IGMM - Institut de génétique moléculaire de Montpellier

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Institut de Génétique Moléculaire de Montpellier

From the

University Montpellier 1

University Montpellier 2

CNRS

May 2010

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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 : Institut de Génétique Moléculaire de Montpellier

Requested label : UMR CNRS

N° in the case of renewal : 5535

Name of the director : M.Jean-Marie BLANCHARD

Members of the review committee

Committee chairman

M. Hughes DE THE (Hopital St Louis, Paris, France)

Other committee members

Mrs. Maria CARMO-FONSECA (Faculty of Medecine, Lisboa, Portugal)

Mrs. Jane MELLOR (University of Oxford, UK)

Mrs. Karla NEUGEBAUER (MPI, Dresden, Germany)

Mrs. Varda ROTTER (Weizmann Institute of Science, Rehovot, Israel)

M. Didier TRONO (EPFL, Lausanne, Switzerland)

M. Philippe AVNER (Institut Pasteur, Paris France)

M. Jonathan PINES (Gurdon Institute, Cambridge, UK)

M. Jean-Pierre de VILLARTAY (Institut Necker, Paris France)

M. Peter VANDENABEELE (Department for Molecular Biomedical Research, Ghent, Belgium)

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

M. Alain EYCHENNE (Institut Curie, Orsay, France), CoNRS member

Mme Catherine FLORENTZ (IBMC, Strasbourg, France), CNU member

Observers

AERES scientific advisor

Mrs. Catherine DARGEMONT

University, School and Research Organization representatives

Mrs. Martine DEFAIS (CNRS)

Mrs. Christine TUFFEREAU (INSERM)

Report

1 • Introduction

- **Date and execution of the visit**

The site visit started on January 20 afternoon and was completed on January 22, evening. This visit had been prepared by a very well-organized and complete document and the evaluation took place in excellent conditions.

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

This is a multidisciplinary reseach unit created some 20 years ago by P. Jeanteur located in the north of Montpellier in an extremely science-rich environment. It is located adjacent to two other institutes, with which links are being developped. The unit is also part of IFR 122, which coordinates most biological research in the north of Montpellier.

- **Management team**

The management team consists of a director, deputy director, an assistant to the director and an administrator.

- **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	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	52.8	51.8
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	23	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	27.6	26.6
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	14	1.2
N6: Number of Ph.D. students (Form 2.7 of the application file)	38	24
N7: Number of staff members with a HDR or a similar grade	37	35

2 • Overall appreciation on the research unit

- **Summary**

The overall scientific level, management, facilities, social and scientifical atmosphere are very good and this is largely due to the director and internal organization. Management has optimized the common infrastructures whilst providing limited lab space to individual groups. Multidisciplinary themes (cell cycle, RNA, cancer, immunology, virology, metabolism) have played an important role in maintaining a broad presence in many fields of biology and have also fostered intensive internal collaborations. The ratio young/senior group leaders appears good. A number of groups have very high international visibility. The unit is highly attractive and plays an important role in the local environment. The unit should be able to continue to attract high profile new investigators and is encouraged to have a dynamic and result-rewarding management. This would include adjusting support (space, personnel…) according to the results achieved and providing mentoring to junior investigators. The directors have stressed the urgent need for technical staff for building maintainance and administrative support. The committee noted that the development of many mouse projects will require significant technical staff input in the near future. Support from the university is low, below 10% of the consolidated budget.

- **Strenghts and opportunities**

Strong international, national and internal collaborations, the most unusual being internal ones. Critical mass in the immediate vicinity, well organized services, strong community spirit, charisma of the past and future directors all contribute to make the unit attractive. Good mentoring of PhD students. Good culture of technology and concept transfer with several important technology-driven projects. Since several groups have health-related project, the unit is advised to seek more medically-trained personnel, notably after the fusion of the Universities. Several high-profile PIs already have very high international visibility; this could be increased for several more PIs, given the right mentoring and support. The last group leader recruitment who is an excellent top scientist is very beneficial to the unit. This will upgrade an important facet of cancer and metabolism that is one of the most cutting age topics in cancer research at large.

- **Weaknesses and threats**

The aging infrastructure of the building is distracting the director away from other important tasks. Several vulnerable junior PI would benefit from tight mentoring to better keep in focus, to evaluate the pertinence of their strategies, as well as to solve internal lab problems. Some more senior groups also appear to have lost focus. The internal culture of the institute (allocation of space and technical support) makes it difficult to reward groups according to scientific merit. This may hamper the maintenance of international visibility. The number of PhD student has decreased from the previous period, suggesting that strengthening the life and visibility of the PhD students could improve the rate of future recruitments. All available human ressources must be used to maximize scientific output. To exploit the potential of mice models that are currently under development, the institute will require a significant increase in technical staff. In this and other contexts , support from the university appears surprisingly low for a laboratory of this quality.

- **Recommendations to the head of the research unit**

The committee recommends to establish a science advisory board and a program for the mentoring of junior investigators. Participation in international meetings, including that of the PIs and young staff scientists is strongly encouraged.

Existing procedures should be adjusted so that groups can be more easily rewarded on scientific merit.

Strengthen the PhD program by allowing students to invite international speakers (e.g. 1-2 per year) and creating a PhD student lunch with all external speakers would increase their participation and exposure.

- **Production results**

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

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	59.8
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	41.3
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	8
A5: Number of PhD granted during the past 4 years	40

3 • Specific comments on the research unit

- **Appreciation on the results**

In general, the research was considered of high or very high quality. Several discoveries made in the unit have had a significant impact on the scientific community. The multi-thematic nature of the unit is a clear advantage, allowing several groups to engage into productive collaborations outside of the primary field of interest. Impressively, 30% of all research articles are collaborative and include members from different groups.

Taken for the whole unit overall, the production of publications is high (over 250 research articles). The overall quality of the output is very high, by French standards, although significant differences exist among the different groups.

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

The committee felt however that the representation/presence of the most successful groups at international conferences did not necessarily match the quality of their publications. This is clearly detrimental to the visibility and long-term reputation of the PIs and is unlikely to favor publication in even higher impact journals. Both PIs and staff scientists/post-doc are encouraged to attend more international meetings.

A large number (8/17) of group leaders were not initially trained in France, which is distinctly unusual for a French research unit. Many groups have foreign students or post-doc, again clearly above French average. Despite this, the committee encourages the implementation of an open advertisement policy for open PI positions in the future. Overall, extremely successful funding records on competitive grants and networks. Highly notable is the number of ANR grants involving several PIs of the unit. Five groups have long-term support from the Ligue National contre le Cancer, again clearly above the French average. Teams are involved in 5 networks, mostly European ones. In addition, two EU networks have coordinators in the Institute. Stable and productive collaborations are clearly above average and to be commended and encouraged in future.A start-up Splicos is currently hosted in the institute and another one Synt:em was previously located within the unit. Based on IGMM discoveries of binding to metabolite transporters by viral enveloppes, a new company is currently being put up.

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

Excellent management. Excellent spirit within the unit, clear satisfaction of the PIs, staff scientists, pos-docs, PhD students and technicians about the unit. The director has organized very regular meetings with most members of the unit, which has ensured excellent internal communication. A multi-thematic institute with interests in cancer, neurology, virology, nuclear organisation, epigenetics, chromatin organisation, gene therapy etc....Excellent communications policy. Interestingly, the institute has organized several workshops on novel technological issues, that have attracted significant audience in the Montpellier aera. The institute also organises general conferences on art/philosophy. Some of the PIs have been exceptionally successful at communicating science to the public.The number of staff with teaching positions seems below average. The institute is attractive for students and hence plays an important role in student formation. The director has a very important local role and is director of the IFR 122, coordinating local efforts aimed at providing coherence and structure. Most professors appear to have heavy teaching duties, which may be seen as an obstacle to the development of their research. Professors are encouraged to apply to the Institut Universitaire de France, allowing them to gain higher visibility and devote a larger fraction of their time to research.

- **Appreciation on the project**

Overall, the project appears of a high level. Some of the Unit's projects were judged as excellent, although a few others clearly require rapid adjustment, as detailed below. Even the most ambitious ones appear feasible. The strengthening of the emphasis on metabolism with the recruitment of a new group leader provides a great opportunity to bridge several projects (cell-cycle, glucose transport..) with metabolism. A 30% tax is currently collected on all contracts.This contributes to the support of the platforms as well as solidarity with the less favored teams. This policy likely contributes to the excellent atmosphere within the unit and may be used to give temporary support to young investigators.Some projects were considered cutting edge. The committee feels that those should deserve special support with space, personnel and/or money (see below).

4 • Appreciation team by team

Title of the team : INTRACELLULAR RNA TRAFFICKING

Team leader: Edouard Bertrand

- **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)	5	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
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	2	2

- **Appreciation on the results**

  - Relevance and originality of the research, quality and impact of the results

The Bertrand lab has positioned itself at the cutting edge of RNA biology, by developing novel imaging techniques to visualize and measure important steps in RNA expression and biogenesis in vivo, namely transcription, processing and transport. The work is not limited to fluorescent microscopy and contributes additional discoveries by exploiting other state-of-the-art technologies, such as genome-wide methods and proteomics. The themes fall into 3 major areas: mRNA, snRNA, and snoRNA biogenesis and RNP formation. Major recent achievements include the measurement of RNA Polymerase II (Pol II) transcription rates in vivo, with relevance to co-transcriptional and alternative splicing outcome; notably, Pol II mutants were analyzed and compared to variation in transcription rates in the in vivo context (eg on UV light treatment). While other labs have exploited similar strategies, none has made contributions of the same high significance. Second, studies of small RNA biogenesis revealed new players: PIP1, a protein that binds small RNAs and some mRNAs with a likely role in intracellular trafficking and RNA maturation, and several factors (nufip, R2TP complex) that function as chaperones in assembly of snoRNPs and Pols I & II. Third, studies of miRNA trafficking revealed roles for P-bodies in miRNA function and retroviral regulation.

The Group has been highly productive, with a total of 24 publications since 2005, some of them in high impact journals such as Cell and Science. However, the Group Leader is often not the senior author of the paper. The group trained 2 PhD students who are currently post-docs abroad.

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

Members of this lab are regularly invited to speak at top institutions and international meetings. The very orginal research performed by this team allowed the PI to productively collaborate with numerous groups both inside his home department as well as internationally.

It is also noteworthy that the PI has been able to recruit several excellent postdocs, who have been well-supported (eg EMBO) and highly productive during their training within this lab. The PI has been very successful to get competitive grants although mainly french. In addition, young investigator in FP6 network EURASNET has yielded productive collaborations and provided funds. The international visibility of this rather young group is remarkable.

- **Appreciation on the project**

The proposed future work is a logical extension, particularly of the two exciting new projects above, and these will provide major insights into novel gene regulatory mechanisms.

- **Conclusion :**

— Summary

This team develops highly original research, contributing novel insights into gene expression – transcription, RNA processing and RNA transport in vivo. The findings, made through high quality analysis, are published in high impact journals and influence the field greatly.

— Strengths and opportunities

This lab has established a niche for itself, by pioneering novel methodologies. This ensures that their findings are well-published, because they by definition represent work that is not to be found elsewhere and contribute unique insights to the cell biology of gene expression. Second, this novelty attracts collaborations, and the PI has productively collaborated with numerous groups both inside his home department as well as internationally. A strength of the lab is the involvement of several experience researchers, who can supervise daily progress in the various areas and provide guidance to junior members of the lab. This is remarkable achievement for a relatively young group.

— Weaknesses and threats

Some of the group leader's major contributions to the field are slightly hidden in collaborative papers. An example is the comprehensive measurement of Pol II elongation rates among mutant versions of Pol II (a collaborator is last author of the Cell paper). The PI should get full "credit" for this important work. Perhaps a follow-up paper or review would be wise to consolidate his reputation in this respect.

— Recommendations to the head of the research unit

This group is to be commended and supported. It should keep going.

Title of the team : Nuclear oncogenes and cell cycle effectors

Team leader: Jean-Marie BLANCHARD

- **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)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0.8	0.8
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	2	2

- **Appreciation on the results**

The group initially focused on the regulation of cyclin A transcription by chromatin modifiers and TGF-beta. The group found that nucleosomes positioned on the promoter correlated with its reduced transcription in quiescence or early G1 phase and depended on the Brahma protein. They further showed that the cell cycle was perturbed in cells lacking Brahma. These results were published in Molecular Cell and in Cancer Research and are the strongest output from the group.

The second project pursued was the role of TGF-beta on cell proliferation and invasion. They found that TGF-beta causes the NF-YA subunit of the NF-Y transcription factor to move to the nucleus. In parallel the group developed a cell invasion assay using trophoblasts and endometrial fibroblasts. They found that TGF-beta inhibited invasion and acted through RhoA/ROCK. These results were published in Oncogene and in Endocrinology.

The third project investigated the effect of depleting cyclin A 2 and found that this caused changes in cell morphology and migration that could be rescued by a non-Cdk binding mutant. The commitee was unable to judge the validity of these data, which are yet unpublished.

This group was quite small for a large part of the review period and thus its modest publication record can be considered to be a good achievement. 2005-2009 publications: 5 articles in good journals (Cancer Res., J.Virol., Endocrinology, J.Cell Sci., Oncogene), to which publications of the research director coming from IGMM to join the group should be added. 1 thesis was defended.

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

The group leader has been Director of IGMM for 7 years. He assumed a heavy load of responsibilities. He received a prize from the National Medicine Academy 2008 but few invitations to international conferences. The recruitment of post-docs appears limited, but the team has recently recruited two CNRS staff scientists.

The group leader and team members have been associated to applications to highly competitive call for proposals granted by french agencies (ANR)

The team has developped fruitfull collaborations with other teams both within and outside the IGMM and established relevant contacts with foreign laboratories, to ensure the required competitiveness in the field.

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

The former responsabilities of the group leader have obviously hindered to maintain a viable team with a high level of scientific production. The departure of senior staff scientists has been compensated by the recent recruitment of two CNRS staff scientists.

The group leader proved very efficient in maintaining and developping an overall high quality rersearch at IGMM. His team benefits from the various collaborations set up within the Institute to develop projects based on animal models and the use of imaging facilities.

- **Appreciation on the project**

There are two main projects proposed. In the first the group intends to focus on determining the role of cyclin A using mouse models. They will generate cells expressing cyclin A mutants using recombination techniques. They propose to assay cell survival and cell cycle progression in adult tissues as well as co-operation with oncogenes in cellular transformation assays. This is by far the stronger of the two projects. In the second project the group proposed to characterise the interactions between Cyclin A and its partner Cdks (Cdk1 and Cdk2) and ubiquitin in vivo using a FRET/FLIM approach. The problem with this is that there is no mention of what has already been published on Cyclin A-Cdk interactions and Cyclin A destruction. Thus it is unclear how much the experiments proposed will add to our current knowledge.

In order to transpose their findings in cell cultures to more physiological situations, the team moved toward the development of animal models and the use of imaging facilities.

The policy for the allocation of ressources is difficult to apprehend. Quantitative informations on the external grants is lacking

- **Conclusion :**

— Summary

The past work on transcription was clearly the strength and expertise of the group. Moving towards the cell biology of the cell cycle is a risk, especially since the proposal appears to lack important knowledge of the current state of the field.

— Strengths and opportunities

The mouse models could be very informative if the right questions are addressed with correctly designed experiments. The charisma and renown of the group leader is an asset for the team, which has developped fruitfull collaborations with other teams both within and outside the IGMM.

— Weaknesses and threats

The former responsabilities of the group leader have obviously hindered to maintain a viable team with a high level of scientific production. The data presented were a little too preliminary to judge whether they could form the basis for a four-year research effort. There is some concern over the long-term future of the young staff scientist of this team.

— Recommendations

The team is recommended to reevaluate its long-term goals.

Team 3 : Assembly and traffic of ribonucleoproteins

Team leader: BORDONNE Rémy

- **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)		
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)	2	
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)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	2
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

One of the highlights from the work of this Group was the discovery that Tgs1p is essential for hypermethylation of the m7G caps of small nuclear and nucleolar RNAs (Mol Cell 2002). More recently the Group has focused on (i) characterization of new factors required for SMN (survival of motor neuron gene) complex formation, (ii) functional relationships between snRNP biogenesis and the SMN complex, (iii) identification of mRNAs showing altered splicing and/or localization in SMA (spinal muscular atrophy).

The Group published a total of 5 papers in internationally strongly recognized journals. The Group Leader is senior author in 2 of these papers. One PhD student has been trained and graduated already. He is currently post-doc abroad.

The Group has established productive and solid partnerships both in France and abroad, but with a few groups only.

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

The Group Leader as well as a senior scientist were invited to present on average two seminars per year, either in France or abroad. Their participation as invited speakers at major interantional conferences in the field remains modest.

A senior member of the Group, is starting to develop as an independent scientist.

This group was successful in attracting national level funding as well during the last 4 years as for the future projects.

The Group is a member of the European Network of Excellence on Alternative Splicing.

- **Appreciation on the project**

The research proposal is focused on SMN, a protein involved in spliceosomal snRNP assembly that when mutated is responsible for Spinal Muscular Atrophy (SMA). The goals are to characterize how the SMN complex forms and interacts with snRNPs, and to identify mRNA abnormalities in SMA cells. Clearly, SMA is a devastating disease and much more research is needed to help the patients. This is a highly competitive field with numerous labs working on SMN all over the world. The strength of the group resides in the yeast fission model system Saccharomyces pombe used. This is a unique "niche" in which the group is expert and can evolve very positively.

SMA is a disease of motor neurons. Given the complexity of analyzing specifically the motor neurons in the spinal cord, the proposed research have been conducted in a neuron-like cell line and will be further developped in the yeast S. pombe. A potential pitfall is that the results obtained might not be relevant for SMA. However, the fission yeast model system is of particular interest since it is best adapted for biochemical and genetic approaches.

- **Conclusion :**

— Summary

This Group has a strong past track record on RNP biochemistry. One of its most cited papers reports the role of Tgs1p in maturation of small nuclear and nucleolar RNAs (Mol Cell 2002).

— Strengths and opportunities

The future research is exclusively centered on SMN and SMA, a very competitive field at international level.

— Weaknesses and threats

Although the Group is a member of the European Network of Excellence on Alternative Splicing, there is little evidence for international activities.

The future research is exclusively centered on SMN and SMA, a very competitive field at international level.

— Recommendations

The group has certainly the hability to gain a broader international visibility. Its projects based on Saccharomyces pombe as model system appear as very promising.

Title of the team : Mechanism of neuronal death

Name of the team or project leader : DESAGHER Solange (E4)

- **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)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade		

- **Appreciation on the results**

The proposal consists of original research plan headed by a promising, enthusiastic and convincing young group leader (GL), previously supported by the highly competitive ATIP program. Before 2005 the GL demonstrated an excellent first author publication record at the time when she was joing her postdoc lab. Despite the low publication record in the recent years, the group has made a number of very interesting observations on a system of primary neurons with respect to the mechanism of excitonergic death induction and the role of the proteasome system. In particular, they have demonstrated that long-term proteasome inhibition induces apoptosis in these cells through stabilization of a pro-apoptotic protein, while short-term inhibition stabilizes a key anti-apoptotic protein and hence prevents cell death. Most of the efforts of the group have been focused on TRIM17, a proposed ubiquitin ligase, whose mRNA is massively induced during neuronal death. They have shown that TRIM17 and its E3 ligase activity is a key player in the death of these cells. They propose to investigate the substrates of this enzyme by a variety of state-of-the-art technologies, including GST pull-down, peptide library screenings, general SILAC approach of proteasome inhibition in proteasome arrested cells and creation of TRIM17 conditional KO mice.

Output is extremely low since 2004, even taking in consideration the submitted manuscript describing the TRIM17 work, which is in review in Cell Death and Differentiation aleading journal in the cell death field (IF 7,6). The GL has proven in the past to be excellent in publication output, therefore the contrast with the actual situation is a significant problem.

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

One invitation for an oral in presentation at the prestigious Gordon Research Conference on Cell Death.

The group only consists of 3 staff scientists. No student or post-doc enrolled at the moment, although some were trained in the past.

The good track records on start-up money (ATIP, ATIP plus, FRM) is reflecting the excellent publication output in the past.

One team member has important teaching duties.

- **Appreciation on the project**

The project is very interesting, focused and clearly important, and the GL gave a strong and convincing presentation. The feasibility will obviously depend on recruitment of additional students and post-docs. At present, it seems much too ambitious in its goals and too diffuse for the limited staff. The group leader must make choices. The committee considered that the characterization of the TRIM17 pathway and generation of the TRIM17 conditional knockout mice story is already multi-faceted and deserves the highest priority. The proposed research is original and could yield high impact results.

- **Conclusion :**

— Summary

Outstanding young investigator with an interesting program on proteasome/dependent apoptosis in primary cells. At this stage it is clear that too many objectives are being pursued. There is a major deficit in publications that would likely hinder future funding applications.

— Strengths and opportunities

The biological system is well defined. The project, if limited to Trim17, is well-focused and aims at unravelling molecular mechanism. The methodologies proposed are state-of-the-art. The PI has a excellent knowledge and insights on molecular mechanisms of apoptosis regulation.

— Weaknesses and threats

Small group, to be extended rapidly. Too many explorative aspects in the project.

— Recommendations

Refocus on the Trim17 project with focus on unravelling molecular mechanisms. Avoid at this stage global scale approaches. Consider to outsource the construction of the conditional knockout vector and the generation of the transgenic mice in order not to spend too much time and energy by a limited group. An external mentoring is required and rapid publication of available data is encouraged to enhance visibility and to reconnect to a previously successful career. The institute is encouraged to support this investigator and provide a complete reassessment of the results after two years.

Title of the team : Genomic Imprinting and Development

Name of the team or project leader : Robert Feil (E5)

- **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)		
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)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
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	2	2

- **Appreciation on the results**

This team works in an exciting and competitive area of epigentics, imprinting and development. They have made a major impact over the last five years in particular through their characterisation of the histone modification profiles characterising imprinted loci and genetic/enzymatic basis of these profiles .

They are authors on 29 pubications over the 4-5 years; over 13 are reviews; 4 are major publications from the IGMM in which the PI is last author and members of the group are first author in journals such as EMBO J (2), EMBO reports and MCB; and the rest are collaborations with other groups (some published in very good journals inlcuding Science). Overall a good output from the group demonstrating high quality work with a high impact. In addition, four thesis were supervised.

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

The PI is consistently invited to present his group work at the major epigenetics/epigenomics international conferences and clearly has a high international profile. This team could attract post-doc researchers from abroad. Some of them already awarded a prize.

One major grant now held to 2011, three grants finishing in 2010, evidence for sustained funding obtained. The PI needs to ensure sufficient funds to maintain high output. No obvious industrial funding.

The group is highly interactive both with other IGMM groups but more widely in the International Epigenetics community (Member of NoE epigenome, ESF stem cells) and this has underpinned their work in both mouse and human.

- **Appreciation on the project**

Three projects proposed. The first, on somatic maintenance of chromatin imprints involves two collaborations to study histone lysine methylation, histone arginine methylation and the DNA sequences that comprise the ICR by testing fucntion in at a distinct locus (IgH). This is well thought out, not too ambitous and achievable by the group in

the time frame proposed. The second project is about epigenetic control of tissue specific gene expression to follow up on previous work and try to understand the molecular mechanisms involved. The third is to study germ line establishment of imprints. Again the last two projects are well thought out and feasible. Both are in very competitive area but many of the tools required (transgenic mice and cell lines) are in place. A sensible and exciting workplan.

- **Conclusion :**

— Summary

This is an excellent group which is highly regarded in the epigenetics/epigenomics community and who have made a major impact over the last five years in particular through their characterisation of the histone modification profiles characterising imprinted loci and genetic/enzymatic basis of these profiles. The group is highly interactive both with other IGMM groups and more widely with the International Epigenetics community. The publications record of the group - some thirty publications – is very good with some 2/ 3 of the publications originating within, or with this team as major contributors. The group should be congratulated on its research.

— Strengths and opportunities

The projects build on, and are in direct continuity with the cutting edge research that the group has been doing up until now. They will continue to exploit productively collaborations both within and outside of the IGGM and this is clearly one of the group's strong points. The project concerning the nature of the germline establishment of imprints is particularly interesting and cutting edge although technically difficult.

— Weaknesses and threats

The project concerning germline imprint establishment is stretching current technologies to their limits. There is obviously some risk involved here but which could be attenuated by making sure that the group has the necessary access to single molecule sequencing technologies as and when they come on the market over the next eighteen months.

— Recommendations

The team could usefully be expanded slightly in size if the PI so wishes. This team would benefit from some technical support.

Title of the team : Phosphorylation control of the vertebrate cell cycle

Name of the team or project leader : FISHER Daniel (E6)

- **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)		
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	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)		
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	2	2

- **Appreciation on the results**

  - Relevance and originality of the research, quality and impact of the results

This group began in 2005 and has focused on the role of Cdk1 and Cdk2 in the animal cell cycle, in particular their roles in DNA replication. The main results from this group were published in a good paper in the EMBO Journal in 2008 where they used a chemical inhibitor to show that reducing the level of Cdk2 kinase activity reduces the number of origins that fire during DNA replication in Xenopus extracts. The group had a minor paper following up these results in human cells, and a more substantial paper investigating the effect of DNA intercalating agents on nuclear formation and replication initiation in Xenopus extracts.

In a yet unpublished work, the group have been developing inhibitor resistant alleles of Cdk2 to help to clarify the effect of kinase inhibitors on cells, and have identified a number of proteins that depend on Cdk activity for their binding to chromatin. Two of these proteins will be followed up in the proposed research.

A rather separate strand of research investigated the effect of DNA damage on cell cycle exit and the relative importance of the Chk1 and Chk2 kinases and the p21 Cdk inhibitor. Some of the research was published in 2008.

The output from the lab is reasonable for a group that started with only the group leader in 2005 (3 papers as a senior author, one of them in EMBO). Most of the data appear to have been generated by one post-doc, who started in 2006. The output should now increase with the expansion of the lab in 2007 and 2008.

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

  - Number and reputation of the awards obtained by staff members, including invitations to international conferences and symposia

The reputation is still limited but the group leader received the prestigious INSERM Avenir Award.

The Group has been very successful in attracting competitive funding at the national level

The participation to international or national scientific networks is somewhat limited but the Group participated, as an associated member, in the European Network "Mitocheck". The Group has collaborations with a lab in the UK and an american company, which is developing kinase inhibitors

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

It appears that none of the team members is involved in teaching. This is perhaps a mistake.

The PI organized a Conference on The Cell cycle in Montpellier and is involved in several local structuring responsabilities.

- **Appreciation on the project**

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

The group has two main long-term objectives, both of which are relevant to the remit of the Institute. The first project aims to determine the exact roles of the Cdks in replication in animal cells, determining the direct substrates and eventually by-pass the requirement for Cdks as achieved by the Diffley laboratory in budding yeast. This is highly ambitious and clearly very long-term. The second project is to characterise the role of Cdk8 both in Xenopus extracts and by the generation of a Cdk8 knockout mouse. The only complication here is that Cdk8 is now a subject of interest in both the cancer and Wnt-signalling fields making it possible that there will be competition to generate the mouse. The group leader is aware of this and has already determined that the most likely interested parties are not planning to generate the mouse. Lastly the group intends to develop inhibitors of Cdk8 and solve its crystal structure, which is clearly outside the current expertise of the group.

The intention to expand into several new areas, eg: transgenic mice, protein crystallisation, screening for kinase inhibitors, and analysis in DT40 cells, is a risk because many of these are highly labour-intensive. Good collaborations will be essential to pursue all these areas, and realistically not all these avenues should be pursued with the size of the current group.

Both of the main projects are in areas of considerable interest and are likely to be pursued by other laboratories. For the first project on the role of the Cdks in DNA replication the inhibitor resistant alleles of Cdks will be original and useful tools that may provide an advantage to the group. The group also intends to collaborate with a group in Sussex to study the role of Cdks in DT40 cells making use of his expertise and excellent reagents. For the second project the group intends to make a thorough characterisation of Cdk8, and here the main question is whether they have the resources and expertise to do this.

- **Conclusion :**

  - Summary

The PI is a successful Junior Group Leader interested in chemical inhibition of cell cycle kinases. The PI proposes a highly ambitious and very broad proposal that asks many good questions but is high risk. The mitigating factor is that the PI is clearly aware of most of the caveats.

  - Strengths and opportunities

Kinase expertise, proficiency with cell free extracts, inhibitor-resistant alleles, well chosen collaborators. The PI has already demonstrated to be capable of securing funds and he is establishing strong collaborations.

  - Weaknesses and threats

Deployment of resources unclear, potential to spread resources too thinly in competitive areas.

– Recommendations

This team should focus on more defined goals and not to undertake too many labour-intensive technologies that are not in the current expertise of the PI. The PI could benefit from higher international exposure, for example by participating in conferences and presenting seminars abroad.

Title of the team : Post-transcriptional mechanism and epigenetic control of gene expression in mammal

Name of the team or project leader : FORNE Thierry (E7)

- **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)		
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)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	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	2	2

- **Appreciation on the results**

This group of seven people has made some interesting contributions to the analysis of higher organisation of the chromatin fiber through its work on and contributions to developing the 3C technology. The results obtained concern principally the Dlk1/Gtl2 and Igf2/H19 imprinted loci . Other work concerns the characterisation of novel non-coding RNAs at the Igf2/H19 locus and the INK-ARF locus. This is a competitive and ambitious area.

The main contribution from this team is optimization of the 3C protocols (published in Nature Protocols 2007) and as original research at imprinted loci (JBC 2008). The team also produced two publications on gene expression at imprinted loci, on one the PI is senior author (Cytogenet Genome Res 2006) and penultimate author (MCB 2008). There is one review from 2005. An independent research in the group led to a review on DNA methylation (2008). There is one thesis from 2005. Given this is a group with 2 (now 3) tenured positions the output is not sufficient.

There is no evidence for any ongoing internal collaborations particularly with E5.

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

The PI has given 5 invited seminars in Belgium and France over the period and has been invited to one major international imprinting meeting in Japan and two in France. The group leader has been involved in the organisation of one international meeting in France and contributed to a workshop also held in France. In summary, the group does not really have yet a marked international reputation – a reflection of its rather low key contributions to the field of epigenetics.

Most of the group appear to be French. A staff scientist has been recently recruited in INSERM.

Most of the money and one of the post-docs has been raised on CEFIC and ANR grants. The PI is part of EpiNet, a small French initiative on imprinting but participation to international and national scientific networks need to be improved.

- **Appreciation on the project**

A very diverse research project is proposed with three areas. However each of these area is so broad that just one would be sufficient for a group of this size with the resources available. Preliminary data is presented for the higher order chromatosome project. This is based on the premise that there is 30nm fiber but this is now questioned. The development of a genome wide 3C protocol also needs scrutiny as deep-sequencing total 3C products will just result in a vast amount of genome sequence and little 3C data. The regulatory elements required for the formation of higher-order structures seems sensible but there is no plan for validating the predictions – just a descriptive project. The third project is on DNA methylation during development and reprogramming. This is a highly ambitous proposal in a very competitive area and it is not clear whether the group has the resource or infrastructure to compete in this area. Many groups are studying target genes undergoing de novo methylation in early development and in primordial germ cells. Finally, it is not clear whether there is sufficient bioinformatics support for all the deep sequencing proposed in these projects.

- **Conclusion :**

— Summary

This group has made an impact in the area of 3C and higher order chromatin structures. Publications taken overall have been rather limited and despite a useful and strong group of international collaborators, the group does not really have either a marked international reputation or high international visibility. The science proposed is ambitious and in competitive areas but the group appears very thinly spread in three highly competitive areas. It is not clear that the group has the resource to compete in all areas at the highest level (required for cutting edge projects).

— Strenghts and opportunities

The group has both important expertise and excellent contacts with the leading groups active in the Chromosome Conformation field. It has also developed an interesting approach to methylation analysis using limited quantities of biological material. Both of these provide opportunities for productive research in the future.

— Weaknesses and threats

The projects concerning chromatin conformation capture which have been the centre of a considerable research effort by the group over the last five years and constitute a major part of its research proposal are likely to be challenged by major international scale up efforts aimed at implementing CC as genome wide technologies. The technologies used are likely to depend on very major access to large scale NGS. Whilst such large scale efforts may produce opportunities for fruitful collaborations it will likely require the group to reposition their efforts in this area and could reduce the impact of their contributions.

— Recommendations

The group should be encouraged to concentrate its research on a more tightly defined number of biological problems in which it will be able to play a leading role and which will allow it to maximise its impact over the medium and long term term .

Title of the team : The biology of tumor necrosis factor (TNF) family members

Name of the team or project leader : HAHNE Michael (E8)

- **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	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
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	3	2

- **Appreciation on the results**

In seminal work The PI originally discovered the TNF-like ligand APRIL. He has an impressive publication and citation record, reflecting his contributions in reknown research groups. He has a long standing collaboration with a group in Netherlands. The projects of the team are centered around the study of APRIL and another TNF-like ligand TRAIL along three sub-projects.

(i) APRIL and tumorigenesis: the team constructed an APRIL-Tg mouse model that develops lymphoid tumors resembling human B-CLL. They analyze the induction of other type of tumors induced by murine leukemia virus (internal collaboration with E16).

(ii) APRIL and autoimmune disease: the report on elevated level of APRIL in serum and synovial fluid of SLE, RA, and Sjögren patients. However they report on an inverse correlation of APRIL levels and SLE disease activity index suggesting a protective role of APRIL. On the other hand inhibition of APRIL in mouse models of lupus prevent disease progression.

These two points highlight the opposing roles of APRIL in these two pathological conditoins and suggest that depending on the disease either APRIL agonists or antagonists may have therapeutic potential. It is however not clear which experimental approach will be followed to understand the basic molecular mechanisms of the different functions of APRIL.

(iii) Modulation of TRAIL signaling in RA and cancer therapy: this project is based on the idea that TRAIL induced apoptosis should be valuable as a therapeutic tool in these two situations. There is a pseudo-tumoral expension of synovial tissue (fibroblast like synoviocytes, FLS) in RA. They have analyzed the TRAIL induced pathways (proliferation and apoptosis) in RA FLS. A transcriptomic analysis of TRAIL induced apoptosis in sensitive vs resistant FLS lead to the identification of 13 differently expressed genes in both groups possibly involved in TRAIL pathway. These factors have been patented as possible biomarkers for senitivity to TRAIL-induced apoptosis, but they were not mentioned in the report or during the presentation, neither validation experiments (expression data, functional data).

The group displays a regular publication output (3-4 publications per year) from which 1 per year is unit specific (first and last author belongs to the unit). The publications have a good impact factor (highest is 1 Blood

(10.4) in 2005. 8 publications with 5.2<IF<7.5, 5 publications with 3.8<IF<4.8). However, a limited number (5/14) is directly issued from the lab. 7 publications are from collborative work with the group inThe Netherlands, including the Blood paper in 2005. 1 Patent has been filed in 2008 co-owned by CNRS/Université of Montpellier I and II.

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

The PI has been invited to 3 international meetings with limited impact (2006 Brazil, 2009 Dijon, 2009 Brazil)

1MCU was recuited in 2009, 1HDR was obtained in 2009. In general, the PI has a very good training activity: 1 PhD Thesis defended in 2008 (now PostDoc in the team), 3 PostDoc, 4 M2, 1 German diploma student, 6 visiting students from Germany and Brazil.

The group leader has demonstrated his ability to raise national money ACI "Jeune chercheur" 2004-2007, FRM nouvelle equipe 2004-2005, Fondation de France 2005-2008, CNRS/FIOCRUZ 2007-2009, ARC 2007-2009, Contrat interface 2005-2010 but no support from ANR.

There is a long lasting and fruitful collaboration with a group in The Netherlands. However, this collaboration apparently looks somehow ad hoc rather than really planned involving a common research plan. The collaboration is not mentioned in the project planning and could hold opportunities to acquire international financing. Four other international collaborations are mentioned.

- **Appreciation on the project**

The project is a continuation of the actual research lines and involves three areas.

1) APRIL and tumorigenesis: development of peptide-based antagonists of APRIL as therapeutics (in collaboration with a Brazilian group). This project looks interesting but might very competitive as it might be also be performed by drug companies. Evaluation of APRIL contribution in inflammation-associated colon carcinoma formation (APRIL expression in colon carcinoma patients + mouse model). This is a more descriptive/correlative project without clear functional questions. It has been noted by the evaluation board that the focus of lymphoid tumours is now shifted to colon carcinoma and intestinal biology. Is the expertise for this present in the group or will be invested in this direction?

2) APRIL and autoimmune diseases: to better define the role of APRIL in SLE, APRIL Tg mice will be crossed onto collagen induced arthritis CIA suceptible strain DBA/1 or NZB mice (model of SLE). The group has access to synovial biopsies from RA patients, from which human synovium mouse chimera in SCID mice xenografting will be performed. APRIL will be injected in the graft and the consequences on proliferation and apoptosis of the xenograft will be analyzed. This involves setting up a new model and acquiring ne expertise. The group will extend the study of APRIL in SLE patients and test the idea that APRIL has a protective role by eliminating autoreactive B cells. Immunoglobulin secreting B cells from SLE vs ctrl will be analyzed for their susceptibility to APRIL in vitro (viability and proliferation) and the signalling pathway triggered by APRIL.

3) Validation of the differentialmly expressed genes identified in TRAIL sensitive vs resistant RA FLS. Functional analysis of these factors by RNAi and overexpression in FLS. Screen for reagents that modulate these target proteins in vivo (cell culture and synovium chimera). The presentation of this part was elusive as to which genes were identified and to which extent some of these were already validated

- **Conclusion :**

  - Strengths and opportunities

The group leader has shown in the past to have contributed to significant insights the biology of APRIL and to the understanding of lymphocyte transformation. This could provide a strong platform for further mechanistic studies on the signal transduction of APRIL explaining the different and some times opposing biological outcomes.

— Weaknesses and threats

The three presented research lines were not convincing. The two projects on APRIL are rather descriptive and involve expertises which are not yet available in the group. The opportunity to work out some precise mechanistic questions is not enough taken. The second project on Trail-mediated apoptosis of synovial fibroblasts is still at a very preliminary and non-validated state. The basis of the research lines is based on clinical studies that maybe too weak to build upon a new research line.

— Recommendations

A reassessment of scientific aims should be rapidly undertaken with appropriate mentorship. The GL should consider to continue on his strenghts and aim at more mechanistic studies based on precise biological questions. Some of the international collaborations should be part of a research line in order to exploit this as an opportunity to obtain international funding.

Title of the team : Apoptosis and hepatic carcinogenesis

Name of the team or project leader : HIBNER Urszula (E9)

- **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)		
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)	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)		
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	2	2

- **Appreciation on the results**

During the last years, the research of the team focused on apoptosis deregulation and carcinogenesis induced by the Hepatitis C virus. Expression of physiological levels of viral proteins gives rise to a deficient apoptotic signaling in hepatocytes contributing to the chronic viral infection. The group has discovered that NS5A leads to a calpain-mediated disappearance of the proapoptotic Bid. Viral infection is also a major cause of liver tumorigenesis. The group found that Twist, a bHLH transcription factor, plays a role in the protection against oxidative stress, and may contribute to tumor initiation and carcinogenesis. The group uses advanced technologies such as 3D hepatocyte cultures as well as trangenic mouse models and transcriptome profiling in their studies demonstrating state-of-the-art experimental approaches. The findings of the role of NS5A in apoptosis resistance and viral evasion opens perspectives for innovative therapeutic opportunities to target calpains to facilitate viral clearance. In a second research line the group will focus on the impact of HCV proteins on hepatocyte pathophysiology using the 3D hepatocyte cultures and IKKbeta deficient animals. In a third research line the role of Twist in hepatocarcinogenesis will be studied.

During the last quadrennial the team had only three group-specific publications, but the limited number is compensated by the high quality of the presented work in high impact journals (Hepathology, Mol.Biol.Cell, J.Cell.Science), providing significant impact and novelty in the field.

One PhD thesis has been defended (2007).

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

The group leader is a regularly invited speaker in international meetings. Of note, she has been recently nominated scientific officer in charge of cancer research at the CNRS and assistant director of the ITMO cancer. As such, she coordinates the national academic cancer-related research and participates to numerous visiting comitees.

The team does not appear to have difficulties to attract PhD students and Post-Docs, including from abroad. The team composition is well balanced, with a staff scientist recruited at CNRS in 2003 and the recent joining of a senior staff scientist (2009).

The group leader recurrently succeeded in highly competitive grant applications (INCa, ANRS, European Marie Curie Program…).

The team belongs to French and European networks in the field of hepatitis and/or apopotosis resistance in tumors. Appropriate collaborations have been opportunely established with national and international groups demonstrating the integration of this research group at national and international level.

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

As mentioned above, the team leader is the scientific officer in charge of cancer research at the CNRS and assistant director of the ITMO cancer. This will be useful in helping the future Director of the IGMM in his management tasks.

- **Appreciation on the project**

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

The proposed research projects are well defined and makes use of state-of-the-art approaches. The research topics apparently recruit sufficent funding. The team seems attractive, but the existing manpower might be however limiting, regarding the number of tasks of the group leader, the number of research lines and taking into account the use of several transgenic mouse strains.

The recent findings of the team opened interesting new tracks and experimental therapeutic opportunities. Original and appropriate in vitro and in vivo models have been already developped.

- **Conclusion :**

  - Summary

The recent findings of the team opened innovative tracks, which will be explored in the next quadrenial.

  - Strengths and opportunities

The team has recently developped original and interesting models both in vitro and in vivo, that should prove useful for the achievement of the proposed competitive projects. The charisma and visibility of the group leader is an asset. Establishment of appropriate and fruitful collaborations with national and international experts.

– Weaknesses and threats

Size of the team: the team is maybe not numerous enough at present and should reinforce its manpower to maintain its competitiveness in the field and to increase the team production. The number of research lines in relation with the number of group members may hamper the required critical mass to unravel the molecular mechanisms of the basic observations.

– Recommendations

To recruit post-doctoral positions in order to keep the projects competitive and to increase the number of publications. To reduce number of research lines and to focus on those in which a major breakthrough can be realized by the discovery of a molecular mechanism.

Title of the team : Adenoviridae : receptors, trafficking & vectorology

Name of the team or project leader : KREMER Eric J (E11)

- **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)	3	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	2
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	2	1

- **Appreciation on the results**

– Relevance and originality of the research, quality and impact of the results

Members of the group appear extremely creative and have successfully touched onto many fields. The group has an excellent know-how in the field of adenovirus biology, gene transfer and immunology. This team has significant implications from both a cellular/molecular virology standpoint and a gene therapy perspective. Key observations include elucidation of the retrograde transport of CAV2 and its endosomal escape, determination of CVA2 structure and the nature of the receptor, gene transfer experiments and elucidation of the interplay between Adenovirus antibodies and DC cells, that enlighten some paradoxical HIV trial results. New collaborations developed accordingly.

Very good publication records. Robust production in top quality albeit mostly specialized journals, with a nice balance between basic and more translationally oriented output.

Many collaborations with prestigious groups were developed. Nicely exploiting opportunities of system in translational direction.

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

The number of invitations to international conferences and symposia is not as proeminent as would be expected from the publication records. No foreign members seem to belong to this lab.

This group presents very good ability to raise funds from France but at an international level and to participate to international networks (MJ Fox, HIV VTN, NHMRC, …)

They got significant grant support on translational aspects. However, patents does not seem to be a prominent priority…

- **Appreciation on the project**

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

The group presented 3 ongoing projects funded by FP7 or ANR, with high scientific and translational value. BRAIN/CAV proposes a structured translational approach aimed at exploring the use of CAV for gene transfer to the brain. ICDCtaxis, developped with E13, aims at comparing the entry of viruses into DC naked or as an immune complex, with respect to traficking and signaling. ParkIron developed in collaboration, adressed the issue of iron overload in the brain, with respect to ROS production and overexpression of a metal transporter through CAV vectors. The committee felt that if this is a true reflection of the planned development, with much less emphasis on basic science, this may be ill-advised. The group has demonstrated its ability to engage into novel projects.

- **Conclusion :**

  - Summary

Thie team develops a robust work on the molecular and cellular biology of adenovirus, with adequately exploited openings towards the gene therapy of CNS disorders. It is an extremely active and creative group with a solid productivity in top level specialized journals and able to get significant competitive funding. This group also develops tight links with physiopathological models.

  - Strengths and opportunities

Nice combination of basic and translationally oriented work. The canine adenovirus system seems capable of yielding a wealth of interesting information.

  - Weaknesses and threats

Applied aspects are interesting, but it is not clear whether the group should redirect a too important part of its efforts towards the development of models of CNS diseases and their treatment, an area in which the PI might not have a significant leadership.

  - Recommendations

Keep placing the emphasis on basic science, engage vigorously but in a controlled fashion in the more translational part.

Title of the team : Control of physiological and pathological angiogenesis

Name of the team or project leader : MATHIEU Danièle (E12)

- **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)		
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)		
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)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	1
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

  - Relevance and originality of the research, quality and impact of the results

The work of this group is focused on investigating the mechanism associated with the formation of new blood vessels by the process of angiogenesis. It is well accepted that angiogenesis is very important for normal organism development, yet it plays a central role in the process of tumor progression, in particular in metastasis. The field of angiogenesis is very broad and entails in addition to molecular analysis, cellular aspects of the system. The project has very important therapy significance. This lab is focused on the role of two bHLH transcription factors (TAL-1 and LYL) in angiogenesis. The project obtains important breadth by considering downstream effects of TAL-1 and LYL activities at multiple levels: cellular responses such as cell migration and inflammation, genes and signalling pathways affected, and the consequences of disruption in human endothelial cells and knock-out mice. Major findings include 1) The discovery that TAL-1 modulates VE-cadherin expression; as a consequence, TAL-1 depleted cells fail to make cell-cell contacts necessary for the initiation of tube formation. 2) The identification through transcriptome analysis and confirmation by ChIP of two new endogenous endothelial gene targets of TAL-1 encoding important actors in angiogenesis provides context for TAL-1 activity and has revealed mechanistic details of TAL-1 function as a transcriptional activator. 3) LYL-deficient mouse lines were established and are non-lethal; however, tumors in these mice grow faster and this is correlated with altered blood vessel morphology. 4) LYL -/- mice also show some vascular defects in other organs.

The quality of publications is good, but the number is too low to maintain a competitive profile. During the review period, the PI has been senior author on only 2 papers in international journals Mol Cell Biol and J Mol Biol (these do seem to report significant, high quality findings) and one patent. 2 PhD defenses occured over the last 4 years.

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

The PI does not appear to take part in any international activities (eg networks, seminars, meetings, collaborations, etc). The PI gives presentations only in France, obtains grants from french organizations and collaborates with french scientist. The international profile of the PI is therefore inexistant. However, one can note that the PI received a Prize from the Roche company.

- **Appreciation on the project**

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

Future plans are natural extensions of the on-going research program; in addition, a new collaborative project relating TAL-1 and LYL to the blood brain barrier in models of epilepsy is worthwhile and broadens medical relevance. Given their past achievements which are summarized in several, important, leading journals as well as in a clearly written report, they outlined a very clear order of future goals:

1. Further elucidate the gene network downstream to the TAL-1 and Lyl.

They had suggested a clear experiment. Nevertheless, in this case, a genomic approach would be very useful.

2. The use of Lyl-K/O mice. This is a well accepted approach which is very time consuming and requires the maintance of large, defined cohorts of mice. However, this approach is expected to validate the in vitro of data in a conclusive way.

3. Pathologic significance of Lyl is metastatic spread.

This is a logical experiment and selected cell lines are very valuable. The comparison between Lyl K/O mice to their intact counter partners is important. It would be of interest to examine transgenic mice which are over-producers of the Lyl gene.

4. Investigating the model of Transgenic Adenocarcinoma of Mouse Prostate (TRAMP).

This is of great significance. However, the fact that these mice are controlled by the large TSV40, which by itself is a very strong oncogene, should be carefully considered.

5. The role of TAL-1 and Lyl1 in restoring blood brain barrier in epilepsy.

This is important and should be carefully addressed. The question is whether the model used is the best model for epilepsy.

6. To dissociate the hematopoetic and endothelial LYL functions

The long-term goal seems to be the understanding of the role of LYL in hematopoetic and endothelial system. Generating such mice, is indeed an important goal, yet very time consuming. It will be of interest to adapt in this case corroborating in vitro models.

- **Conclusion :**

  - Summary

This is not a large group for a very competitive topic. The group has obtained some results, but the publication records are modest. The project was considered interesting, but needs focusing and defining priorities, taken that the proposed mouse models are likely to be very labour-intensive.

— Strengths and opportunities

Angiogenesis is a wonderful cell biological problem that deals with how cells form tissues. It is also medically important. The lab addresses this with model systems and by considering the roles of the transcription factors studied in a holistic manner, with both molecular and cell biological assays. This is to be commended. The use of genetically modified mice is a lovely complement to experiments on human endothelial cells in vitro.

— Weaknesses and threats

PI's visibility and own work would probably be helped if she could improve on this record. This would also increase her chances of recruiting international staff. On the other hand several important manuscripts are in preparation or submitted, so perhaps the lab is already getting back on track. Productivity of the group in recent years judged by publication rate is poor.

— Recommendations

Good quality, original research that could nevertheless benefit by broadening the aims. It is suggested to exploit the two systems (KO mice and ECs) more in parallel for the 2 transcription factors of interest would allow the group to solve the problems more efficiently (i.e. identification of transcriptional targets in vivo and in cell culture).

Team 13: Oncogenesis and immunotherapy

Team leader: M. Marc PIECHACZYK

- **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)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	5
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)	0.8	0.8
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	1
N7: Number of staff members with a HDR or a similar grade	4	4

- **Appreciation on the results**

The team has developped two distinct projects. The first one focused on the post-translational regulation of several members of the AP-1 transcription factor family, through phosphorylation, ubiquitylation, degradation and sumoylation mechanisms. By looking at their intermingled or antagonistic effects on AP-1 proteins dimerization, transcriptional activity and subcellular localization, the team have made pertinent and sometimes unexpected observations. The other project aims at understanding the immunomodulatory actions of monoclonal antibodies (mAb) in antiviral immunotherapies. This is a follow-up of previous findings of the team demonstrating that short immunotherapies with neutralizing mAb can induce a long-lasting antiviral immunity protecting infected animals on the long-term. This part of the project shows potential therapeutical opportunities and have resulted in several patent applications both in Europe and US.

During the last 4 years the team produced numerous (11) original publications in high quality journals (Oncogene, MCB, J.Virol). Most of them are signed by the group leader as last and/or corresponding author. They also produced one patent application. Three thesis and two HDRs were defended. One scientist was recruited at CNRS.

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

The group leader is frequently invited to give lectures at national and international meetings.

His reknown expertise has led to numerous participations in thesis and lab visiting comitees.

He is the former deputy Director and proposed future Director of the IGMM, strongly supported by his colleagues.

The team looks attractive for PhD students (3 thesis defended in the 200-2009 period) and Post-Docs. The team includes 5 staff scientists with permanent positions, one being recruited at CNRS in 2006.

The team was "labelled" by the LNCC during the 2005-2010 period. The group leader recurrently succeeded in highly competitive grant applications (ACI, ANR …).

The group leader is a member of several french scientific networks. Fruitful collaborations with foreign labs have been established (Germany, Spain, Italy US). The team also collaborates with several research groups in Montpellier.

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

The team displays a strong manpower, with half of the members holding permanent positions. This stability should prove useful considering the future responsabilities of the group leader, as head of the IGMM. Several members of the team are involved in teaching tasks, as well as in scientific animation, including workshop and meeting organization.

- **Appreciation on the project**

The team has a long-lasting and reknown experience in the field of protein degradation and post-translational modifications, which is acknowledged by numerous collaboration requests and publications. The projects appear funded and are ambitious, with potential therapeutical applications. Some aspects, such as the development of antibodies specific to sumoylated proteins, are particularly inovative. The ROS/SUMO/AP1 can be considered cutting edge. The existence of very distinct projects testifies the curiosity and the passion of the group leader, although the obvious disparity between both of them is not devoid of dispersal risk.

- **Conclusion :**

— Summary

This is an active and creative group, well-established in their fields of investigation. They develop two complementary approaches on transcriptional regulation and immunology and very strong internal collaborations.

— Strengths and opportunities

The team displays a strong manpower, with half of the members holding permanent positions.

The group leader shows dynamism and charisma, and seems appreciated by his colleagues at IGMM.

— Weaknesses and threats

The existence of obvious disparity between the distinct projects combined with the future responsabilities of the group leader are the obvious weknesses of this group.

— Recommendations

Given its strengths and past achievements, the team should attempt to reach an even higher level in terms of scientific production quality.

Team 14: Cell Cycle, transcription and cancer

Team leader: M. Claude SARDET

- **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)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	2
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)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	1
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

A group of five permanent scientists, supported by two post-docs and three graduate students working on the transcriptional and chromatin networks that control the cell cycle and cancer. Studies of this group are focused on the analysis of specific cell cycle control genes. In particular, the research deals with the understanding of the cellular function of E4F1. It was shown by this group that a connection of E4F1 and other cell cycle proteins such as p53 and pRB exists. In a publication in Cell (2006), the investigators reported on the fact that E4F1 is an atypical E3-ligase that modulates p53 function in a degradation independent manner. That was an important observation, which was also confirmed by other groups. High impact science in all three areas involving high level collaborations.

This group have a relatively small number of extremely high quality publications over the period. Primary work from the Sardet group at IGMM has resulted in 6 publications in journals such as Cell PNAS BMC bioinformatics, Oncogene, J Cell Biol, and EMBO reports. The group has been involved in a furhter 7 papers as junior authors or in collaborations published in Nat Cell Biol (2), JBC (2), FEBS letts. PLOS ONE and EMBO reports. Four theses over the period.

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

French prizes were won by three members of the group including the PI. International profile should be higher given quality of publications and range of collaborations. The committee feels that this group is too insular and orientated to French issues and institutions rather than internationally. No CSH, Keystone or FASEB meeting appear on the list for any member of the group.

Many grants end this year leaving only two funding work until 2011 or 2012. This might be a potential area of weakness.

The report provided good evidences of productive collaborations in France, Europe (inc. Israel) and the USA.

- **Appreciation on the project**

At present this group is focused on two major facets that are highly likely to result in publications.

1. Understanding of the physiological function of E4F1 in mammalian development with a focus on cell cycle control, cell survival, Redox balance, and mitrochondrial hemostatis. This direction is taking advantage of using a conditionally induced inactivation of E4F1 mouse. Using that model they were able to show that E4F1 is a key regulator in mitrochondrial hemostatis. Based on their published and unpublished data they propose very defined lines to continue with this direction.

2. Deciphering the control mediated by E4F1 on the cell environment and analysis and identification of specific target genes. This direction involves among others studying chromatin remodeling of the specific target genes as well as post-translation modifications of the specific encoded target proteins.

- **Conclusion :**

— Summary

This is a very productive group and published a number of important papers in leading journals. The group also established significant collaborations with other local and other groups in the world. This group is recognized as an important contributor in the p53 field.

— Strengths and opportunities

The group developed high level collaborations; focused questions; it displays an excellent track record.

— Weaknesses and threats

International recognition of this team should be improved. Participation to more seminar and conferences abroad is encouraged.

— Recommendations

More funding should be found.

Team 15 : Dynamics and control of chromosome replication

Team leader : M. Etienne SCHWOB

- **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	
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)	0.2	0.2
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	1	1

- **Appreciation on the results**

  - Relevance and originality of the research, quality and impact of the results

The group which is composed of eight people including two tenured CNRS researchers and one University assistant professor is addressing highly pertinent questions concerning DNA replication and genome stability outlined in the report. These are studied both in yeast and in the mouse in fibroblasts engineered to change G1 progression. The group has invested heavily in DNA molecular combing as an analytical tool for analysing chromosome replication and structure in single cells and outline approaches to allow both higher throughput and selection of particular regions of the genome for detailed analysis. Whilst this technology has the advantage of allowing single cell analysis it appears likely quite rapidly to be outflanked for many applications by sequence based applications which will also likely allow for zooming in on particular regions of the genome. Surprisingly little is said in the report/proposal about the technological advances/choices that may be implementable. Moreover, having established the technique of DNA combing the group appears to have become a little unfocused in its research, which is reflected in the dip in its primary publication record.

The output from this established group (5 publications in very good journals but only one with the PI as a senior author in MBC, 1 patent) has been somewhat disappointing and this is indirectly referred to in the report, like kids in a candy store , we opened many boxes, tasted the sweets but did not close many of the boxes. 3 PhD thesis were defended over the period.

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

The group leader is well known and respected for his work in the DNA replication field , notably as a collaborator who can contribute DNA combing to a project. He has also been awarded a prize by the Fondation pour la Recherche Médicale. The PI participates to the organization of national and international meetings and staff scientists are regularly invited for speaking in international meetings.

The ability of this group to get grants is reasonnable but only at a national level.

Having established a DNA combing facility this is now in demand by other researchers nationally and internationally. Accordingly, the PI developed fruitful international collaborations that gave rise to commun publications.

- **Appreciation on the project**

The group proposes three main projects. To deregulate G1 phase control and analyse the effect on DNA replication and genomic stability. To improve the DNA combing technique to be able to analyse DNA replication in single cells. To analyse how DNA replication patterns alter in differentiating cells, beginning with yeast and expanding this to mouse stem cells. These projects are all long-term and relevant to the remit of the Institute.

The project to analyse DNA replication patterns after deregulating G1 phase controls is very vague in its aim to identify the chronology of events leading to instability and aneuploidy, and somewhat naive in proposing to use transcritome analysis and time-lapse microscopy to pinpoint the source of aneuploidy. The proposal to characterise replication timing in differentiating yeast and in mouse stem cells is an interesting first step but it is unclear what is the aim beyond the initial description. The project to improve DNA combing with a view to analysing individual chromosome replication was the most concrete.

- **Conclusion :**

— Summary

This group has been too unfocused in the past and perhaps should focus even more than they have set out in this proposal.

— Strengths and opportunities

DNA combing is a powerful technique and the group are clearly leading experts in this.

— Weaknesses and threats

The group seems to lack a driving overall strategy at present, and there is a clear danger of becoming over-involved in contributing to other groups work through the combing facility. There is moreover a real danger that the rapid advances in sequencing technologies could lead to combing technologies losing part of their cutting edge advantages within the next two years to eclipse the DNA combing strength of the laboratory. A contingency plan needs to be developed and actively persued. Scientific production appears to have been insufficient over most of the period under review.

— Recommendations

To focus more on the question of how origin timing is regulated and how its deregulation is linked to genetic instability, and to prioritise the group’s research over collaborations to ensure improved scientific production.

Title of the team : Retroviral replication and pathogenesis

Name of the team or project leader : SITBON Marc (E16)

- **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)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

The team identified Glut1 as the HTLV receptor (Cell 2003). This story is remarkable, and of high impact and is mostly pursued by team 17.This discovery is at the basis of the present and future research project on interactions between virus envelope glycoprotein and cellular receptors, among which the RBD as metabolic markers is of great interest. The work is divided into 4 sub-projects:

1. Interactions retrovirus envelop / cellular receptors: using soluble receptor binding domain (RBD) of HTLV they clarify the interaction with Glut1. They develop a method to identify all possible HTLV env and show that like for other retrovirus, Env variants are under strong selective pressure. They identified BLV Env recept as a marker of activzated B and T lymphocytes.

2. They analyze the impact of retrovirus env on cell metabolism in collaboration with team 17. This is done by using the soluble RBD they developped. This molecule blocks the Glut1 receptor activity as a glucose transporter.

3. They analyze the molecular basis of retrovirus infection and transmission which could represent important therapeutic targets. They analyze two restriction factors (Fv1 and TRIM5alpha) through in vitro mutagenesis approaches to map the elements of the restriction. They initited a dual approach to identify co-factor of these restriction elements: 1) Co-Ip+spec mass and 2) genetic approach using hamster/human radiation hybrids+high resolution chrom. Mapping. They alreaddy identified cytoskeletal protein as candidate factors. They use mouse models of FMLV infection to test the antiviral potential of various compounds (collaboration with J. Tazi at IGMM and outside collaborations).

4. They search new human retroviruses by developping (patented) a method of PCR to amplify variable region of all HTLV genome. This technique is sensitive enough thet previously “seroindeterminate” patients were finaly ascribed to HTLV1 and 2. This represents a large part of their project in the future.

2 Outstanding publications through internal collaboration with team 17 (Cell 2008, 2009) were recently produced. Other publications (3.2/year) include 8 with 5.2<IF<10.4 and 6 with 2<IF<4.6. The output from the team 16 itself is somewhat lower.

This group also produced 2 patents in 2009 and 1 reagent distributed commercially by Abcys under CNRS-FIST licencing agreement

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

The PI received the Infectious Diseases award in 2001 and Contrat d'interface INSERM/Hopital 2005-10). He also received a Research visiting professor award (Canada, 2009), a visiting expert scientist NCI (2009). Jean-Luc Battini, a senior scientist in the group, received the FRM-Line Renaud award in 2005.

An average paticipation in meetings was mentioned with 9 invited speakers at international meetings

And 11 international seminar invitations.

3 INSERM/CNRS scientist were recruited over the past 4 years (2006,06,09) whereas 3 PhD (2005,06,007) were trained as well as 5 PostDoc and 4 undergraduates students

The ability to raise fund is good with grants from AFM 2005-2006, ANRS (with team17) 2005-2006, Japanese Health Science found 2005-2010, ANR young scientist 2006-2008, ANRS 2006-2008, ANRS 2006-2010, SIDACTION 2008-2010, ARC 2009-2010

One can note an Interesting lead to explore Env RBDs as potential metbolic biomarkers, with perspective of a possible spin-off.

- **Appreciation on the project**

The projects as they appear in the document are focus on two main questions:

1. The impact of Glut1 and other receptors for retrovirus on cell metabolism with the idea that glucose metabolism has a major role in cancer developement. As a first step to understand this issue, the AKT pathway will be analyzed. These studies will be done by using the solubel HRBD reagent they developped. They are developping a library of RBD from other mammalian retrovirus Env to try to identify new receptors. They will concentrate (through a functional screen) on those that alter cell metabolism.

2. They develop a large program aimed at identifying new human retroviruses by utilizing their sensitive PCR approach on "seroindeterminate" patients. They chose to analyze pediatric patients presenting various idiopathic infectious diseases. This is a large collaborative project that involves a deep sequencing strategy.

Many of the proposed projects are at the stage of "screen" (risky) and one may question the capacity of the team to make a mark in some of these very competitive areas. Some of the projects seem merely superficial diversions from more novel and inventive lines of research. RBDs as potential metabolic markers stand out, although this project is still at a very early stage.

- **Conclusion :**

— Summary

The HTLV receptor/Glut1 story was a real coup, which led to a very nicely productive line of research in collaboration with group 17 who took the lead now on this project. The RBD/metabolism project is interesting and illustrative of the PI's inventiveness, but it is still at a very early stage. Other projects of the team (TRIM5 project, search for new retroviruses) seem somehow too superficial a style to have major impacts in areas of high competitiveness or in fields that have been worked over for a long time.

— Strengths and opportunities

The group has a clear creative potential and developed and nice synergy with the group 17.

— Weaknesses and threats

Overdilution and overly superficial approach to several projects.

— Recommendations

The PI should focus and impose the lab's mark on clearly defined cutting-edge projects.

Team 17 : Immunomodulation and immunotherapy

Team leader : Ms. Naomi TAYLOR

- **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)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3.8	3.8
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0.5	0.5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	
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	3

- **Appreciation on the results**

This team presents a solid work in the area of T cell development, and high impact story in collaboration with the previous team (16) on Glut1 biology. The projetcs involve three major themes:

1) Improving gene and cellular therapy for immunodeficiencies, taking the defect in ZAP-70 as a model both in man and mouse. The idea is to deliver gene and/or corrected cells directly into the thymus. They show that intrathymic injection but not iv injection of wt HSC can reconstitute non irradiated ZAP70 deficient host. They try to directly inject ZAP70 gene into the thymus using AAV as vehicule. As a more basic research project, they analyze the role of ZAP70, in particular the effect of ectopic ZAP expression, during T cell differenciation.

2) They described in col Glut1 as the receptor for HTLV1 and found that Glut1 is a marker of a unique subset of Double positive thymocytes. They also analyzed the role of Glut1 during erythropoeisis as Glut1 expression is the highest in human erythrocytes but not in other mammals including mice. They link this observation to defective vitamin C synthesis.

3) They analyze T cell homeostasis in condition of lymphopenia in the context of anti-tumor immune response to define conditionning regimens that would improve homeostasis if transferred T cells.They already noted a major difference between irradiation or Busulfan/cyclophosphamide induced lymphopenia. Using an insulin Promoter-HA Tg model, they show that induction of autoreactive CD8 T cells under lymphopenic conditions (irradiation) requ!ire Ag specific CD4 T cell help.

The list of publications is very good : 2 Cell (2008, 2009), 3 PNAS (2008, 2x2005), 3 Blood (2x2008, 2007) and others.

The team developed 2 Industrial partnerships with Cytheris (Paris, France) for rIL7 for clinical use and Xcyte/Invitrogene for CD3/CD28 beads for T cell expension.

They also establish a nicely stable and productive partnership with team 16.

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

The PI has a good international visibility with the organization of 4 meetings: Global Thymus network, ROLDUC thymus/T cell workshop (Netherlands 2007), RIMO New therapies Workshop (Montpelliezr 2006), T cell homeostasis (Montpellier 2006) and 15 invitations to international scientific metings (2 session chairman)

The ability of the team to attract high level scientists is very good as attested by 5 students who obtained their PhD Thesis between 2006 and 2009, 2 HDR in 20072 recruitments (CR2 in 2005 and IE in 2007), 4 PostDocs, more than 10 M.Sc. and undergraduase from France and foreign countries

This team displays a very good abilty to raise funds from national and international sources : NIH RO1 award (2007-11), European FP6 (2005-10), European FP6 reintegration grants, European FP7 international training network (2009-13), French grants: ANRS, Sidaction, AFM, ARC, PHRC

However the participation in networks/collaborations is modest. The PI is board member for European Society of Gene Therapy, European Society of Immunodeficiencies and Thymus Network.

- **Appreciation on the project**

The projects cover a wide array thematics, from basic biology of T cell development to their participation in anti-tumoral immunity, and from vitD metabolism to gene therapy of immunodeficiencies. A delicate equilibrium, which is so far managed with success. These various projects are in the continuity of the already obtained results

find conditions to improve thymic gene transfer in vivo

Continue to study human T cell based immunodeficient patients, and pursue the study on ZAP-70 in pathological conditions (B-CLL)

adressing the role of GLUT1/GLUT4 in hematopoietic cell differentiation.

Optimization of anti-self tumor Ag responses in lymphopenic conditions

Altogether these various projects may appear a little bit disperse but given the scientific quality of the team and the “critical mass” this should not represent a problem.

The Glut 1 story is a coup, which the PI nicely follows up on by examining the role of metabolism in thymopoiesis and hematopoiesis, a highly original line or research. Takes the overall record from good to excellent !

- **Conclusion :**

  - Summary

This is a very active team with an excellent momentum, which nicely manages to give a strong body to what looks at first like a thinly spread portfolio. The group leader should be given high marks for the success of her operation !

  - Strengths and opportunities

Solidity of the group leader, acuity of Glut1 project

— Weaknesses and threats

Risk of over-dilution. Lack of space

— Recommendations

The strategic priorities should be defined more clearly. This team should greatly benefit from the arrival of the new team to analyze the impact of metabolism (Glut1 story) on lymphocyte developement and maturation

Team 18 : Metazoan messenger RNA metabolism

Laboratoire coopératif SPLICOS Therapeutics

Team leader : M. Jamal TAZI

- **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)	3	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

Research by this lab focuses on gene expression in the context of development as well as health and disease. Major themes include how SR proteins govern alternative pre-mRNA splicing regulation and genome stability; in addition, how mRNPs are released from sites of transcription and subsequently regulated in the cytoplasm is investigated. As model systems, the lab exploits human cell lines, the mouse, and Drosophila melanogaster. Major accomplishments in the recent period include 1) Identification of endogenous RNA targets of SR proteins in vivo, an elusive and important challenge to the field. 2) Discovery that interactions between SR proteins and DNA topoisomerase I link DNA replication, transcription, and splicing. 3) Identification of several classes of chemical inhibitors of splicing, including the recent demonstration that some inhibitors could be effective against retroviral pathogenesis. Two ambitious projects – one investigating the role of SR proteins in promoting exon definition by the spliceosome in normal and human disease-associated alleles, and one investigating how mRNP-rich cytoplasmic stress granules participate in neuronal signaling and plasticity – are coming to fruition. The proposed future work is a logical extension of these projects, seems feasible and important.

It's an highly original research program, contributing novel insights into gene expression and genome stability by determining the activities of SR proteins and DNA topoisomerase I. Studies of pre-mRNA splicing in vitro and in vivo have relevance to human disease and are enhanced by chemical screening, interactions with clinicians, and the use of model organisms (mouse and fly). The findings, made through high quality analysis, are published in high impact journals and influence the field greatly. This is also obvious from the number of invitations to speak at top institutions and meetings.

The production of the group is excellent, with 5 patents and 20 publications (most of which in highly ranked international journals). Many efforts are also made towards diffusion of science to non-scientific communities. 4 PhD students have graduated within the period and 4 new students are preparing a PhD.

The group leader of theis team is one of the founder and one of the scientific advsiers of « Splicos », a biotech company created in 2008. He is also the scientific supervisor of Splicos therapeutics, a new cooperative laboratory aiming at drug discovery, created jointly between Splicos, CNRS, INSERM, Université Montpellier I, II.

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

The group leader has co-organized a Jacques Monod Conference in 2005 on Alternative splicing and diseases, as well as 4 workshops linked to EURASNET. He has been invited as speaker to a large number of conferences and seminars at national and mostly international level.

The PI was awarded the "Prix Grallet-Breton de l'Académie de Médecine" in 2006.

The ability to recruit high levels scientists is excellent. The size of the group is expanding. 3 post-Docs and 4 PhD students joined recently.

The ability to attract numerous french as well as european funds appears excellent. Establishment of the start-up company Splicos Therapeutics is likely a good way to advance the chemical screens and provide a future for the development and distribution of chemical inhibitors of medical relevance.

The PI is a member of European Network on Alternative Splicing « EURASNET » 2006-2011, and the leader of a WP « Chemical Biology . Investigator in FP6 network EURASNET has yielded productive collaborations and provided funds. The PI is also a Coordinator of European Associated Laboratory on Alternative splicing, proteome diversity and diseases (2008-2012).

- **Appreciation on the project**

Two ambitious projects – one investigating the role of SR proteins in promoting exon definition by the spliceosome in normal and human disease-associated alleles, and one investigating how mRNP-rich cytoplasmic stress granules participate in neuronal signaling and plasticity – are coming to fruition. The proposed future work is a logical extension of these projects, seems feasible and important.

- **Conclusion :**

— Summary

This group performs very well. It is solid and its projects are feasible and important. Strong implication of the group leader in teaching duties and in setting-up the start-up company are especially valuable.

— Strengths and opportunities

The strength of the research program is the combination of in vivo and in vitro approaches to gene expression. Of particular importance is the exploitation of a genetic model system (fly) and the continual reference to disease relevance of splicing regulation. PI's interactions with clinicians is exceptional and noteworthy; this has perhaps led to his important status as a spokesperson to the public. PI's performance in communicating science to the public is examplary. The brave move to screening chemical compounds in vivo and in vitro is also a strength, creating the potential for drug-discovery and forming the basis of the start-up complany Splicos Therapeutics. This multi-disciplinary approach places this group leader in a unique position in the international research scene.

— Recommendations

It was recommanded that the PI applies to Institut Universitaire de France, to be able to devote more of his time to research, should he wish.

Team 19 : Metabolism and cancer

Team leader: M. Lluis FAJAS-COLL

- **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)		
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	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
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	2	2

- **Appreciation on the results**

  - Relevance and originality of the research, quality and impact of the results

The team is presently located at the IRCM (Institut de Cancérologie de Montpellier). This team displays an outstanding level of scientific production for these last 4 years, thanks to the development of a forefront research characterized by a strong conceptual originality.

The topic of research if this group, metabolism and cancer, is recently being investigated in many top labs around the world. Warburg's concept put forward by him in the late 1920's, that cancer and metabolism are linked, is now being re-addressed through molecular approaches. It is well accepted today that facilitated metabolism in cancer cell at its different levels (glucose metabolism, fatty acid metabolism, amino acid metabolism) are all modified in cancer cell. This team is taking the molecular biology approach to resolve the possible cross talk between metabolism and cell cycle control. They have already shown in a number of studies, the involvement of cell cycle controlling genes such as E2F1, cdk-4 and cycD3 in the regulation of metabolism in fat cells and in ¤ cells. Their working hypothesis is that cell cycle control and metabolism are inter-connected by feedback loop mechanisms. They base their theory on the fact that they showed that cancer cells exhibit stable metabolic alterations, along with defined deregulations in cell cycle.

Among others, one should mention the identification of previously unknown functions of both the cdk4-pRB-E2F1 and CXCL5 pathways in the regulation of cell metabolism.

By demonstrating that the different mechanisms and partners identified also operate in normal cells, the recent findings of the team furthermore impact on other metabolic diseases such as diabetes and obesity, with potential therapeutical opportunities.

The team displays an impressive record publication (Cell Metabolism, Nat.Cell.Biol., MCB, …) during the last 4 years period and 2 patent applications.

Three thesis and one HDRs have been defended. One staff scientist was recruited at INSERM.

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

The group leader was promoted to DR1 position in 2009 and is frequently invited to give lectures at international meetings abroad.

The team is obviously attractive for Post-Docs (7 recruitments since 2004) including from abroad. It also recruited one staff scientist (permanent position) at INSERM. The team looks dynamic with an important turnover of PhD students and Post-docs. The two staff scientists are involved in grant applications, and participate to PhD supervision, invited seminars and meetings.

The team was labelled "AVENIR" by INSERM during the 2002-2006 period and labelled "FRM team" since 2007. The group leader regularly succeeds in highly competitive grant applications (INCa, ANR, FRM …).

The team already collaborates with research groups at IGMM. Fruitful collaborations have also been established with foreign labs (Spain, Denmark, Switzerland, US). The group leader is the coordinator of a french-catalunya network.

- **Appreciation on the project**

In their proposal they are outlining very simple and forthright experiments that are aimed at elucidating such a mechanism. The proposed model they suggest is very much based on their previously publish data that was also validated by other published studies. In particular, they will focus on the insulin pathways, the cdk4-pRB-E2F1 involvement of CXCL4 in metabolism with particular emphasis on Jak2/STAT5/SOCS2 pathway. They will also focus on the direct involvement of oncogenes such as Ras and wnt, in the regulation of fatty acid metabolism.The team projects will continue to characterize the molecular mechanisms that mediate the integration of metabolic control and oncogenesis. They also aim at identifying and validating new metabolic targets implicated in cancer progression. The team will further use top-notch experimental approaches (tissue ChIP, Chip-Seq, Mass spec, knockout animal models…) to develop these ambitious cutting-edge projects, which are funded by consistent grants.

- **Conclusion :**

— Summary

This team proved efficient in performing an outstanding research, comparable with that of the very best research groups at IGMM. A very productive group investigating one of the cutting edge subjects in cancer research in a very successful way. The recruitment of this group leader who is an excellent top scientist is very beneficial to the IGMM. This will upgrade an important facet of cancer and metabolism that is one of the most cutting age topics in cancer research at large

— Strengths and opportunities

The arrival of this team will certainly represent a very important added value and strong asset for the IGMM.

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: INTRACELLULAR RNA TRAFFICKING

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: NUCLEAR ONCOGENES AND CELL CYCLE EFFECTORS

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	A	non noté	C

Team 3: ASSEMBLY AND TRAFFIC OF RIBONUCLEOPROTEINS

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: MECHANISM OF NEURONAL DEATH

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	C	B	non noté	A

Team 5: GENOMIC IMPRINTING AND DEVELOPMENT

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: PHOSPHORYLATION CONTROL OF THE VERTEBRATE CELL CYCLE

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 7: POST-TRANSCRIPTIONAL MECHANISM AND EPIGENETIC CONTROL OF GENE EXPRESSION IN MAMMAL

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 8: THE BIOLOGY OF TUMOR NECROSIS FACTOR (TNF) FAMILY MEMBERS

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

Team 9: APOPTOSIS AND HEPATIC CARCINOGENESIS

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: ADENOVIRIDAE : RECEPTORS, TRAFFICKING & VECTOROLOGY

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: CONTROL OF PHYSIOLOGICAL AND PATHOLOGICAL ANGIOGENESIS

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 13: ONCOGENESIS AND IMMUNOTHERAPY

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 14: CELL CYCLE, TRANSCRIPTION AND CANCER

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 15: DYNAMICS AND CONTROL OF CHROMOSOME REPLICATION

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	A	non noté	B

Team 16: RETROVIRAL REPLICATION AND PATHOGENESIS

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 17: IMMUNOMODULATION AND IMMUNOTHERAPY

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 18: METAZOAN MESSENGER RNA METABOLISM

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 19: METABOLISM AND CANCER

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 MONTPELLIER 2
SCIENCES ET TECHNIQUES

La Présidente

Montpellier, le 30 mars 2010

Monsieur Pierre GLORIEUX
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Monsieur le Directeur,

Je m'associe aux remerciements formulés par la direction de "**l'Institut de Génétique Moléculaire de Montpellier (IGMM)**" pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise.

Comme nombre d'autres sites universitaires en France, le site de Montpellier est en cours d'évolution avec la récente création d'un pôle de recherche et d'enseignement supérieur (PRES), ayant deux missions essentielles : accompagner les trois universités montpelliéraines dans un processus de fusion et assurer la mise œuvre de l'opération Campus.

Dans le respect de nos engagements, cette évolution s'est traduite récemment au sein de l'Université Montpellier 2 par la création de Pôles de Formation et de Recherche (PFR) permettant d'accroître la visibilité de notre activité scientifique à l'échelle nationale et internationale.

Le PFR Biologie-Santé, auquel l'IGMM est rattaché, est l'un des cinq PFR créés par l'Université Montpellier 2 qui ont pour missions :

- de promouvoir l'excellence de la formation, de la recherche, de l'innovation et de la culture scientifique sur les champs thématiques qu'il porte, d'en renforcer la visibilité internationale et d'organiser les interdisciplinarités en interne et avec les autres PFR;
- de promouvoir la mise en cohérence des politiques de formation et de recherche en son sein ;
- de mutualiser en son sein, les plateaux techniques, les ressources documentaires, mais aussi d'harmoniser les services en charge de la communication, des relations internationales et de la valorisation, des structures de recherche impliquées dans le pôle, dans le cadre de la politique de l'établissement;
- de fournir aux services centraux de l'établissement les données pertinentes en matière de formation et de recherche, mais également d'insertion, de valorisation, et de gestion des ressources humaines, nécessaires au pilotage de l'établissement en matière de politique pédagogique et scientifique.

1809-2009
Bicentenaire de l'UM2

Il est bien évident que la relocalisation de cette unité dans un nouveau bâtiment (dont la construction touche à son terme), sur le site du CNRS, à proximité d'autres laboratoires de biologie (CRBM, CPBS), constitue une réelle opportunité pour l'IGMM d'accroitre sa visibilité et son attractivité. L'Université Montpellier 2 accompagnera, dans la mesure de ses moyens, l'IGMM dans cette évolution.

En réponse au comité d'expertise, nous souhaitons préciser qu'un effort particulièrement significatif a été récemment réalisé par notre établissement en soutien à ce laboratoire par l'affichage, dans le cadre de la campagne d'emplois 2010, d'un support de Maître de conférences (Virologie, équipe IGMM E9, U. Hibner) et d'un support de Professeur (Immunologie-Infectieuse, ouvert sur trois laboratoires dont l'IGMM).

Enfin, il faut également noter que notre établissement contribue par une importante allocation de moyens (fonctionnement, équipement, personnel) à l'activité de plateformes technologiques et structures fédératives (ex-IFR) du domaine scientifique concerné. A ce titre, l'Université Montpellier 2 assurera, comme il le fait aujourd'hui, les coûts associés à l'infrastructure, la maintenance et les moyens en personnels (5 BIATOSS à ce jour) aux animaleries conventionnelles et de sécurité A3/L3, localisées sur son site universitaire du Triolet et qui appartiennent au réseau des animaleries montpelliéraines (RAM).

Je vous prie d'agréer, Monsieur le Directeur, l'expression de mes respectueuses salutations.

Danièle HÉRIN
Présidente de l'université Montpellier 2

Institut Génétique Moléculaire Montpellier
Directeur : Jean-Marie BLANCHARD

Montpellier March 22nd 2010

Object : *Response of the Director to the evaluation committee*

We thank the evaluation committee for the excellent work performed in such a small amount of time especially as respect to the size of our laboratory and the complexity of its structure. We do think that the critiques will help us to get better in our scientific output and, to rephrase one of the major comments of the committee, we will continue to improve IGMM production in such a way that it will be considered even better at any international standards in the future.

However, since this report is going to be made public we feel it necessary to correct some misunderstandings. Even though the report has rightly pointed out some of the strengths and weaknesses of the groups, there are several points we think unveil some aspects of IGMM that escaped the attention of our committee. We should also point out that some indicators have also evolved between the six months period separating the closure of our AERES dossier and the site visit.

I- With respect to the overall appreciation on the research unit three comments should be reassessed in the "weaknesses and threats" chapter:

1)"Some vulnerable junior PI would benefit from tight mentoring…as well as to solve internal lab problems"
While we agree on this very constructive point, we would like to point out that the director devotes 5 hours a week to working with one of the groups of the institute, listening to their work in progress and discussing difficulties encountered in order to help them solve various problems. When necessary, the deputy Director is also present. Moreover, specific meetings with PIs are held when critical problems occur, leading to constructive decisions and solutions.

2) *"The internal culture of the institute (allocation of space and technical support) makes it difficult to reward groups according to scientific merit"*
On one hand, the IGMM policy has always been to share all facilities on an equal basis and provide all PIs with free and open access to all of the operational structures. IGMM pays for all major expenditures and groups are heavily supported at the level of the common facilities. This last point has been accepted by all PIs in the institute since it is a prerequisite to join IGMM and one of our major strength. The tempo of basic research is not that of productivity and very often, risky projects require an apparent outrageous unproductive time that might be perceived as undue, but is for us the essence of science. We think that those to be helped are emerging groups as well as groups experiencing new avenues, which, in the current system, have difficulties in obtaining decent funding.
On the other hand, it should be stressed that the French system does not provide the Director with many possibilities to carry out a merit-based support of successful groups or individuals. However, the Director has resorted to two incentives to successfully carry out his scientific strategy:
i) The space allotted to groups at IGMM is not fixed and has varied according to their scientific development. Whereas the standard space allotted to a group is 1 module (roughly

60 m^2), two leading groups (E17 & E18) have 1.5 modules. Moreover, very recently the E18 group has been allotted with an extra module to allow the development of the *Splicos* associated laboratory. Along the same line, two junior PIs (E4 & E6) who shared 1 module during the previous mandate, have benefited from a full module when they succeeded in obtaining an ATIP and AVENIR grant respectively. As a counter example, the E2 group that had the benefit of 2 modules prior to the nomination of its PI as Director of IGMM reduced its scientific activity and accordingly, restituted 1 module to the community.
ii) IGMM has supported the installation of one group (E5) as well as specific technological investments made by two other groups (E13 & E16) through the transient recruitment of research assistants. More recently, the E6 and E17 groups were allotted tenured research assistants for development and technological advancement. I would like to point out that research assistants are not definitively associated to specific groups and in the past, several have switched from one group to another (E17 to E2, E12 to E6, E7 to E9)

3) *"The number of PhD students has decreased from the previous period, suggesting that strengthening the life and visibility of the PhD students could improve the rate of future recruitments"*
This remark probably stems from the fact that our report was not clear enough. If we refer to the exact numbers:
As of 1/10/2005: 35 PhD students; 22 PhD defenses during the 1/10/2001-1/10/2005 period; 25 staff scientists with an HDR.
As of 30/06/2009: 38 PhD students, 40 PhD defenses during the 1/01/2005-30/06/2009 period; 35 staff scientists with an HDR.
With respect to the international visibility of students, IGMM is involved in an Initial Training Network (ITN) that started in November 2009 bringing together 16 different European laboratories (ATTRACT). Moreover, IGMM has applied to several other ITN devoted to "RNP", "Metabolic control of cell proliferation", "Adenovirus biology", "Ubiquitin proteasome system", etc…

With respect to the "Specific comments on the research unit" the committee felt that the "*representation/presence of the most successful groups at international conferences did not necessarily match the quality of their publications*".

Whereas this is likely true for junior PIs, this comment is surprising for several senior PIs; just to take two examples: E11 and E17 groups.

For the E11 group it is stated in the appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners, that :
"The number of invitations to international conferences and symposia is not as prominent as would be expected from the publication records. No foreign members seem to belong to this lab"
This comment is due in part from the fact that some indicators were omitted from the dossier. Amongst the 28 invitations of group E11 members during the considered period we note 7 invitations for the PI, 9 for the staff members (with 2 for a PhD student).
With respect to the second sentence, it should be noted that the PI is American, the two CR1s (HW 2005-2008 and VK 2005 – 2009) are German and Australian respectively, and have very recently left the lab to start their own groups. HW post-doc'd in at Scripps before joining

this group, then applied for and obtained the CR1 position. Master students from Germany, Poland and Spain have trained in the lab from 2005- 2009. Seven PhD students from collaborating labs (Spanish, Australian, American, UK, Portuguese) spent time (from 1 to 8 months) in the lab during this period. The group is currently hosting a Professor from the University of Liepzig (Johannes Schwarz) for a one year sabbatical. In 2009, Pr David Curiel Director of the Gene Therapy Centre at the University of Alabama-Birmingham (USA) asked to pass a sabbatical year in this lab in 2010.

Similarly, for E17 group and in the same item, it is stated: *" however, the participation in networks/collaborations is modest "*
If we limit the calculation to meetings outside France, the PI of this group has been a chairperson in at least 6 international meetings since 2005 (Kyoto Thymus Conference-2009; Cellular Therapy of Cancer, Milan-2009; ESGCT, Brugge-2008, ESID, Herzengenbosch-2008; Cancer Therapy, Manchester-2006; ESGCT, Prague-2005). With respect to networks the PI is a WP leader in WP6 integrated project (ATTACK, 18 teams) where she leads 10 international teams; she is a WP leader in a WP7 international training grant (ATTRACT; 14 teams) as well as in a newly submitted Network of Excellence Proposal (ClinAct). JH in the same group is a partner in another EU FEDER grant, SUDOE.
This PI has been at the leadership (directory board) of 2 European Societies (ESGCT and ESID) and has helped forming the recent Global Thymus Network (see article in Trends in Immunology; Yokahama et al., 2009 (30:191-192). She was invited by Al Singer to be a guest scientist in his prestigious Experimental Immunology Branch at the NCI (NIH) between 2008 and 2009 and the NCI requested that she maintains an honorary appointment (and an active collaboration).

Similar comments for groups E1, E5, E18….

II- Other specific comments on groups

p18, E6 : ***"****Lastly the group intends to develop inhibitors and solve its crystal structure, which is clearly outside the current expertise of the group. The intention to expand into several new areas, eg: transgenic mice, protein crystallisation, screening for kinase inhibitors, and analysis in DT40 cells, is a risk because many of these are highly labour-intensive. Good collaborations will be essential to pursue all these areas, and realistically not all these avenues should be pursued with the size of the current group".*

The group does not intend to develop inhibitors or solve the crystal structures themselves, but are collaborating with excellent groups who will undertake this work. *idem* for the second point, they do not intend to perform analyses in DT40 cells: as mentioned in the report, this work is being conducted by a collaborator.

p19, E7: It is stated in the report that "*There is no evidence for any ongoing internal collaborations particularly with E5*".

This is incorrect. This group has daily interactions with the E5 group On an outside level, this is most elegantly shown by the fact that the PI of group E5 is a major partner in an important

grant coordinated by a member of the E7 group. The group also collaborates with the E13 group.

p 23, E8: *"The two projects on APRIL are rather descriptive and involve expertises which are not yet available in the group."*

The respective mouse models are already established in the group, as described in the scientific report and explained during the oral presentation.

p 23, E9: *"The team is not numerous enough at present and should reinforce its manpower"*.

Team 9 has recently recruited an additional post-doctoral fellow and is in the process of recruiting a researcher with teaching activities (*Maître de conférence*). This should ensure sufficient manpower to carry out the team's projects.

p 26, E11: "*Applied aspects are interesting, but it is not clear whether the group should redirect a too important part of its efforts towards the development of models of CNS diseases and their treatment, an area in which the PI might not have a significant leadership"*.

The paradox that this comment creates is interesting. The first comment/question from the committee following the PI's expose was that his lab has "the reputation of being a gene therapy lab (i.e. applied research), but that his current work was more about fundamental research projects." This group will continue to concentrate >50% of its manpower on its "new found" fundamental strengths.
Yet, we would argue that applied research should be, and is, made up of the nuts and bolts of fundamental projects. It is also clear that if this group doesn't take the initiative to demonstrate the potential of CAV-2 vectors, no one else will. The advantages that this vector platform could have in the clinic will be buried by more proactive colleagues. Therefore, leading the development of models of CNS diseases and their treatment is a bane that the PI initiated several years ago and will (gladly) pass on to his colleagues when enough momentum has taken hold.

p 31, E14: The comments of the review committee on this team concern only project 1 on E4F1. The report does not mention their second project on the role of lysine and arginine methyltransferases (PR-Set7/H4K20me, PRMT5/COPR5 complex) in the control of cell proliferation and differentiation, despite the fact this project was clearly and extensively described in the AERES application form and during the oral presentation. We want to stress that this second project is supported by ongoing grants, has already led to several publications (J. Cell Biol, EMBO Rep, PNAS) and involves 50% of team members.

p33, E15: *"Whilst this technology has the advantage of allowing single cell analysis, it appears likely quite rapidly to be outflanked for many applications by sequence based applications"*.

Arguing that single-molecule analyses of DNA replication (using DNA combing) will rapidly be outflanked by sequencing technologies is ignoring the fact that origin firing is stochastic, which means that each cell uses a different set of origins, something that is completely masked by population-based approaches such as sequencing. Replication parameters of the utmost importance for genome stability, such as cellular origin density and fork progression

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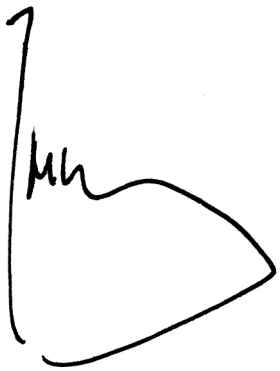
rates, are accessible only through single-molecule approaches.
The report, based on the recent publication record of the group, gives the wrong impression that it is mostly providing technical expertise to collaborators. This is ignoring the important work that is currently being carried out in this lab, focusing on the study of replication dynamics and genome instability, for which manuscripts have been written-up or submitted.
Little or no mention was made of the structuring role of this group in the development of cutting edge replication analysis tools which have been made available to the broader local community working on DNA replication, increasing the group's international visibility and competitiveness. Given the number of groups worldwide who wants to collaborate with E15 (most of them are actually turned down), DNA combing has not been eclipsed by other technologies and the group is in a good position to make important scientific contributions.

Jean Marie Blanchard
Director



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