive investigator, who has taken the analyses of specific neuronal responses intelligently into different, conceptually highly important problems using the mouse or chick as model systems. This team uses a good combination of developmental, cell biological and genetic approaches to analyse exciting problems in developmental neurobiology. It certainly is one of the most prominent team of CGMC. The team had a very good publication output in the period between 2005-2010: They published 11 papers in good or excellent journals including 1 review article.

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

The scientific impact and visibility of the team can be assessed by the standard and rate of publications. The group leader has been invited to present her work at the national and international (European) level, and her presence as invited speaker at international meeting likely will increase in the next period. She was involved in the organisation of two meeting and has trained 2 PhD students.

Of particular note are collaborations with the team of an other group of the center, as well as regular collaborations at national and international level, which contributed to the overall impressive list of publications of high impact and to her standing in the scientific community. Still, the group leader needs to make additional efforts to attract post-doctoral scientists, in particular from abroad, but she shares this deficit, which should be remedied at the institute level, with other groups.

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

The team consists of 3 full time researchers, 2 engineers/technicians, and 1 PhD student - all working on interdependent but entirely independent project. Thus, the organisation is appropriate for the four new research activities currently being pursued. There is a great deal in synergy between individual projects, which might result in impressive new data.

- Appreciation on the project

This team aims to focus its future research on questions regarding the function of axon guidance molecules during the establishment of neuronal polarity. A series of interesting studies, for example, the role of Semaphorins in determining apical-basal orientation of proliferating neuroprogenitor cells in the neuroephithelium of the spinal cord, already provided compelling evidence of the potential of axon guidance molecules and their importance during neurogenesis.

Ongoing research also proposes to detail the characterization of the development and orientation of nascent DRG neurite processes within the sensory ganglion, using combinational electroporation and time lapse approaches in the chick embryo.

Projects are well thought out, with clear lines of investigations and sets of feasible experiments. It is reasonable to expect that future work will consolidate the position of the group leader as an expert in the field of developmental neurobiology.

- Conclusion

The team has acquired a very strong expertise in a number of relevant techniques, which cover a set of complex cell biological assay system, experimental manipulation in the developing chick embryo, as well as mouse genetics. The team has excellent visibility, which has enabled the group leader to continue to lead numerous collaborations with scientists of international repute. Her international visibility should also enable the group leader to recruit additional post-docs with their own fellowships.

The only weakness may be seen in potential limitations of the team's access to high-end time-lapse microscopy systems, which are absolutely necessary for a number of proposed projects. The evaluation panel was overall very impressed by the group leader research breath, as her ambitions don't stop at analyzing the connectivity of neural circuits. Her new work on the polarity of diaphragm innervations, for example, embraces questions regarding the pathology of respiratory syndromes, which she may want to apply more directly to biomedical research with translational potential.

In summary, this team is central to the success of the CGφMC.

Team 10 : Functional genomics of nuclear receptors,

Team leader: M. Gérard BENOIT

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	0
N7: Number of staff members with a HDR or a similar grade	0	0

- Appreciation on the results

This team is a novel team proposed to be part of CGφMC for the next four-year period. The research performed by the proposed group leader, previously research assistant at the ENS (Lyon), was mainly about the role of REV-ERBalpha in the circadian rhythm. He identified two alternative transcripts encoding two protein variants referred to as REV-ERBalpha1 and -alpha2, and showed that REV-ERBalpha2 exhibited a reduced half-life when coexpressed with REV-ERBalpha1, suggesting that the relative expression levels of the two REV-ERBalpha variants tune the circadian period length by regulating REV-ERBalpha half-life. This finding is interesting as it increases complexity of the clock, and places nuclear receptors as more important regulators of its functioning as initially thought. In parallel, the proposed group leader initiated a genome-wide analysis project, aimed at identifying the direct target-genes of the retinoic acid receptors (RAR) in F9 cells. This study is at the basis of one of the ambitious projects proposed for the CGφMC (see below). Although not yet publishable as such, preliminary results demonstrate the reliability of the proposed approach, the expertise of the group leader in the field of genome-wide analysis (both on the cellular and molecular side), as well as his ability to set up collaborations with computer scientists to analyse the data (actually, the required bioinformatics pipelines are set up and mastered in the group).

During the last 4 years (2005-2009), the proposed group leader has published a total of 8 papers most of them in specialized journals devoted to development, evolution, and endocrinology, some of which rank in the top 20 in their categories. Of note are one important review on orphan receptors (Pharmacol. Rev) as first author, attesting for his recognition in the field of nuclear receptors, and two original papers as last author in *J. Mol. Endocrinol.* and *Mol. Endocrinol.* in 2009, demonstrating his potential as an emerging young group leader.

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

The proposed group leader should increase his visibility through presenting his work in international congresses. Its capacity to recruit was limited up to now, as he was not yet independent. However, he recently hired a post-doctorate, who is joining the group in January 2010, while an engineer from CNRS asked for a mobility to follow his move to CGφMC, attesting thereby for his attractiveness as a young group leader. The proposed group leader is successful in raising funds (ANR Programme Jeune Chercheur in 2005), and currently participates to an INCA consortium (ARTOn 2009-2011) and one ANR project (ODESSA 2009-2011). He was involved in several collaborations directly related or not to nuclear receptors. Those medium-term collaborations were fruitful since they yielded 5 articles or reviews in high-rated journals. Collaboration with the Karolinska Institute in Sweden, where the group leader did a post-doctorate, are still ongoing.

External communication appears good, as assessed by the development of active collaborations abroad, notably with future neighbours at CGφMC. Initiating a genome-wide analysis of binding sites for transcription factors is an ambitious project. Yet, the group leader has established the necessary collaborations with members of the above-mentioned consortium, with local facilities and with mathematicians to model the involvement of REV-ERBalpha in clock regulation (ANR ODESSA, Programme Systèmes Complexes et Modélisation Mathématique). The involvement of the group leader in teaching activities appears rather modest at the moment (a few lectures at Université Ouverte de Lyon on a yearly basis).

- Appreciation on the project

The first part of the project addresses one of the long-standing questions raised in the field of nuclear receptors: to identify, at the DNA level, the features (e.g., DNA sequence, flanking sites, associations with other transcription factor binding sites, chromatin status) determining the specificity of retinoic acid response elements (RARE) in the regulation of gene expression by a given RAR isotype.

This is approached through the identification of the DNA sequences recruiting RAR, genome-wide and under several experimental conditions, using a versatile cell-system as a model (F9 cells), which allow testing for isotypes specificity thanks to the availability of mutant sub-lines lacking one RAR or one RXR. This project nicely complements other projects, ongoing for example at IGBMC (Strasbourg), using other cell-types. In this context, the proposed project cleverly invests a niche with promising outcome, since understanding RAR specificity may lead, upon modelling and on a long-term prospect, to the discovery of novel methods to tune gene expression in pathological conditions.

The second part of the project proposes to refine, through mathematical modelling, the scheme of clock functioning taking into account their new data on the involvement of REV-ERBalpha2, and to built up a cellular model (mouse fibroblasts expressing two distinct fluorescent reporters) to functionally monitor the clock. Although the strength of the cell system may critically depend upon the half-life of the reporter proteins, this elegant model should allow testing the clock at the single cell level, preventing thereby the need for artefactual synchronization of cell populations. On the other hand, this project may have to face hard competition from other strong groups in the field of nuclear receptors and clock. Support from the engineer (IR CNRS) moving to CGφMC with the team leader will undoubtedly help in the success of this project, thanks to his 10 year-long expertise in the field.

At first glance the two axes of the project may appear distantly related. They are nevertheless linked together as the ultimate, long-term, objective of the project is to understand how retinoids may modify regulation of the clock, combining genome-wide studies and cell system-guided modelling, which constitutes an original approach.

- Conclusion

The project is ambitious but well thought. The team leader masters the methodologies that are included in the projects of many other CGφMC teams and, in return, the expertise of other CGφMC teams in computational and mathematical biology will be invaluable to develop top-level integrated biology/functional genomics.

This is a unique and strong opportunity of synergism within the research unit.

In addition, the size of the group is still limited, while its visibility should be strengthened. This team fits well within CGφMC project and its creation should receive all the necessary support.

The committee advises further prioritisation between the two aspects proposed in the project (see above), and/or rapid reinforcement of the human resources. It also encourages the group leader to highlight the biological questions raised by his projects, rather than defining projects with respect to technological approaches.

Team 11: Excitability and Signaling in Normal and Diseased Skeletal Muscle

Team leaders: M. Vincent JACQUEMOND and M. Bruno ALLARD

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	1
N7: Number of staff members with a HDR or a similar grade	5	5

- Appreciation on the results

This team is joining the lab for the new contract (2011-2014) and originates from UMR5123. It is one of the three/four most referred "cellular muscle physiology" groups in France, well known in the muscle field. It is recognised at the national/international level, in the domain of calcium transfers and excitation-contraction coupling, and recently contributed to resolve controversial issues in the field. The team had 18 publications in international peer-reviewed journals. Generally, publications are of good level: the team publishes in the best journals specialised in the field of physiology (5 papers in Journal of Physiology), as well as in journal of broader interest (3 papers J Biol Chem and J Mol Biol).

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

In the past, the team developed international partnerships, in particular with a Hungarian group. Several members of the team were trained as post-docs abroad. Members of the team are regularly invited in international meetings, in particular at the European Muscle Conferences. During the last contract the team attracted three scientists: 1 professor, 1 assistant professor (MCF) and 1 full-time investigator (CR CNRS). The group raised funds from a large diversity of supporting institutions or charities (1 ANR, 1 AFM, 1 grant from the Ministry of Foreign Affaires (Partenariat H. Curien - Balaton), 2 grants from CNES).

The group has taken important innovative steps forward to develop new techniques on single muscle fibres (vaseline gap voltage-clamp method, in vivo gene transfer, confocal coupling to voltage-clamp) or applying them to new preparations (C. elegans) leading to an increasing demand of collaborations from other groups. The involvement in teaching is central in this group as 7 people (over 12 permanent staff people) are half-time dedicated to this task.

- Appreciation on the project

The team project includes two main lines of research: (1) role of calcium entry through voltage-dependent channels in adult muscle cells and relation to muscle fatigue and diseases; (2) relations between intracellular calcium and the ROS signaling pathways. These research axes deal with the key role of calcium in muscle cells, but through an increased level of methods and techniques (in vivo gene transfer, screening molecular partners of Ca channels using C.elegans model, giant liposomes, silent Ca pathway, Ros imaging). Considering past experiences of the group and envisaged or already established collaborations, the research project appears feasible and ambitious. Based on previous contracts we anticipate that the group will retain the capacity to raise the funds necessary. Originality lies particularly in the ROS part of the project. On the other hand, the continuation of other lines of research makes the overall team project well-balanced, between risky and secured investigations.

- Conclusion

The team is a high rated muscle group with a national and worldwide recognition, which promotes a large number of collaborations. It publishes in the best specialized journals, and is technically innovative. Its strengths is its know-how in the muscle field, and its weakness is the limited visibility in fields other than muscle domain. A potential concern is the ability to attract students and post-docs: the team presents an unusal and heavily unbalanced ratio between permanent and non-permanent scientist. Recognizing the quality of the work produced by the team, the committee encourages the group leader to publish in higher impact non-specialized journal whenever possible. This would increase the international visibility of the group, and provide attractiveness for post-doctoral fellows. Joining the CGMC is definitively a pertinent decision from the perspective of creating a larger sized Research Centre in Lyon. It will strengthen existing collaboration with a CGMC team, and expose the group to techniques and concepts to which they may not be familiar. This may play a decisive role in getting their present research of more interests outside the muscle physiology field.

Team 12 : Muscle Pathologies in C. elegans

Team leader: Mrs. Kathrin GIESELER

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1.5	1.5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	4	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	2
N7: Number of staff members with a HDR or a similar grade	3	4

- Appreciation on the results

This research group has developed extensive and unique expertise in elaborating C. elegans as a model system to investigate the molecular mechanisms of muscular dystrophies. Interesting screening approaches have been established, with support from the AFM, to screen mutants of this organism for modulators of muscle diseases. This is a relatively unique effort where the power of the cell lineage and genetics can be combined to discover interacting partners of the dystroglycan complex, and to study the role of the neuromuscular junction on muscle degeneration. The research activity is divided into several axes including morphological descriptions of costameres and the sublocalization of DYS-1, a screen to identify kinases, ubiquitin-ligases and proteases that act in the dystrophic process and identify interacting partners. Finally a metabolomics approach involves NMR imaging of C. elegans exhibiting dystrophies. Preliminary results are encouraging and they provide another scope for the analysis of dystrophies. These are all innovative approaches that can potentially produce mechanistic information on dystrophies. One hopes that some of the mechanisms that will be unravelled can be extended to humans. Indeed, a drug screen of about 800 compounds validated the C. elegans model, as prednisone which is already used in the clinic was identified as a hit.

The team had 19 publications in international peer-reviewed journals (15 with leaders as last author; 8 as reviews). The research papers are of good standing. Furthermore, there have been 3 international patents awarded. Teaching responsibilities are intense, and several books directed at the general public have been written. National and international links have been established and on one notable case of C.elegans metabotyping was performed (PNAS 2007). This research angle will continue. Also, the group has a unique resource of 14 000 mutants that are available for the C. elegans community.

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

The group has several international and national links that have lead to publications (e.g. PNAS, J. Mol. Biol., J. Proteome Res.) in recent years. One expects that this will continue, and work with mutants may also provide other sources of collaboration. Although the number of invitations to international conferences remained limited, the vulgarisation of science in the form of books is considered to be a positive sign. The teaching responsibilities of the future group leader are prohibitive. To achieve international level and high impact publications, this would have to be reduced. EU network participation has extended the reach of the team. Collaborations with Labouesse/Schwab (IGBMC, Strasbourg) and Benian/Qadota (Emory, USA) have been established. Fruitful collaborations with the Allard/Jacquemond groups in the University will continue in the long term.

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

The group has a healthy balance between permanent and non-permanent researchers with students and post-docs. The former and future group leaders direct 2 topics of research each. This appears to be done in a concerted and coherent manner as one axis involved the physiological and morphological analysis of dystrophic mutants whereas the other aspect is more metabolomics oriented. The compound screen for molecules that ameliorate regeneration in dystrophic models, as well as the metabolomics screen are important and significant initiatives that should generate interesting information in the near future. External collaborations (e.g. IGBMC) are complementing the expertise.

- Appreciation on the project

The screens mentioned above have already proven to be fruitful and these hold promise. They are feasible given the expertise of the group and their stature. Solid funding from the AFM, as well as other smaller grants, have sustained the group. We anticipate that this pattern will continue. Using C. elegans as a model for human dystrophy involves high risk, given that many researchers have questioned mouse as a relevant model. The group has focused on certain aspects, and if these will hold promise, at least some of the mechanisms relevant to dystrophies can be worked out in the worm model.

- Conclusion

The group has established a unique model for investigating human disease, and one that can be manipulated readily. This is an important initiative since in some cases the model has proven to be useful. The committee anticipates that in the future the group will focus on those aspects that can be translated to the understanding of muscle degeneration. Since the worm is a unique model for dystrophies, and the group has a rich resource of mutants, this position can be exploited scientifically. The screens allow a level of analysis that is rapid and potentially very useful for testing clinically relevant drugs. In recent years, high impact publications involving the team leaders as principal investigators are lacking.

The committee hopes that the long-term investments can ameliorate this weakness and improve the international visibility of the group. This will also attract foreign researchers with a wider diversity of expertise. The group can now make a concerted effort to exploit their unique resources and place their research in a more internationally visible light.

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

Team 1: Regulation Networks in Normal and Pathological myeloid Cells

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

Team 2: Molecular Bases of Self-Renewal and Alterations

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

Team 3: Epidermis Stress and Differentiation

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

Team 4: Molecular Genetics of Herpes Simplex Virus Type 1

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

Team 5: Virus and Centromere

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

Team 6: Stress Response to Protein Misfolding

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

Team 7: Epigenetics and zygote formation in Drosophila

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

Team 8: Genetic control, development and ciliogenesis

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

Team 9: Neurodevelopment and guidance cues

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

Team 10: Functional genomics of nuclear receptors

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

Team 11: Excitability and Signaling in Normal and Diseased Skeletal Muscle

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

Team 12: Muscle Pathologies in C. elegans

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

Université Claude Bernard Lyon 1

Le Président
Lionel Collet

Villeurbanne, le 19 Mars 2010

M. Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne

75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité de recherche :

«Centre de Génétique et de Physiologie Moléculaire et Cellulaire» rattachée à mon établissement.

Ce rapport n'appelle pas de commentaire particulier de la part de l'université.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

Lionel Collet

Centre de Génétique Moléculaire et Cellulaire UMR 5534
Domaine Scientifique de la Doua - 16 rue Dubois, Bâtiment G. Mendel - 69622 Villeurbanne Cedex
Tel : (33)472448085 / (33)678535488 - Mel : pierre.couble@univ-lyon1.fr - Web : http://www.cgmc.univ-lyon1.fr/

COMMENTS ON AERES REPORT

Present and future directors of the research unit as well as team leaders have gone over the AERES report. Overall, this is a detailed and objective assessment of our research unit, which provides the direction with a critical appreciation that will be useful to refine CGφMC project strategy. However, we would like that a few issues become clarified, as follows.

Comments concerning appreciation of the research unit

1. In several parts of its reports, the committee raised the issue that our research unit is not attractive enough for post-docs. We agree that efforts should be made to recruit more post-docs, in particular at the international level. However, we would like to stress the fact that the number of post-doctoral fellows given for each group (N3) is generally underestimated since several post-docs will be recruited this year. Therefore, these statistics should not be interpreted as a decreased attractiveness of our research unit for post-docs.

2. Concerning team 6, the proposed change was not just "change in leadership of the team" (page 7, last paragraph, line 8). This is accompanied by a new scientific orientation at the initiative of the proposed team leader.

Comments concerning team-by-team appreciation (where needed)

Team 2: Molecular Bases of Self-Renewal and Alterations
As far as the team is concerned, its leader wishes to make the two following comments:
1. The INRIA has decided (decision n° 71144, 10/02/2010) to create the Dracula team-project, in which the BM2A group is actively participating.
2. The committee wrote: "the team has hosted seven PhD students, most with neighbouring laboratories". We presume that the committee refers to the fact that most our PhD students have been co-directed by two mentors, one being a biologist (O. Gandrillon), one being a computer scientist (JF Boulicaut, G. Beslon) or a mathematician (F. Crauste). We feel that this co-direction of PhD students is a key asset of our global strategy and should be formally stated.

Team 3: Epidermis Stress and Differentiation
1. Page 13, "Appreciation on the results", line 4 : the remark " they both have heavy teaching loads and had to adapt to work on skin ... " is somewhat inaccurate. In fact, two permanent scientists have teaching loads and one had to adapt to work on skin as a new model system.

2. Page 13, “Appreciation on the impact, ...”, ligne 4 : the report that “Two grants have been raised” is not accurate. In fact, several grants have been raised: a one-year EDF grant already expired, a three-year ANR grant running until 2011, four iterative one-year grants from *la Ligue contre le Cancer* since 2007 and a valorisation grant from the *PRES-Université de Lyon.*

Team 6: Stress Response to Protein Misfolding

The proposed team leader agrees with the overall appreciation of her project. However, the two major issues raised by the committee were already a matter of concerns to her. Indeed, she presented experimental objectives corresponding to suggestions or recommendations made by the committee.

Concerning the first issue, following experiments were planned:

1. Assessment of NFkB activity in cells with different degrees of protein aggregation (scientific project, page 57, left column);
2. Restricting the list of NFkB target genes implicated in heat shock-induced autophagy by performing a second round of microarray analysis with cells under protein aggregation stress (scientific project, page 58, top left column);

Concerning the second issue, the team previously observed heat shock activation of NFkB independent from IKK1 or IKK2 (J Biol Chem, 2001), which led to the idea that a non-classical NFkB activation process might be activated following protein aggregation. As suggested by the committee, similar analyses performed under protein aggregation stress would help to test this hypothesis.

In its conclusion, the committee was right when stating that NFkB and autophagy are vast and competitive fields. However, its concern that “a small team with only little experience in either domain need to identify its unique niche” should be balanced by the following points. First, the team leader has solid experience in the NFkB field as shown by 6 publications (first or last author) and 5 congress invitations on this topic since 1999, yet she has only recent experience in the field of autophagy. Second, the team was the first to describe positive regulation of autophagy by NFkB. Moreover, it showed essential role of aggregated or aberrantly folded proteins in the signalling pathway leading to NFkB activation and autophagy, suggesting a novel NFkB function in protein quality control and clearance of protein aggregates. Therefore, studying the links between protein aggregation, NFkB and autophagy is original and constitutes a yet unexplored niche.

Team 7: Epigenetics and zygote formation in Drosophila

The team thanks the committee for its pertinent expertise of research activity of the group and only has a minor comment.

It can be read in the current version:

“This work led to 5 publications and 3 reviews since 2005, generally in high impact journals (Nature, Current Biology, Plos Genetics)” (page 21, first paragraph, last sentence), and “Although the actual group leader has no major papers as last author, ...” (page 21, second paragraph of conclusion).

In fact, the group leader is actually the last author in the *PLoS Genetics* paper (Orsi et al., 2007).

Team 8: Genetic control, development and ciliogenesis

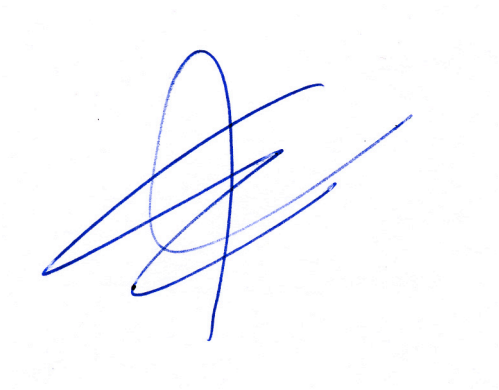
Page 22, paragraph “Appreciation on the impact, ...”: concerning the participation to international meetings, please note that altogether team abstract were selected four times for oral presentations in international workshops among which two major cilia biology meetings (2007, 2009).

Team leader’s comment on the last sentence of page 22: I would like to address any misleading interpretation of this sentence regarding the longstanding and fruitful and especially faithful collaboration developped with W. Reith. This collaboration is fruitful

based on the complementary expertise of each teams. For instance, we have identified the pancreatic phenotype that was further analyzed by W. Reith and collaborators. This work would not have being so efficient without the excellent expertise in pancreatic development of the Department of Pathology and Immunology in Geneva. As well, our comparative genomic study in Drosophila was helpful to identify positive controls to set up ChIP experiments in Geneva. Conversely, the unique expertise of W. Reith in ChIP methodologies, was essential to characterize and identify target genes in mouse. In the future, we will each focus on specific RFX functions that open important new research directions in completely different fields of research. Because we will develop complementary approaches and focus on very different aspects of RFX function and because we always exchange on all results and respective collaborations, there will be no ambiguity on the due credit and no risk of dispersal in the future.

Team 11: Excitability and Signaling in Normal and Diseased Skeletal Muscle
Page 29, last paragraph, line 2: the term “vaseline gap” should be read as “silicone voltage-clamp”. Indeed, the « vaseline-gap » is a technique of voltage-clamp that has never been used in the group. Instead they have developed and are routinely using a technique called “silicone voltage-clamp”.

Fait à Villeurbanne, le 17 mars 2010



Guy Mouchiroud