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

Department for the evaluation of research units

AERES report on unit:

Institute of Molecular Genetics of Montpellier

IGMM

Under the supervision of the following institutions and research bodies:

Nouvelle Université de Montpellier

Centre National de la Recherche Scientifique - CNRS

January 2014

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr Moshe YANIV, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.
The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Institute of Molecular Genetics of Montpellier
Unit acronym:	IGMM
Label requested:	UMR
Present no.:	UMR 5535
Name of Director (2013-2014):	Mr Marc PIECHACZYK
Name of Project Leader (2015-2019):	Mr Marc PIECHACZYK

Expert committee members

Chair: Mr Moshe YANIV, CNRS, Institut Pasteur

Experts:

Mr François-Loic COSSET, CNRS, Lyon

Ms Magali FRUGIER, Université de Strasbourg (Representative of CNU)

Mr Olivier JEAN-JEAN, CNRS, (Representative of CoNRS)

Mr Saadi KHOCHBIN, CNRS, Grenoble

Mr Tomi MAKELA, Institute of Biotechnology, Helsinki, Finland

Mr Michael H. MALIM, King's College London, United Kingdom

Mr Marcos MALUMBRES, CNIO, Madrid, Spain

Mr Seamus MARTIN, Trinity College, Dublin, Ireland

Mr Nicholas PROUDFOOT, Oxford University, United Kingdom

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Scientific delegate representing the AERES:

Mr Jean-Antoine LEPESANT

Representatives of the unit's supervising institutions and bodies:

Mr Olivier COUX (Representative of Doctoral School CBS2)

Mr Bernard GODELLE, Université de Montpellier 2

Mr Thierry GRANGE, INSB

Mr Jacques MERCIER, Université de Montpellier 1

1 • Introduction

History and geographical location of the unit

IGMM celebrated its 20th anniversary in 2013. It was founded by Mr Philippe JEANTEUR who was, at that time, Professor at the University of Sciences of Montpellier and director of the Biochemistry Unit of the Cancer Center of Montpellier (Paul Lamarque and then Val d'Aurelle Cancer Center), presently Montpellier Cancer Institute or ICM. Jean-Marie Blanchard, CNRS DR1, took over the directorship of IGMM from Mr Philippe JEANTEUR from 2003 until 2010. Mr Marc PIECHACZYK, CNRS DR1, became the director of IGMM in 2011 after having been its deputy director for 6 years under Jean-Marie Blanchard.

IGMM is located on the historical Montpellier CNRS campus of the "Route de Mende" which is close to the University of Sciences of Montpellier (UM2). IGMM (4,000 m2 + a recently opened animal facility of 700 m2) is physically connected to its neighboring partner Institutes, with whom it shares numerous research programs and technological platforms. These laboratories are the Center for Research in Macromolecular Biochemistry (CRBM; www.crbm.cnrs.fr; Dir: Anne DEBANT) and the Center for Studies of Pathogens and Biotechnology for Health (CPBS; www.cpbs.cnrs.fr; Dir. Christian DEVAUX). These institutes have an expertise complementary to those of IGMM in cell biology and infectiology, respectively. Currently, 450 people work in the three institutes, which constitute an exceptional intellectual and technological environment. Importantly, one major reason for the construction of IGMM on the "Route de Mende CNRS campus" was its long-standing collaborations with CRBM in the fields of cell cycle and cancer.

With the prospects of the opening of the new CRBM and CPBS at the beginning of 2011, the 3 institutes decided to mutualize their support services. These include (i) a logistical and workshop service, (ii) an electronic service (SEM), (iii) a computer service (hardware and network) (SI2C2), (iii) a shop, (iv) a web delegate and (v) a communications delegate.

The IGMM is also within walking distance or short drive from several other Institutes including IGH, IGF, the Cancer centre as well as the university labs.

Management team

The IGMM is directed currently by Mr Marc PIECHACZYK who has been previously deputy director for 6 years. He is assisted by a full time deputy director, and an administrator.

Internal consultations are held at three levels: a non-statutory restricted scientific board consisting of three senior scientists that advise the director on important issues for the life of the Institute, the Group Leaders Council that meets to discuss predominantly scientific issues and the Laboratory Council that meets at least three times a year to discuss issues related to the internal functioning of the Institute.The decision to pool together resources at the CNRS campus and all over the Montpellier life science community is an excellent step forward to pool forces and means together however it generates a considerable burden for the director and team leaders who are taking part in supervising common facilities, in coordination committees, etc.

AERES nomenclature

SVE1 LS XXLS1, LS2, LS3

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	6	6
N2: Permanent researchers from Institutions and similar positions	51	46
N3: Other permanent staff (without research duties)	28	29
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	28	
N6: Other contractual staff (without research duties)	22	
TOTAL N1 to N6	**135**	**81**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	38	
Theses defended	42	
Postdoctoral students having spent at least 12 months in the unit	19	
Number of Research Supervisor Qualifications (HDR) taken	7	
Qualified research supervisors (with an HDR) or similar positions	29	37

2 • Overall assessment of the unit

The Institute of Molecular Genetics of Montpellier (IGMM) is one of the leading biological research institutes in France. It groups around 230 scientists, students, technical and administrative staff in 19 research teams. The research programms span from curiosity-driven investigations in molecular and cell biology to health-oriented research involving cancer biology, gene therapy of immune deficiencies or lysosomal storage disorders, research on HIV growth inhibitors, inflammation and immune protection. The publication output is excellent to outstanding with a considerable number of publications in the most prestigious international journals.

During the years the IGMM attracted a considerable number of foreign principal investigators and became a really international institute. This is also reflected in the recruitment of students and postdoctoral fellows.

A considerable number of the scientists trained at the Institute got permanent positions at CNRS, INSERM, University, Biotechnological and Pharmaceutical companies or abroad. A number of junior scientists got group leader positions in France or elsewhere and senior principal investigators disseminated in Montpellier or elsewhere.

IGMM teams have also jumped the gap between research and application and created three biotechnology companies to exploit ideas and preliminary results obtained by its scientists. Others have intensive collaborations with the clinics and several of its scientists have medical school or hospital positions.

Finally, the Institute was at the basis of an effort to regroup technical platforms at the site and in the city. The Institute faces difficult staff and financial problems even though its scientists were very successful in securing national and international funding.

Strengths and opportunities related to the context

The IGMM is an extremely dynamic Institute that is constantly adapting to the progress in scientific knowledge and novel technologies to achieve its goals concerning understanding the biology of living organisms and applying it to understand and cure human diseases. It has the good mix of curiosity-based research to disease-oriented research. Several of the Institute members have built very strong links with the medical community in Montpellier and elsewhere.

IGMM has gathered excellence in RNA biology with outstanding achievements in imaging of RNA synthesis at the single cell level, RNA trafficking, splicing control and the discovery of small molecule inhibitors. IGMM has built excellence in epigenetics, a field that was reinforced by the recent recruitment of two young group leaders.

Cancer research has been and remains a major axis of the Institute and spans areas from cell cycle and DNA replication control, the role of the AP1 transcription factor complex in breast cancer metastasis and the role of inflammation in the development of liver cancer. Several teams are involved in the development of tools and protocols for gene therapy and immune protection against viral infections. Other areas include the identification of receptors accounting for viral infections, inflammatory diseases and neurodegeneration.

The Institute has developed the extensive use of mouse models for the study of diseases. It has reinforced its international nature by pursuing the recruitment of principal investigators, students and post doctoral fellows from all over the world, by participating in a large number of European networks and programms and by extensive international collaborations.

All the groups at the Institute secured outside funding from both national, European and even NIH institutions in one case. The part of external funding in the Institute's budget (team research contracts) has increased considerably. A number of teams are also part of a Montpellier EpiGenMed Labex, as well as other Labexes.

The initiatives taken by the Institute direction and members to federate several technology platforms and services at the level of the site and global Montpellier area should be praised.

The IGMM government system was extremely well appreciated by the visiting panel. It had the impression that the director and his staff are doing excellent work, that the principal investigators participate actively in the decision making processes and that the entire staffs are extremely happy to work at the IGMM.

Several of the principal investigators in the Institute participated in the founding of three Biotechnology companies based on their scientific output. In addition, a common laboratory between the IGMM and a biotechnology company is housed in the building. This is a remarkable jump from basic science to application that creates jobs for young scientists and permits to exploite commercially discoveries made in the Institute.

Weaknesses and threats related to the context

The scientific portfolio of the IGMM is rather wide and diverse and one can wonder whether building more strength in one or two areas may increase the international visibility of the IGMM. Diversity is very positive and it is facilitated by the existence of close contacts and collaborations with neigbouring Institutes but one may consider some increased focusing.

Some of the groups are too small; this is caused by difficulty to secure funding and recruit students and postdoctoral fellows. There is certainly a need to increase the Institutional budget but also to secure additional external funding including ERC grants. There is a shortage of PhD students in Montpellier and harsh competition for the existing ones. A serious consideration should be given to the possibility to increase the number of fellowship by the university and the regional government. A similar problem exists at the level of postdoctoral fellows. French science and the IGMM are suffering from regulations that limit the period length for hiring postdoctoral fellows. This is a major disadvantage compared to Anglosaxon science and a major handicap for places like the IGMM.

Another issue concerns the support staff, technician and engineers for common facilities and research groups. A major effort should be done to replace retiring staff and to guarantee that the new animal facility can function with adequate staff.

Recommendations

The IGMM has to pursue the current trend of linking curiosity-driven research with disease-oriented research. It should pursue its goal of gaining strong internatioal stature by recruiting the best possible young group leaders and by maintaining attractiveness to national and international students and postdoctoral fellows. The government structure seems very appropriate and the common spirit should be maintained.

IGMM should consider increasing the focus on a limited number of areas to increase critical mass and international recognition.

Several group leaders should do an effort to focus their research and to publish in the highest impact journals possible. A transparent scheme where junior principal investigators and staff scientists are mentored (at least once per year) by senior members of staff should be established, this should be entirely distinct from performance management and should assist in helping staff to develop strategies for building their careers and research programms.

Further efforts should be done to recruit additional graduate students and postdoctoral fellows.

All efforts possible should be done in order to increase the institutional allocation in funds and positions.

3 • Detailed assessments

Assessment of scientific quality and outputs

IGMM scientists excel in a number of fields where they are among the world leaders. In a non exhaustive list, one can mention the studies in the field of RNA biology, including the biogenesis and trafficking of RNAs with the development of imaging techniques that allow real-time tracking of the transcripts from a single gene. Another field concerns the assembly pattern of RNP particles and RNA polymerase and the cross talk between initiation, splicing and termination of transcription. Another aspect involves the regulation of alternative splicing during development and neurodegenerative diseases and the development of inhibitors of alternative splicing that are going into clinical trials as inhibitors of HIV infection in the context of a company that started at the IGMM. The role of non coding RNA, DNA methylation and chromatin marks in imprinting is another area where the IGMM gained internationl recognition.

Another area of high impact concerns the study of receptor for retroviruses that were revealed to be nutrient receptors that play key roles in hematopoiesis and HIV infection among others. These studies also reveal a major role for metabolism in T cell homeostasis and differentiation. Envelope Receptor-binding domains homologous to viral glycoproteins were shown to be an interesting tool to classify breast tumor cells (in a context of a founded company), for invivo imaging etc.

In the field of cancer related research, there was an important advance in the understading of the role of Fos family members in the onset of breast cancer metastasis and an unexpected discovery on the link between reactive oxygen species, protein Sumoylation and resistance *versus* sensitivity of acute myeloid leukemia to chemotherapy.

Interesting observations are related to HCV infection and HCC, it was clearly shown that certain viral proteins inhibit the apoptosis of infected cells and induce the inflamatory pathway. An interesting role of viral immune complex in stimulating the immune response was revealed. IGMM has also strengths in the study of the control of DNA replication at the single cell level, the interplay between DNA damage and cell cycle control and the search for specific inhibitors for kinases.

The IGMM scientists published a considerable number of articles in very high impact journals including Cell, Mol. Cell, Cell Reports, Nature, Nature Genetics, Nature Cell Biol., Nature Neuroscience, Nature Communications, Nat Struc. & Mol. Biol., J. Exp. Med. , Genome Research, PNAS, Blood, EMBO Journal, J. Cell Biol. , EMBO Reports, RNA, Plos Pathogens, Plos Genetics, Development, Mol Cell Biol., Oncogene, J. Virol. , JBC, NAR etc…

Assessment of the unit's academic reputation and appeal

IGMM members take part in a considerable number of National and European networks, in many cases as coordinators. Several of the teams were labelized as excellence teams and supported by the Ligue Nationale Contre le Cancer, FRM , ARC etc. Several young principal investigators were supported by ATIP/AVENIR projects. The majority of the team leaders are part of European or international networks and many have extensive national and international collaborations.

Several of the IGMM members assume responsibilities for on site or the entire Monpellier community of technical platforms with state-of-the-art-facilties: imaging, flow cytometry, DNA combing, massive cloning, mouse transgenesis etc. Some of these are even open for the national or international community.

As mentioned above, the IGMM is broadly open internationally, a considerable fraction of group leaders is non French. The same is true at the level of postdoctoral fellows, PhD and Master students. Among others the IGMM established close links with several universities and research Institutes around Europe bringing in trainees at different levels.

Several of the Institute principal investigators received distinguished national prizes.

Several of the principal investigators are members of editorial boards of high impact journals and all of them contribute to refering for very high impact journals.

A number of prestigious meetings, including EMBO meetings, were organized by IGMM members in Montpellier or elsewhere in France or Europe on topics relevant to their research.

Several of the IGMM members were invited to write reviews in very high impact journals placing again the Institute at the forefront of international science.

Assessment of the unit's interaction with the social, economic and cultural environment

Several of the IGMM scientists were extremely successful in taking the initiative to employ results and ideas generated by their laboratories for the set up of biotechnology companies or licencing to other companies. One should mention the building 2 biotechnology companies and the establishment of a common cooperative research laboratory, *Splicos Therapeutics*, inside the Institute. A biobank for inflammation-related diseases was also established in collaboration with medical departments as well a collaborative European project (and GMP laboratory) for the production of Canine Adenovirus vectors for animal and human gene therapy.

The IGMM scientists have been also very active in reaching the ordinary citizen to increase interest and awareness to the input of science for the wellfare of the general population.

Assessment of the unit's organisation and life

The IGMM has a long tradition of a well governed and organized Institute. As demonstrated by the organigram provided, the director is helped by a pyramidal structure with a full time deputy director, heads for administration and personals. Scientific issues are discussed within a compact scientific board and the bi-monthly meeting of the principal investigators assembly. The Institute's council meets at least three times a year to discuss general issues. In addition to the permanent principal investigators, the different teams include a considerable number of junior or senior research scientists with CNRS, INSERM or University positions. A certain number of these scientists head subteams at their respective laboratories. The panel had the impression that this group of scientists were happy at the IGMM, felt respected and contributed enormously to its success.

During their meeting with members of the visiting committee, the technical and administrative staff collectively declared that they were happy to work at IGMM. However, they pointed out the high number of employees with short term contracts and the fact that only half of IGMM groups benefited from technical support by a technician or an engineer, as these personnel were assigned to platforms and core services. They also collectively expressed their fear about the future of some platforms that depend solely on short term contract staff for their existence. In particular, they mentioned the problems of the new mouse facility which, due to the lack of animal technicians, is presently housing only 6,000 mice despite a capacity of 20,000 mice and the DNA combing platform (one part-time person with temporary contract) which has no other equivalent in the academic world and has attracted many national and international collaborations (the DNA Combing Facility contributes significantly to the international visibility of the IGMM).

Many of the resources are pooled at the level of the Institute and more recently at the "route de Mende" site and Montpellier more globally.

There are no statutory internal coordinating structures. However there is a strong collaborative spirit and many interactions and common publications between teams.

The IGMM has a permanent international Scientific Advisory Board comprising leading scientists in fields related to its research portofolio that meets regularly. This is an excellent tradition that should be maintained.

Assessment of the unit's involvement in training through research

As stated above, the IGMM trains a considerable number of Master students, Erasmus trainees, PhD students and postdoctoral fellows from France and abroad. PhD students are part of the doctoral school for biological sciences in Montpellier, they are supervised by an effective thesis committee and have to follow a number of university courses. Both students and postdoctoral fellows sound very happy in the Institute considering that they have excellent conditions for their research. An issue raised by a number of students/postdoctoral fellows concerned the language of teaching at the university. A consideration should be given to the fact that in many places graduate courses are given in English.

The doctoral school (ED 168, CBS2: Chemistry and Biological Sciences for Health) organizes a number of career training programmes. These are opened to postdoctoral fellows, an activity that could be enhanced. The committee also recommends that both PhD students and postdoctoral fellows, separately or together elect representatives who

could contribute to the social and scientific activities of these communities, help the newcomers on arrival and be in contact with the director of the IGMM.

A large number of the IGMM permanent scientists participate in graduate teaching at the university, both in science and medicine and several have faculty or CHU positions

Assessment of the strategy and the five-year plan

The research vision of the Institute for the next five years is clearly exposed at the level of the Institute globally and for each of the research groups. The Institute plans to pursue a multithematic research project spanning from curiosity-driven research to search for cure for human diseases. The IGMM will continue its interest in RNA biology, epigenetics and gene expression, cell differentiation, inflammation, cancer and metastasis, gene therapy and sensitivity and resistance to viral infections and its consequences.

The research interests of the Institute are rather broad. However strong interactions between the different groups is an advantage and an opening for making important discoveries at the interface between different scientific and medical research programms.

The selection of new young principal investigators by international open calls is an opportunity that is employed by the IGMM to acquire new expertise and reinfoce existing ones. The recent recruitment of two young principal investigators in the field of epigenetics, one working with yeast and the other with high throughput approaches and bioinformatics is a good example. The emphasis put on the extension of bioinformatics, image processing etc... is very judicious and should be favored further.

The IGMM clearly demonstrates its capacity for renewal and keeping up with the explosive development of biological sciences.

The SWOT analysis by the different principal investigators and the director is very realistic and emphasizes the strengths and the dangers for the future. It is obvious that limiting financial support, positions for technical and administrative staff, difficulties in assuming the running costs and personnel of the animal faclity, funding for PhD and postdoctoral fellows constitue barriers for further development and success in the international competition.

4 • Team-by-team analysis

The visiting committee examined 16 teams who will take part in the future project of the Institute. The committee regretted that, for lack of time, it could not learn about the past work of two retiring group leaders, as well as that of a principal investigator who is taking the directorship of the Cancer Centre. The committee had however access to their written report.

Team 1: RNA Biogenesis and Trafficking

Name of team leader: Mr Edouard BERTRAND

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	6	6
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	10	10

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs

This a ~12 strong group that was established in 2003. During the evaluated period they have used highly sophisticated imaging techniques to visualise single mRNA molecules in live and fixed cells and measure RNA poymerase II activity at single gene level. They have explored the role of the human HSP90/R2TP co-chaperone complex and found new complexes that bind to RNA cap. They have also found a new function for AGO2 in retroviral packaging. They have published 35 primary papers consistently with a strong record in higher impact journals including Cell, Molecular Cell, EMBO Journal, Journal of Biological Chemistry, RNA and in the top Cell Biology journals like Journal of Cell Biology. Another positive feature of this group is that they collaborate widely with other Molecular and Cell Biology groups worldwide that focus on aspects of gene expression (Kornblihtt at Buenos Aires Argentina, Lammond at Dundee UK, Jensen at Aarhus Denmark).

Assessment of the team's academic reputation and appeal

The principal strength of this group is their focus on RNA/transcription imaging in both living and fixed cells. The team leader and his team are recognized as a leading researcher in the field of RNA synthesis and trafficking and as a developper of cutting edge technologies to follow specific RNA synthesis at the single cell level.

Assessment of the team's interaction with the social, economic and cultural environment

A member of the team was involved in the creation of a biotechnology company. It is important to mention that the team leader is in charge of the common Montpellier imaging facility as well as the high through put cloning facility.

Assessment of the team's organisation and life

Organisation seems to be fully appropriate.

Assessment of the team's involvement in training through research

The team has trained seven master students as well as four PhD students defended their thesis. A team member defended his HDR.

Assessment of the strategy and the five-year plan

1) mRNA biogenesis in living cells: The approaches planned are dependent on difficult imaging technologies coupled with mathematical modelling. Clearly improving this technology will be critical to future success. The interesting concept of RNA polymerases transcribing genes in “trains” will need further developments especially by obtaining independent biochemical evidence to back up image analysis. Looking at gene topology (looping) during transcription will be a very exciting avenue for this Cell Biology expert lab to focus on.

2) HSP-90/R2TP: This macromolecular assembly complex looks to be a very attractive system and one that this lab has a unique expertise in. Especially how RNA polymerase I, II and III assemble and then are imported to transcription sites in the nucleus is a fascinating and understudied process. The other complexes to be studied, CBCAP/N are equally interesting, comprising the mRNA Cap binding proteins and various mRNA maturation or export factors. A combination of biochemistry, genomics and imaging is proposed and should continue to yield interesting results.

3) miRNA/HIV-1: This part of the lab research proposal is a separate though connected research project. Here experiments to determine the role of viral Gag in modulating RNAi response are envisioned. The work could also extend to other medically significant areas such as cancer and stem cell biology.

Conclusion

- **Strengths and opportunities:**

Worldwide expertise in the image analysis of RNA and associated proteins in the cell nucleus.

Strong expertise in the biochemistry of protein complexes associated with gene expression in mammalian cells.

- **Weaknesses and threats:**

Possibly needs to focus on more productive experimental directions.

Slow Too many group members are on permanent contracts therefore hard to achieve a healthy turnover of group members.

Hard to fund such a large group from external grants.

- **Recommendations:**

The committee felt that the two main parts of the proposal look to be very interesting and challenging. Most importantly the team has already demonstrated substantial success in these research areas as judged by several strong publications in both areas. Clearly, the future plans should maintain this high scientific output. This is clearly a leading team at the international level both for its past contribution and for its future programm. The team leader should consider applying for an ERC senior award. The final part of the laboratory proposal project is effectively a separate though connected series of experiments that will be the focus of a senior and independent member of the research team

Team 2: Assembly and Trafic of Ribonucleoproteins

Name of team leader: Mr Rémy BORDONNÉ

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	4	4

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

This team, created in 2002, has performed an elegant and innovative study on the molecular defects associated to the loss of the Survival of Motor Neuron (SMN) protein. Amongst other things, (i) they have uncovered that SMN deficiency specifically decreases the assembly of the minor spliceosome leading to splicing defects of pre-mRNAs carrying U12-type introns and (ii) they have identified mRNAs species that bind the SMN complex in motor neuron-like cells. Altogether, this work allows a better knowledge of the different roles of SMN in RNPs assembly and transport, and thus contributes to the understanding of the potential mechanisms leading to Spinal Muscular Atrophy (SMA).

The team has worked on the m_3G cap formation, a former research topic. They have been active in characterizing the two isoforms of the protein, as evidenced by the publication of 2 research articles. They also published an article on the functional analysis of the *S. pombe* ICln protein (methylosome subunit).

The team has published a total of 13 articles in very good to excellent journals during the last 5 years (*EMBO J, Human Molecular genetics, Mol. Cell. Biol. RNA, J. Biol. Chem)*. In 5 of them the team is leader, with students or post-doctoral fellows being first or second authors. The work performed is excellent and, at least two of these articles are major contributions to the field. They have been published in *Human Molecular genetics* in 2011 and in *RNA* in 2013. With this background, the team is well positioned to explore these pathways.

Assessment of the team's academic reputation and appeal

SMN/SMA is an important and competitive area of research in RNA biology, which has direct clinical implications. The team has a very good visibility in their research field both nationally and internationally; the team leader is frequently invited to international conferences. The team joined 2 international scientific networks (a “European associated laboratory” and the “minor U12 splicing in brain development” network). Its drawing power is expected to increase with the development of the projects. The team has established collaborations with a number of other groups nationally and internationally. Given its rather small size, the funding is very good (1 ANR coordinated by the team leader, 1 ARC, 2 AFM and 1 SMA Europe).

Assessment of the team's interaction with the social, economic and cultural environment

The work carried out by the team is of a fundamental nature but it is to be expected that the results of this research may lead to the development of novel approaches to cure the SMA disease to which SMN deficiency is associated. The team has developed partnerships with patient associations and contributed to AFM Telethon.

Assessment of the team's involvement in training through research

The team has trained 3 Master students and 3 PhD students during the evaluation period. PhD students signed at least 1 publication as first author and 1 publication as co-author and they attended 1 international meeting per year.

Assessment of the strategy and the five-year plan

The research project of the group is predominantly focused (i) on the identification and characterization of mRNAs, whose splicing is changed upon SMN deficiency and which are essential for motor neuron survival/pathology and (ii) on the study of “alternative” functions of SMN proteins involved in axonal trafficking. This decision is a reasonable strategic move. Indeed, projects include research that is a logical follow-up to the previous work and that should yield results in the medium term. The proposed RNA Seq approach should lead to the identification of common features in unspliced minor (and major) introns. The risky aspect of the planned research is inherent to the chosen biological models: cells isolated from whole spinal cords from SMA mice, induced pluripotent stem cells differentiated in motoneurons and a zebrafish transgenic line. However, these models have been already tested and are functional in the laboratory or will be handled in collaboration with local experts (Zebrafish). The second project will take advantage of the microfluidic chamber system to isolate and characterize mRNAs associated to purified axonal SMN mRNPs. Both projects are ambitious and should lead to high impact results.

Also already well advanced is the use of the S. pombe model organism as a tool for establishing genetic interactions into SMN-dependent pathways and maybe identify new pathways able to compensate for defects induced by low levels of SMN proteins.

Projects involve collaborations with a team in the USA (S. pombe project) and local collaborators, which should strengthen the working power of the team.

Conclusion

- **Strengths and opportunities:**

The overall project is highly ambitious given the size of the team, a small team that has produced good work in the SMN/SMA field and that has a strong potential. It is expected that its international visibility will increase significantly in the coming years. The project reflects a good balance of more secure projects that are the logical follow up of the recent work of the team and ambitious projects that could lead to high impact results. Moreover, appropriate collaborations are proposed with excellent groups with complementary expertise that should widen the national and international connections of the team.

- **Weaknesses and threats:**

This team has no significant weakness although they should put effort in recruiting PhD students and post-docs and increase external funding.

- **Recommendations:**

Considering the small size of the team, the leader needs to be especially careful to keep the team well focused.

Team 3: Molecular Mechanisms of Apoptosis Regulation

Name of team leader: Ms Solange DESAGHER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	5	3

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

Since its inception, the group has focused their work primarily on the role of an E3 ligase, Trim17, which is upregulated during growth factor deprivation-induced neurons apoptosis. The group has shown that this Ub ligase is both necessary and sufficient to trigger neuronal apoptosis and have identified the Bcl-2 family member, Mcl-1, as a substrate for Trim17. They have also conducted Y2H screens to identify other binding partners of Trim17 and have identified at least two putative interactors: NFATc3 and ZSCAN21. The transcriptional activity of NFATc3 appears to be regulated by Trim17, but in turn, NFATc3 may also regulate the expression of Trim17. The group has also found that Trim17 regulates the stability of ZSCAN21, which is a regulator of alpha-synuclein, a protein implicated in Parkinson's-associated neurotoxicity.

The originality of the work is high and there is still much to learn concerning how neurons integrate stress and growth/survival factor deprivation signals, upstream of the Bax/Bak mitochondrial checkpoint of apoptosis. There are relatively few known regulators of the commitment point to apoptosis and Trim17 could be a very interesting protein in this regard. So the work has originality as there are few other laboratories working on this molecule and none in the context of cell death control. This can be viewed as a strength (original research question, few competitors), as well as a potential weakness (lack of interest by the community due to lack of common ground/interests, Trim 17 possibly not a major regulator of cell death but very context specific).

The team has published two nice articles in *Cell Death and Differentiation*, the major speciality journal in the Cell Death field (impact factor approximately 8). In addition the team leader co-signed, among a considerable number of authors, a Cell paper. This is a very good start but we would encourage the team to increase its output over the next evaluation period. This may happen naturally as the group gathers momentum, but it is advisable that the team leader sets a target for the output of her group. Similarly, it would be nice to see some additional collaborative articles from the group, but this is less important than the primary papers from the group.

We would also recommend that the team strives to publish in high impact journals in order to get the best critical feedback to (a) help improve the work and (b) to generate the best profile for the work.

Assessment of the team's academic reputation and appeal

The work of the team is very careful, highly reproducible and highly regarded. It has the potential to develop an international reputation. It would be helpful for the team to develop a higher profile within the community by getting involved in the organization of a meeting in its field, and for the team leader by doing more reviewing for international journals and by attending more meetings to promote her work. In this regard, an excellent opportunity would be the International Workshop on Cell Death which runs a bi-annual meeting. The latter meeting is also an excellent recruiting ground for post-doctoral fellow as a great many attend this workshop series.

Assessment of the team's interaction with the social, economic and cultural environment

No mention of any interactions in the report of the team.

Assessment of the team's organisation and life

The team is quite small at present and it is hoped that the critical mass can grow by several additional people, mainly PhD students or post-docs, over the next couple of years to enable them to be competitive in their field. This is also essential to enable the team to take on a small portfolio of projects (revolving around a central theme) to minimize the risk of overexposure to a single project or pathway. The team organization appears to be very satisfactory.

Assessment of the team's involvement in training through research

The team has trained 2 post-doctoral fellows, 1 PhD student, 11 master students. The post-doctoral fellows and graduate students are encouraged to attend scientific meetings. The team leader is teaching Master students in

Monpellier and is giving a course to biology students at Ecole Normale Superieure in Paris. The team leader and members of the team participate in thesis juries and have responsabilities in Doctoral school and coommittes for selection of students.

Assessment of the strategy and the five-year plan

The future work of the group all revolves around the role of Trim17 and related Trim proteins as regulators of NFAT transcriptional activity as well as ZSCAN21 and the implications of the latter in Parkinson's disease. The plan is well described and the aims are logical and coherent. However, the initial goal of exploring neuronal cell death is becoming significantly diluted as it gets more and more into the details of the Trim17 pathway.

The committee would suggest that the team also pursues the other gene transcripts that were upregulated during neuronal cell death to ensure that they are working on the key proteins involved in this process. It is important not to become unfocused, however it is equally important not to become overfocused too early in a project when the relative importance of the various players involved are unclear.

The focus on Trim17 is original but not without risk. Trim17 may well turn out to be a peripheral player in neuronal cell death control and they will need to decide whether they are working on neuronal cell death control, or whether the primary research question has become: "what does Trim17 do?". If it is the latter, then Trim17 would need to do something very important indeed for the community to share the interest in this molecule. For this reason, it is advisable to have a portfolio of well-defined projects all addressing related but distinct questions within the same broad problem.

For the above reasons, it would be beneficial for the group to diversify somewhat, staying on the topic of neuronal cell death control, but broadening their focus to study molecules that are established to play key roles on determining neuronal fate and which have strong disease implications. For example, the Parkin/Pink1 pathway is strongly implicated in regulating neuronal cell death, but how this is achieved remains entirely unclear. Given that Parkin is also an E3 ligase, the team would be well placed to explore the role of Parkin in neuronal cell death control. Similarly, how alpha-synuclein promotes neuronal cytotoxicity still remains unresolved and is an another good problem to pursue.

Conclusion

- **Strengths and opportunities:**

Overall, the team is performing very high quality work and should now be in a good place for its work to gather momentum. But it does need to gather momentum over the next 5 years. The strengths are in the knowledge of neuronal cell death control, still an area of significant research interest.

- **Weaknesses and threats:**

The threats are that they may have chosen a molecule (Trim17) to work on that could well turn out to be a peripheral player in cell death control. The additional threat is that it will be hard to publish high profile papers on a molecule that few laboratories work on.

- **Recommendations:**

The opportunities in the research field are in areas such as Parkin/Pink1 and alpha-synuclein as research is gathering pace on these important molecules, but few specialists in cell death are working on these topics. It is recommended that the team places significant effort towards increasing its output to publish more primary papers over the next five year period, and that they take on one or two additional topics (aside from the Trim17 project).

Team 4: Genomic Imprinting and Development

Name of team leader: Mr Robert FEIL

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	3

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

The team leader has a strong track record in mouse epigenetics especially as applied to imprinted gene loci. The team has consistently published well during a first period up to 2008. The laboratory (currently ~ 6 scientists) has arguably done less well during the last 5 years. Still, during the last 5 years there have been published papers in EMBO Journal and EMBO Reports as well as some other more specialist journals. The team leader has also published as a collaborator in top journals such as Science and PNAS. This is in part due to funding and recruitment difficulties and presumably the highly competitive nature of his research area.

Assessment of the team's academic reputation and appeal

The team is internationally well known for its research into the molecular/genetic analysis of allelic gene imprinting in mouse. While this is a very competitive research area, this group is well able to provide a valuable contribution to the understanding of this complex and medically important research area. The team leader is a frequent speaker and organizer of international meetings and has co-authored a number of authoritative reviews in prestigious journals such as Dev. Cell, Nature, Nature Review Genet and book chapters. He is a member of a number of European/international networks on epigenetics and imprinting and is a member of a number of editorial boards.

Assessment of the team's interaction with the social, economic and cultural environment

The team collaborates with clinical teams in UK and Spain to explore deregulation of imprinting in humans and its involvement in growth disorders and cancer.resentations.

The team leader was a member of the national bioethics committee panel and gave a number of popular science presentations.

Assessment of the team's organisation and life

Organization of the team is fully appropriate.

Assessment of the team's involvement in training through research

The team leader is involved in teaching at the University and participates in a number of PhD/HDR examination committees. Eight master, 3 Erasmus and 3 PhD students were trained in the team.

Assessment of the strategy and the five-year plan

The team plans to stay with imprinted genes and their mechanism of allele specific regulation and biology.

1) ChIP-seq analysis of repressive chromatin marks using ES and MEFs from mouse strains genetically deficient for various histone methyltransferases (eg G9a and PRMT7) is planned as well as the search for specific patterns over imprinted loci. Similarly, HP1 profiles will be established (and TRIM28). The committee encourages the laboratory to employ CRISPR/Cas9 approaches as a new facile way to manipulate genomes, whether in cell lines or mice.

2) ncRNA and its role in imprinting loci will be studied by looking at a new imprinted locus (Dlk1-Dio3). Like other imprinted loci, ncRNA (Gtl2) will be studied. This will in part be looked at in collaboration with another team at IGMM by imaging of MS2 tagged ncRNA and represents a very promising project. However, it is unsure whether new information on the role of ncRNA in gene imprinting will necessarily be added to by looking at another imprinted locus.

3) Experiments on imprinting establishment. How are DNA methylation patterns established and how do these get maintained and then lead to imprinting and consequent histone modification associated with ncRNA? No novel approach is proposed on this topic. However, it is clear that defining the chromatin marks associated with imprinting

is an important objective. One aspect that could also be investigated is the potential of transcription-induced R-loops in restricting ncRNA synthesis as it has been shown for the PWS/AS locus.

Conclusion

- **Strengths and opportunities:**

Strong expertise in epigenetics and imprinting.

Good imaging expertise, especially in collaboration with another team at IGMM.

Valuable mouse models and associated cell lines

- **Weaknesses and threats:**

Must get unpublished data completed and well published.

Mouse facility delays are a serious problem.

Hiring new postdocs and graduate students will be critical to the groups future success.

- **Recommendations:**

The team needs to build on his current exciting, but mainly unpublished research studies, and aim to publish this new work in high profile journals. They appear to be on track to reach this objective. With success in recruiting new people to the laboratory as well as getting the work well published, the team hould be able to achieve the highest possible international recognition.

Team 5: Phosphorylation and Cell Cycle Control

Name of team leader: Mr Daniel FISHER

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	5	5
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	7	7

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

This is a mid-size group that includes several senior scientists, postdoctoral researchers and PhD students. The laboratory is mostly interested in the phosphorylation networks that control the cell division cycle, nuclear architecture and chromatin, and the alterations of these processes in cancer. The team leader is an expert in these topics. The laboratory started in 2006 and it is now well established, maintaining several collaborations with different labs in Europe or USA.

The record of publications includes since 2008 articles in high-quality journals such as *EMBO J.* or *Mol. Cell*, in addition to other manuscripts (Chem Biol, Nucleic Acids Res, Cell Cycle). In general, the productivity is good in terms of quality and acceptable in terms of productivity. It is somehow surprising that no articlesin collaboration with external groups are listed. It is also important to highlight that one of the senior investigators in his lab, a former group leader who joined the team in 2007, is also last author in a couple of publications (*Cell Cycle* and *Oncogene*). Some more recent projects presented by the principal investigator have resulted in very interesting results that are yet to be published.

The team has focused their research interests on Cdks as major engines in the cell cycle. During the last years, the group has been involved in the analysis of the regulation of cell cycle progression by major Cdks, mostly Cdk1 and Cdk2. They have analyzed the relative and cooperating roles of these kinases in DNA replication using *Xenopus* or human cells as model systems. Most of the articles in the last years come from this project, as well the analysis of Cdk-counteracting phosphatases, PP2A, in the control of protein dephosphorylation during cell cycle exit. From this work, and the results from a proteomic screen for proteins whose abundance on chromatin depends on Cdk activity, the team is now interested on Cdk8, a member of the Mediator complex. Similar studies led the group to investigate the function of Ki67, a molecule whose protein levels are of great interest in the clinic, but whose function is unknown. In both cases, mouse models for these molecules have been generated and their phenotype is currently under analysis. The progress so far in these projects is appropriate. Other projects currently under development are related to the cross-talk between checkpoint pathways in response to DNA damage and the control of mitotic entry.

Assessment of the team's academic reputation and appeal

The team has an established expertise in cell cycle kinases and cell cycle regulation. They have coordinated or participated in several consortiums including international laboratories and frequently participate in international seminars or meetings. The team maintains multiple international collaborations. The team is involved in the coordination of two consortiums (international and national) and the laboratory has received funding from different national agencies. Only one of these grants seems to be active until 2016.

Assessment of the team's interaction with the social, economic and cultural environment

Several of the projects in the group have a clear therapeutic relevance and the group is interested in maintaining collaborations with pharmaceutical companies. However, this is not a major goal for the group at this moment as it first needs to increase the international visibility in the generation of scientific results. The team leader has also given several international seminars (Europe, USA) for promoting the relevance of basic research.

Assessment of the team's organisation and life

The group is formed of three staff scientists, two postdoctoral fellows and two students and new members will join in the near future. The organization of the group is well established with the other staff scientists participating in both scientific and organizative duties in the lab. The laboratory is highly international and several members participate in other duties at the IGMM. Lab meetings are weekly and they often share scientific discussions in an organized manner with other teams at the IGMM.

Assessment of the team's involvement in training through research

The team leader, as well as the other staff scientists, supervises several PhD students and posdoctoral fellows and people trained in the laboratory have found positions in other institutions. Several members of the group are involved in different master courses, schools or programmes for graduate or undergraduate students in France. From 2008 to 2012, the group has trained 3 PhD (two in 2010 and one in 2012), 4 master and 2 Erasmus students of various nationalities.

Assessment of the strategy and the five-year plan

The plan for the future includes some projects as a continuation of previous lines and new ideas based on recent results. The group is interested in continuing with the analysis of Cdk and Cdk-dependent effectors on cell cycle progression. Some of the research lines are based on the use of large-scale RNAi screens to identify novel interactions through synthetic lethal and suppressor interactions. These large-scale projects are always uncertain and risky and the specific design is elaborated in detail for CDK2. Since this molecule has been considered as a major cancer target for several years, these projects could result in findings of interest from the therapeutic point of view. In general, this part of the future projects are a continuation of the previous expertise of the team leader in the field.

In addition, the laboratory is now focused onto two new projects to analyze the relevance of two molecules, Ki67 and Cdk8, also of great relevance in the Clinic. These two projects are interesting but yet to be validated. Thus, the team is interested in a detailled analysis of Ki67 relevance using multiple approaches, from mouse genetics to screens to explore in detail its involvement in human cancer. The group has generated genetic models for both proteins in mouse cells and also *in vivo* and several of the preliminary data are very attractive. It is very important that these projects do not suffer from the problems in the animal facility and a very important fraction of the group research at present is based on these animal models.

Additional projects in progress or for the future include the analysis of the cell-cycle-dependent control of nuclear architecture and chromatin, including the study of new phosphorylations in histone H3.

These projects are accompanied of the proposal for new technologies although to what extent the group will be involved in the development of these technologies is not clear as they are in most cases not necessary for some of the scientific projects. For the future, the group is interested in applying new gene-editing technologies, proteomics and microscopy, mostly focusing to mammalian cells, but keeping *Xenopus* as a complementary model for specific questions. Targets of interest will be mostly Cdk2 and Cdk8, as well as other candidates from genetic or proteomics screens. The project on Cdk8 has received specific funding and Daniel has been acting as the coordinator of an ambitious project with participation of several groups with expertise not only in mouse models but also in proteomics and drug discovery.

Conclusion

In general, the focus of the laboratory is well established and the written report clearly describes the evolution of the projects incorporating cutting-edge technologies, network of collaborations and a clear interest in the application of their results into the clinic. Productivity is not very extensive but maintains high quality. It will be very important to design the future projects to select those research lines that are likely to generate high-impact publications. The genetic models are a good example although the group needs to ensure that the proper infrastructure will be available at the IGMM or collaborative institutions to obtain the best from these projects. Also, the selection of new targets such as Cdk8 or Ki67, and the analysis of their relevance in tumorigenesis and cancer therapy, may open new opportunities in areas that are not well explored at the moment. Finding the proper niche in these areas will be a very important challenge for the group in the near future to establish a well-recognized laboratory with international relevance. It is also important to address the possibility of using these projects to attract possible pharmaceutical companies interested in new cancer targets.

- **Strengths and opportunities:**

Good expertise in the field.

Combination of biochemical and genetic approaches in different animal models (*Xenopus*, mice).

Good selection of new cancer targets for validation.

- **Weaknesses and threats:**

Insufficient international recognition and moderate number of outstanding publications. The use of mouse models and advanced technologies may help in improving these two aspects.

- **Recommendations:**

It is very important to select one or two of the more advanced and more attractive research lines for which preliminary results have been obtained and dedicate a significant effort to generate high-quality publications in the next months. This should be prior to dedicating a major effort to setup new technological advances in the lab.

Mouse models are a major technical requirement for the laboratory at this moment. The team leader should ensure that the infrastructure at the IGMM and the expertise required to obtain the best results for these expensive and long projects are available to generate high-level results from these projects.

Team 6: Genome Organization and Epigenetic Control

Name of team leader: Mr Thierry FORNÉ

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	4
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	4	6

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs

Research programs developed by the team aim at investigating the higher order chromatin organization and its functional impact. Additionally, research was also conducted on the developmentally regulated genome programming by DNA methylation.

Two specific research axes are developed in the frame of this research program both relying on a technique developed and validated by the team. That is 3C-qPCR.

The first axis considers the functional impact of higher order chromatin on two imprinted loci: Dlk1/Gtl2 and Igf2/H19 that led to the publication of interesting observations.

The second axis follows a multi-disciplinary approach including the investigation of chromatin topology by 3C-qPCR and the mathematical modelling of chromatin dynamics revealing specific states of chromatin dynamics at the gene-rich loci.

Finally, an ex-member of the team developed a genome-wide approach to investigate the state of DNA methylation at the very early stages of embryonic development and in PGC.

All the three axes were successfully conducted and interesting observations and discoveries were reported in high quality publications. A total of 12 publications (and one review) is presented.

In general, all this research has been led on a collaborative basis. 5 publications have involved at least one member of another IGMM team. 6 publications resulted from collaborations of the team with other laboratories (first / senior authors is not a member of the team), relying on the technical expertise of the team or on both technical and conceptual contributions of the team.

The publications appeared in outstanding (Nature Genetics) as well as in high profile journals (Genome Res., Genome Biology, Development, NAR, MCB, JBC).

Assessment of the team's academic reputation and appeal

The team is attractive and has hosted and given the possibility to talented young researchers to produce high quality work and construct their carrier. More precisely, one MCU and one CR2 (CNRS) have been recruited. The latter later obtained an ATIP grant and is now pursuing his work elsewhere.

Additionally, the multidisciplinary approaches developed by the team attracted researchers with physics background from other institutes (Paris) wishing to be affiliated to this team (from 2014) an and further explore the higher order structure of chromosomes.

The level of publications illustrates the potential of the team to lead or be part of national and international collaborations (UK, Japan, Switzerland).

The team members have been involved in national and European networks. They actively contribute, at different levels, to the evaluation of science and scientific activities (members of evaluation committees, referee for journals, etc…). They are regularly invited to national and international meetings.

Assessment of the team's interaction with the social, economic and cultural environment

A member of the team who developed a research on genome programming by methylation was a coordinator of a grant from European Chemical Industry Council, also involving another team of IGMM.

Finally several team members have contributed to the diffusion of scientific information to the public.

Assessment of the team's organisation and life

The team has provided the environment necessary for the development of new research programs by young investigators (emergence of an ATIP team).

The team is run on an interactive basis with attested contributions of other members in each specific project.

Assessment of the team's involvement in training through research

The team ensures a regular training activity in research (5 PhD, 8 master and one licence) and team members regularly participate to teaching programs and various student evaluation processes.

Assessment of the strategy and the five-year plan

The team organization has been remodelled. A CR2 developing DNA methylation studies during development and differentiation has left and therefore the corresponding projects have already stopped. In contrast, the team has attracted physicists to develop the modelling of chromatin dynamics.

Overall, the proposed programs are in line with and based on the achievements of the team during the past 5 years. Two major axes will be considered: the biology of Igf/H19 lncRNAs and the dynamics of higher order chromatin organization. This part will also include additional methodological developments to better investigate genome organizations and the organisational and functional impacts of genomic regions in contact with nuclear domains/matrix.

The proposed projects present original aspects and could lead to new methodological and conceptual developments. However the committee feels that a better focus on a specific theme is required.

Conclusion

- **Strengths and opportunities:**

The team has served as a ground for the establishment of a talented young scientist. Methodological and conceptual developments have resulted from it's activity. It has in house, national and international collaborations. At the IGMM, it can have the benefit of other teams' activities developing useful methodologies as well as conceptually similar projects.

- **Weaknesses and threats:**

Its small size does not allow the team to tackle several very competitive research topics. Both the biology of lncRNAs and the dynamics of higher order chromatin organization are of interest to many high profile groups. Without any efforts to find specific "protected niches" that could be investigated deeply and comprehensively, the team might encounter difficulties to lead its research in the future.

- **Recommendations:**

The committee recommends that the team focuses its efforts over one of the two research axes and develops a more comprehensive investigation of the chosen research program.

Team 7: The Biology of TNF Family Members

Name of team leader: Mr Michael HAHNE

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent EPST or EPIC researchers and similar positions	1	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	7

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

This research group focuses on the role of APRIL as a regulator of cancer and more recently of inflammation. APRIL is a member of the TNF family identified previously by the team leader.

In opposition to the prevailing view, the group has found that APRIL exhibits anti-inflammatory properties and may be involved in dampening inflammation in certain autoimmune contexts such as arthritis.

The group uses a number of different experimental systems to address the role of April including tumour mouse models, spheroid cultures of tumour-initiating cancer cells and determining levels of APRIL in serum from cancer patients.

The group is quite prolific at present in terms of number of publications. The work during the evaluation period was published in specialized journals with an impact factor between 3 and 9 (Cell Death and Diff, Arthritis Rheum Dis, Arthritis Rheum, one additional in Blood, not cited in the written report yet). Going forward the group might be advised to generate a higher profile for their work by publishing in less specialist journals. The team leader has an overall h index of 30. The team has an increasing number of publications since 2011, after a period of low productivity since 2000, however papers are generally still well cited (overall average of > 200/year). Senior scientists in the lab have also published a limited number of last author papers in specialisty journals.

Assessment of the team's academic reputation and appeal

The team leader is the cofounder of the bi-annual European Workshop on Cell Death. He is a guest lecturer at the University of Chieti, Italy and the AMC, Amsterdam, Holland. The team is well known internationally for its contribution to the field of TNF family members, in particular April.

Assessment of the team's interaction with the social, economic and cultural environment

The group participated in two clinical trials, and established a biobank for samples from rheumatoid arthritis patients. He is consulting for industry and one patent has been filed.

Assessment of the team's organisation and life

The group is comprised of six full-time members in addition to the PI (2 PhD students, 1 technician, 1 post-doc and 2 staff scientists). The interface with the clinic is well established with the integration of senior clinicians in his lab.

Assessment of the team's involvement in training through research

The team has trained 4 PhD students and 19 undergarduate students. The clinicians teach in clinical programms.

Assessment of the strategy and the five-year plan

Previously, a major aspect of the group's work was exploring the role of APRIL as a tumor-promoting cytokine in colorectal cancer. However, the focus has now shifted towards the elucidation of the anti-inflammatory properties of APRIL, particularly its effects on the induction of Bregs, B-cells that secrete IL-10. The future research is focused on exploring the role of APRIL in Breg development, with a particular focus on identifying the receptor involved (BCMM or TACI). Another aspect of the future work proposes to characterize regulatory B-cells in humans and to explore the prospects for their expansion in vitro using APRIL as a therapeutic strategy.

APRIL may have potential as an immunotherapy for autoimmune disease. The future plan will provide the background knowledge to develop reagents that target these molecules into safe and efficient therapeutics. The group is extending its translational programm by a biomarkers discovery programm in rheumatoid arthritis. This may

potentially lead to markers that predict whether patients will respond to anti-cytokine therapy. Due to the high costs of these biological therapeutics, there is an urgent need for this type of work.

Conclusion

While the publication rate of the team is currently on the increase, the team should strive for publications in journals with higher impact factors. The committee suggests that deciphering the molecular mechanisms behind the *in vivo* effects of APRIL (ligand, signalling etc) would help for reaching this goal. This combined with non-hypothesis driven approaches (microarray, proteomics, siRNA or drug library screen), to discover unexpected pathways, targets and drugs would additionally expand the knowledge around these molecules as a therapeutic target.

The committee would suggest that the group collaborates with a strong B-cell laboratory (as well as a Treg laboratory) to ensure that their proposed B-cell studies are conducted with the most relevant models and focus on the most relevant secreted factors.

- **Strengths and opportunities:**

Good expertise in the field.

Combination of experimmental approaches in mice and human

Good international visibility

Good link to clinical research

- **Weaknesses and threats:**

Moderate number of outstanding publications (rising again recently)

- **Recommendations:**

Decipher molecular mechanisms

Collaborate with B reg and Treg laboratories

Use non-targeted approach to discover signalling pathways, targets and drugs

Team 8: HCV and Cancer

Name of team leader: Ms Urszula HIBNER

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	3	4
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	5

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

The team investigates the role and mechanism by which Hepatitis C Virus (HCV) proteins contribute to the development of Hepato-Cellular Carcinoma (HCC). They use both mouse models as well as human biopsies in close contact with clinicians. As a matter of fact, one of the laboratory members got a position at the medical school/hospital.

The focus of the group appears to be quite diffuse, covering varied research topics ranging from Epithelial to Mesenchyme Transition (EMT), cell death, the immune response to viral proteins and tumor evolution/competition. These are all very competitive fields in their own right and it is difficult for the team to compete on all of these topics even though the common focus that bridges all of these disparate research areas is HCV. The group published an average of one senior author article per year over the past 5 years, in journals of considerable impact: PloS Pathogens, J. of Hepathology, Hepatology, PloS One, J. Cell Physiol. etc. More senior author articles in high profile journals is to be encouraged, especially for a group of this size.

Assessment of the team's academic reputation and appeal

The team leader is very active on national committees and organizations and has also presented her work at a good number of international meetings over the reporting period. The editorial work is satisfactory but the committee did not see that any of the team serve on editorial boards of international journals. The team leader organized a number of national and international meetings and is currently a short term visiting scientist at the Institute for advanced studies in Berlin.

Assessment of the team's interaction with the social, economic and cultural environment

One member of the team has led and coordinated clinicals trials and acted as consultant for several pharmaceutical and biotechnoly companies The team leader has given interviews to CNRS and French newspapers and helped selecting public lectures while other members of the team have taken part in the initiation of secondary school students to research.

Assessment of the team's organisation and life

The group is relatively large with six full time members (2 post-doctoral fellow, 2 PhD students, 2 staff scientists) as well as three Erasmus students. The specific research questions addressed by the group could be more coherent.

Assessment of the team's involvement in training through research

The laboratory was involved in a lot of training of junior scientists with many ERASMUS students as well as PhD students during the reporting period. The team leader is also involved in international training networks and has set up strong fruitful interactions with universities in Poland.

Assessment of the strategy and the five-year plan

The proposed experiments are interesting, although the metabolism experiments appear to be somewhat of a "fishing" exercise and risk diluting the focus of the group even more. The inflammation experiments have potential although it is unclear whether virus-induced inflammation is a deliberate viral strategy to promote replication, or simply a host response to viral-derived Pathogen- Associated Molecular Patterns. It would also be important to confirm that Lymphotoxin β production is a significant component of a natural infection. The involvement of an innate immunity research group would also be advisable to help shaping the precise questions that are being addressed. Immunology is a complex area that should not be dabbled in.

The tumor heterogeneity experiments appear to be a distraction from the other studies.

Conclusion

- **Strengths and opportunities:**

Research on a medically extremely important issue: how chronic infection with HCV causes liver cancer and metastasis. Coupling of both research with animal models and with human patients. Developped good links with clinicians. Excellent international connections.

- **Weaknesses and threats:**

Too much spread of the research effort. Dilution of focus by tackling too many questions, lack of critical mass/knowledge on some of the research themes (metabolism, immunity). More focus on one or two key projects is to be encouraged.

- **Recommendations:**

In summary, the work of the group is satisfactory but it is suggested that the team reduces the number of research topics under investigation and places more focus on one or two key projects so that progress in these can be accelerated. It is also suggested that the group endeavours to publish papers in higher profile journals, as one of the benefits of the rigorous peer review processes employed by these journals is that it helps to raise the level of research conducted within the group. Another benefit of the latter is, of course, that the work receives greater attention within the wider research community.

Team 9: Adenoviridae: Receptors, Trafficking & Vectorology

Name of team leader: Mr Eric J KREMER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	3

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Scientific quality and outputs

During the past evaluation term, the team has been involved in 4 projects, three of which connected with the biology or the engineering of canine adenovirus-2 (CAV-2), and a new project addressing mucopolysaccharidosis (MPS) type VII pathogenesis. The team has published 31 publications including 9 review papers in very good journals including Mol Ther, J Exp Med, PLoS Pathogens, and J Virol. The team has also contributed to several collaborative studies due to their expertise in CAV-2 vectors. *Receptors and trafficking*. The team has characterized some interesting aspects of the function in neurons of CAR, a receptor of CAV-2 that allows its internalization and axonal retrograde transport. *Maturation of DCs by adenovirus-immune complexes*. The team has discovered how adenovirus-immune complexes (Ad-IC) induce the maturation of human DCs and some cellular and immune pathways involved or induced when Ad-IC are administered to DC mixed to primary T and B cells. *CAV vectorology*. This group is well known for the initial development of vectors derived from CAV-2. They have set up a vector core facility and continue the technical development of this vector platform aiming at exploring its clinical potential. *Mucopolysaccharidosis (MPS) type VII*. This group has been involved in the study of lysosomal storage disorders (LSDs) that alter the turnover of glycosaminoglycans (GAGs) and in the development of a therapy for neurodegeneration, such as MPS VII in small and large animals using CAV-2 vectors.

Team's academic reputation and appeal

The group is well known for its contribution to the biology and vectorology of canine adenovirus type 2 (CAV-2) and its receptors and, as such, has developed an interesting continuum from basic to translational research, with strong potential to lead to biotherapies. It collaborates with several other groups, mainly interested in using CAV for neurobiology research, and is involved in several national or EU-level consortia that were eventually coordinated by the team leader and that have provided useful international connections as reflected by several collaborative publications. The team leader is frequently invited to international meetings and institutions for seminars. He participates or chairs several national and international grant review committees. He and another team member are members of the editorial boards of scientific journals that include PLoS One. The team has (co-)organized national-level meetings.

Team's interaction with the social, economic and cultural environment

Thanks to the translational nature of part of the research activity, the team is active in promoting interaction with patients' organizations (e.g., VML, AFM). The team leader is involved in or has initiated partnerships with the industry through collaborations and consulting activities. As for technology transfer, the team leader has developed with private structures in Portugal GMP-quality platforms for CAV-2 vectors production and purification.

Team's organisation and life

The team consists in the PI, a permanent junior researcher and an assistant professor as staff scientists, 3 post-doctoral fellows, 3 PhD students and an engineer (paid on a contract with the industry). The research is organized as sub-groups involving 2-3 people in the different themes, under supervision of the PI. The senior laboratory members participate to grant application writing. All team members gather weekly to exchange results and provide critical analysis to lab meetings. They have the opportunity to participate in national, European or overseas meetings.

Team's involvement in training through research

The team demonstrates a strong training of PhD's and post doctoral fellows. Four students have obtained their PhDs during the last period. Two HDR have been obtained. The team members are involved in teaching at UM2. The senior lab members are encouraged to supervised master and PhD students.

Strategy and the five-year plan

The 2015-2019 projected structure of the team research activity concerns 4 topics, most related to CAV investigated as a pathogen or, alternatively, as a tool for (therapeutic) gene transfer.

A first line of investigation concerns the functions and trafficking of CAR (coxsackievirus adenovirus receptor), which is a well-characterized adenovirus receptor. Although CAR plays a role in synaptic plasticity, its role in uptake and transport of pathogens, as well as its role in neuron biology, remains unclear. The team will study neuron-specific CAR-deficient mice through both physiological and cellular approaches. Secondly, they will focus on how CAR internalization is induced in neurons by studying the role of lipid rafts, dynamin, actin in CAR endocytosis, where CAR is targeted post-internalization after somato-dendritic internalization or axonal transport, and in vivo in the rodent brain.

A second line of investigation is to study the intricate interactions between viruses and DC at the time of primo-infection. How immune-complexed viruses (ICV) interact with DCs has been largely neglected despite the many situations where these interactions can occur with these recurrent pathogens and their diverse biological consequences. Through a combination of genetic and pharmacological approaches, the aims are to understand how Ad-IC induce the maturation of human DCs and what are the cellular and immune pathways involved or induced when Ad-IC are administered to DC mixed to primary lymphocytes. This project will have practical input in the development of non human adenovirus vectors as potential clinical tools for clinical gene transfer.

A third line of investigation is to study Mucopolysaccharidosis (MPS) type VII. This group has used MPS VII induced pluripotent stem (iPS) cells to better understand the cellular defects associated with GAG accumulation and mechanisms associated with neuronal impairment in MPS VII cells. Using iPS cells from patients differentiated into neural precursors cells and neurons, the group aims to continue preliminary studies to characterize synapse functions, vesicular transport and autophagic flux. Analysis of neuron functions in MPS VII will be performed combining real-time imaging, biochemistry, electrophysiology and microfluidic chambers, which will potentially open new avenues to design novel therapies directed to the CNS.

Finally, the team will pursue the development of vectors derived from CAV-2, that afford long-term expression, preferential transduction of neurons and 30 kb cloning capacities, and will continue the technical development of this vector platform aiming at exploring its clinical potential. In collaboration with private and academic labs, they will also develop Parkinson disease animals in rodents and primates that will be then used to screen for drugs affecting different Parkinson disease parameters.

Conclusion

- **Strengths and opportunities:**

Solid team that has acquired a strong expertise in the different fields of research originally derived for the study of CAV and development of vectors for therapeutic research. Overall, the research topics are interdisciplinary, well focused and relatively complementary. They form an excellent continuation of the previous plan. The technical, financial and scientific feasibility of the 2015-2019 plan is excellent. The scientific and technical expertise is recognized internationally and provides important collaborative opportunities.

- **Weaknesses and threats:**

No permanent technical help has been available since the team was created in 2001, with a risk of losing lab memory.

- **Recommendations:**

There is a difficulty to conduct very high profile research in several totally distinct areas and the team may consider placing focus on a more reduced number of topics.

Team 10: Oncogenesis and Immunotherapy

Name of team leader: Mr Marc PIECHACZYK

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	5	5
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	8	8

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Scientific quality and outputs

During the evaluation period the team has worked on exciting and important questions relating on the role of AP-1 and ubiquitin/proteasome/sumoylation in oncogenesis and on immunotherapy using a retroviral model system. Regarding the oncogenesis studies, the team has published 18 papers in very good journals including Mol Cell Biol, J Immunol, NAR, Oncogene and e.g. discovered an unexpected oncogenic role for JunB in the G2 phase of the cell cycle, where its degradation through a phosphorylation/ubiquitin-dependent mechanism is required for progression (Mol Cell Biol 2008). The team has also launched on a new project in this area aiming at understanding how AP-1 components Fra-1 and Fra-2 are deregulated in breast cancer and contribute to breast cancer metastasis (submitted). Another important observation for future studies is that the sumoylation pathway is important for chemosensitivity in acute myeloid leukemia (AML) and further that forced activation of the pathway restores chemosensitivity to chemoresistant AML cells (submitted). Additionally, the team has published 5 papers immunotherapy studies in very good journals including PLoS Pathogens, Blood, and J Virol. and where the key observation is that monoclonal antibody treatments can act as vaccine-like therapies. In addition, the team has participated in several collaborative studies due to their expertise in the ubiquitin/proteasome/sumoylation area totalling 30 publications during the evaluation period including eight where the Group Leader is senior/corresponding author. Publications in the ubiquitin/proteasome/sumoylation area have received most interest based on citation numbers.

Reputation and appeal

This is one of the founding groups of IGMM and has made a great contribution to the IGMM effort as a whole since 1993 including the role of the group leader as deputy director 2005-2010 and director of IGMM since 2011. The current international group consists of three staff scientists (CR1) as well as 3 post doctoral fellows and 3 graduate students. The group has received a number of external grants during the evaluation period including the "Equipe Labellisée" of the French National League Against Cancer and several of these continue until 2014-2015. Several EU projects where the group leader has significant responsibilities are providing very useful international connections reflected also as a number of collaborative publications. The group leader is an active organizer of scientific national meetings and e.g. co-organized a "Proteolysis in Cancer" EMBO workshop in Spain during the evaluation period. He is frequently invited to European meetings and institutions for seminars. The team has also been active in technology transfer in the way of licensing a patent on encapsulated cells producing antibodies to a biotechnology company.

Team organization

Although the team leader acted as director during the evaluation period, a clear description of responsibilities for senior personnel in each large theme has enabled impressive accomplishments during the evaluation period. Despite this, the team leader presented a plan to reduce number of projects in the 2015-2019 period considering the continuing significant responsibilities. This involves refocusing efforts to the ongoing breast cancer and AML projects whereas the immunotherapy program (3.5 persons out of 11-12 group members) is planned to become independent by 2017 possibly in conjunction with reorganization of research in infectious diseases on the campus and/or with another group at IGMM.

Involvement in training

The report described a careful general plan and organization for training of PhD's and post doctoral fellows. Team members are involved in excess of 20 hours/year of teaching. The team has supervised 4 PhDs and one HDR during the evaluation period.

Five-year plan and strategy

The team's plans for 2014-2019 plans have a significant part dedicated to the question of how Fra-1 and Fra-2 are involved in metastasis. The approach is to use MDA-MB-231 cells to characterize Fra-1 and Fra-2 DNA-binding sites genomewide and to analyze transcriptomic effects following downregulation of Fra-1 or Fra-2. Potentially interesting genes identified from these analyses are tested in regard of their contribution to metastasis in more detailed

approaches including xenograft models. In this part, selecting the right targets may be a challenge and, to this end, setting strict criteria will be important. The team should also be very confident that high Fra1/Fra2 truly drives metastasis, which currently apparently has been demonstrated by others using a single cell line as this forms the basis for this line of investigation. One option would be to use the xenotransplanted tumors available as a collaboration.

A second major line of investigation is to establish the mechanism by which chemotherapy-induced desumoylation is involved in apoptosis of the AML cells and to try to reactivate it in chemoresistant cells. The approach is to identify proteins desumoylated in chemosensitive cells but not in chemoresistant following addition of AraC or daunorubicin and integrate these results from both transcriptome changes and ChIP-seq results (upon anti-sumo immunoprecipitation) to identify potential target genes important in AML cell death. The niche of the team would be in identifying targets specific for the chemoresistance as both analysis of sumoylated proteins and Sumo binding sites in the genome are very competitive areas. A significant advantage in this is the clinical material from Toulouse and possibly Montpellier.

Regarding the immunotherapy part, the goals for 2015-19 include elucidating the cellular and molecular mechanisms responsible for the induction of the protective antiviral immunity, with a particular emphasis on the interaction between immunotherapy-induced immune complexes and the various immune cell types. The proposal that this theme is separated from the team leaders responsibility is supported.

Conclusion

The team leader is a strong leader with an outstanding track record and continuing very good production of important new scientific results regarding AP1/ubiquitin/proteasome/symoylation and immunotherapy studies.

- **Strengths and opportunities:**

Scientific and technical expertise and recognized position internationally in the field.

Future plans are well focused on transcriptional reprogramming underlying metastasis in breast cancer and AML and contain realistic translational aspects.

- **Weaknesses and threats:**

Future plans are partly based on unpublished work: team would like to aquire first-hand knowledge that Fra1/Fra2 have roles as drivers of metastasis as well as establishing that desumoylation mediates chemosensitivity in broadly in clinical AML.

- **Recommendations:**

If possible the team leader should delegate some managerial aspects of the director's position to ensure sufficient time for the scientific endeavour.

Team 11: Chromatin and DNA Replication

Team leader: Ms Marta RADMAN-LIVAJA

Worforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	4	3

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		1

• Detailed assessments

Assessment of scientific quality and outputs

Taking into account the recruitment of the team leader as a permanent junior staff researcher at CNRS in 2013, this section was not evaluated.

The team leader here describes mostly the results of her research as a post-doctoral fellow. Her plans for the next 5 years clearly rely on and continue these achievements.

Assessment of the team's academic reputation and appeal

The team leader has just recently joined the IGMM and started to build her team. Her achievements as a graduate student and especially as a postdoctoral fellow were very favourably appreciated by the CNRS / ATIP committee since she was selected by this very selective international jury.

Assessment of the strategy and the five-year plan

The team leader proposes an ambitious research program mostly relying on her post-doctoral work. This program encompasses 4 themes that, in general, consider the impact of DNA replication on epigenetic issues (histone and histone mark inheritance) and genome organizations in yeast as a model system. The first project concerns whether or not the distribution of the Sir complex bound to subtelomeric chromatin is maintained during replication and what is its turnover? A second aspect concerns the inheritance of the maternal histones and their spread. This will be further investigated with an original tritium pulse labeling approach followed by chromatin immunoprecipitation. The third related project will investigate the rate of histone assocciation and covalent modifications in newly replicated DNA on both leading and lagging strands. Finally, the effect of changes in chromatin pattern establishment on phenotype determination and maintenance will be studied. The proposed projects concern important conceptual issues although they sound too broad in a very competitive area.

Conclusion

- **Strengths and opportunities:**

The team leader is a talented young investigator. She has obtained a strong support from IGMM and CNRS. The team is very well complementing the IGMM epigenetic community and can benefit from their methodological and conceptual expertise.

- **Weaknesses and threats:**

The proposed projects are too ambitious considering the present size of the team (one assistant engineer and two post-docs). The team leader has been very active in asking for additional funding. She has established a priority order in her projects and has considered their development as a function of additional human and financial means. However, she should remain vigilant in remaining focused on her priorities.

- **Recommendations:**

It could be advisable that the Institute chooses a senior mentor to help her develop her project in the most effective way.

Team 12: DNA Replication, Genome Instability & Cell Identity

Name of team leader: Mr Etienne SCHWOB

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	2

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team was created in 1996 and has published high impact articles. In the last years, the group has investigated the role of G1 regulation and excess replication origin licensing in genomic stability in yeast and mammalian cells. The team was also interested in chromosome instability as a result of mitotic entry in the presence on incompletely replicated genomes. In addition, the team was involved in additional projects to investigate the role of centromeric replication or the interplay between metabolism and mitochondrial function in genome stability. Since 2008, the productivity has been lower with few publications with members of the group as first or last authors. The team leader has published, as senior author, several manuscripts in journals such as *Mol. Cell. Biol.* (2008; on the role of DDKs in replication), *G3* (Genes, Genome, Genetics. Bethesda) (2013; on metabolism and genomic instability in yeast), and more recently a manuscript in *J Cell Biol* (to be published in 2014) reporting the checkpoint activities required for delaying mitosis during DNA replication. In addition, he has collaborated with multiple international teams in publications in journals such as *PNAS*, *EMBO J.*, *Genes & Dev*, etc. These collaborations are in most cases a consequence of the technical expertise of the group in single-molecule techniques for the analysis of DNA replication, and these collaborations are likely to be maintained, increasing the international visibility for the group in the field. This record of publications is quite limited in terms of the work originated in the laboratory although it seems to be improving significantly in the last months.

In addition to these publications, work in the laboratory has described the formation of breaks in late replicating DNA as well as the dynamics of DNA replication in cancer cells using different genetic models. The group has also shown that these problems in replication can cause mis-orientation in sister chromatids leading to chromosome numeric aberrations. Some of this work is shown as “in preparation” or “submitted”. In addition, some of the preliminary results on the differential DNA replication dynamics in different genetic backgrounds are very interesting for understanding cell identity in mammals and will be the basis for the plan of research in the future. Finally, the group is very interested in new technologies for the analysis of these problems, including high-throughput assays, automatic software etc. The team leader is director of the Montpellier DNA Combing Facility, a technique that has been a significant addition to the field and has originated many collaborations in the last years.

Assessment of the team’s academic reputation and appeal

The team leader is recognized at the international level as an expert in DNA replication and single-molecule techniques such as DNA combing. He maintains a high number of collaborations at the national and international (UK, Spain, USA, etc.) level. He heads the DNA Combing Facility and, given the multiple collaborations, this is helping to increase the academic reputation of the group not only in publications but also in international meetings etc.

The group participates in several networks and committees although only at the national level. Similarly, the team leader has been involved in the organization of several national meetings and some conferences in Europe and Japan, in addition to France. The group only receives funding from national agencies.

The team leader is member of the editorial board of F1000 Research and has received the L. Tartois Prize in 2008.

Assessment of the team’s interaction with the social, economic and cultural environment

The team participates in several social and cultural activities, including conferences in schools and associations etc., and is responsible for Public relations at the IGMM. The group is responsible for the DNA combing Facility, used by many groups worldwide and also generated a patent recently. This Facility is very important for the visibility of the group and participation in many cultural aspects.

Assessment of the team’s organization and life

The size of the team is reduced at this moment although all different levels from staff scientists to technicians are represented. New staff scientists and postdoctoral fellows will be recruited soon improving the manpower in the group. Routine activities such as meetings, discussions, etc. are appropriate. Several members of the group participate in multiple activities and local responsibilities.

Assessment of the team's involvement in training through research

The team leader supervises 1 PhD student and 1 postdoctoral fellow and people trained in the laboratory have found positions in other institutions. He has also participated as jury member and part of the committees for several theses and HDR. The group also organizes practical courses at the international level.

Two theses have been defended over the period and 9 additional students were trained in the laboratory.

Assessment of the strategy and the five-year plan

The plan for the next 5 years is well organized and partially based in the expertise of the group and previous projects. Some of the proposals are related to the use of yeast or mammalian cells to address fundamental questions in DNA replication and genome stability. These projects are mostly based on the use of yeast as a model system and are well based on the previous expertise of the group. Their last publication shows how DNA replication can be uncoupled from mitotic entry and this surprising finding opens many questions, molecular mechanisms, parallel processes in mammals, etc. that the group wants to address. In addition, the expertise in DNA replication techniques will be now applied to a number of genetically engineered mammalian cells to describe in detail how specific mutations modify DNA replication dynamics or what is the relevance of individual molecules involved in the cell cycle control (e.g. retinoblastoma protein, etc.). Second, they are interested in studying the unusual S-phase in pluripotent cells and how the specific dynamics in these cells compare to tumor cells. Finally, they are also interested in using yeast to explore the role of asymmetric kinetochore deposition. These ideas will be accompanied with the development of methods for single-cell replication analysis, a brilliant idea for the future in which quantitative biology in single cells is a must. These projects are likely to result in solid data and important publications as they are fully supported by the technical and scientific expertise of the team.

Some new projects are related to cell identity in pluripotent cells and are very attractive although some technical setup and collaborations will be required to start these projects. The plan is very good and the group has to make an effort to make original contributions from the laboratory, in addition to establish or maintain collaborations to strengthen some particular aspects of the project.

Conclusion

The team emerged in 1996 with a clear focus on cell cycle regulation, DNA replication and genome stability originally using yeast as a system model. This expertise is well recognized at the national and international level as indicated by the number of international activities and collaborations. However, the activities and productivity of the group have been limited in the last few years, and as a consequence the funding of the group is also reduced. The number and quality of unpublished results however suggests that the group will recover the levels of high-quality publications. Current interests for the group include the analysis of replication patterns in progenitor cells and the connection between regulation of DNA replication and the establishment of pluripotent chromatin or the asymmetric segregation of cell fate determinants. First objective is based in the analysis of molecular mechanisms regulating late replication, a continuation of the previous projects. This objective will benefit from genetic models and technologies developed in the last years. In general, the design of the projects is appropriate, based in the expertise of the group and promoted by technical innovations. The group, however, should be able to publish some of the recent works to get the appropriate funding for these projects. Promoting international (European) collaborations for EU funding, perhaps based on the cutting-edge technologies available at the lab would also help in the development of these projects.

- **Strengths and opportunities:**

Scientific and technical expertise in the field.

Good vision on how to apply these techniques to biological processes of high interest at the moment.

Recruits scientists with high technical skills and motivation.

- **Weaknesses and threats:**

The group needs to recover a critical size and funding.

The group needs to accumulate a few more publications to increase visibility (and likely funding).

- **Recommendations:**

Generating high-quality publications from the preliminary results already obtained is a must at this moment.

It would be essential to start new collaborations in the iPS field, but it would be also very important to incorporate this expertise to the group to avoid complete dependence on external groups and to facilitate the proper extension of these projects in the future.

Team 13: Retroviruses, Envelopes and Metabolic Markers

Name of team leader: Mr Marc SITBON

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	6
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	10	10

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs

The work of this team is largely based in the field of retrovirus biology, with two evident strands of activity. 1) Retrovirus Envelope glycoproteins and their cellular receptors; 2) Cell-encoded factors that suppress virus infection (restriction factors). The team is highly collaborative, publishes in prestigious peer-reviewed journals (e.g., Cell, Nature, PNAS, Cell Reports), and senior authorships are distributed within the team and with colleagues at IGMM. A major focus has been the cloning of retrovirus receptor binding domains (RBDs), and their exploitation as probes for identifying entry receptors, leading to their development as tools for tracking cell surface expression especially in the context of oncogenic and metabolic processes. Highlights include the identification of GLUT1 as a receptor for HTLV-1 (with another team at IGMM), the discovery that the receptor for xenotropic MLV (X-MLV) – XPR1 – is a cellular phosphate exporter, and the concept that RBDs may be useful tools for characterising nutrient transporter expression profiles. The studies on retrovirus restriction have not featured as prominently to date, though preliminary evidence indicating the existence of additional intracellular SIV/HIV restriction factors (i.e., a saturable activity called Ref2) that operate through Capsid is tantalising. Lastly, the team also contributed to the body of evidence that disproved connections between XMRV infections and human disease.

Assessment of the team's academic reputation and appeal

The team is recognised internationally for its contribution to retrovirus biology as testified by high profile publications, international collaborations, organisation of international meetings ("International Workshop on Retroviral Pathogenesis" , ANR workshop on Transmission", and invitations to speak at different forums such as Gordon Conference on Transporters, "International Workshop on Retroviral Pathogenesis, "International HTLV meetings", "BMC meetings", Linda Wolff Symposium-NIH/NC. The team participates in 2 Labex and the team leader has initiated a consortium including a number of clinical departements for the use of RBDs as biomarkers. They have received several european grants. The team leader has been invited as visiting scientist in Canada and USA. The team has recruited 1 CNRS and 1 INSERM permanent staff researcher.

Assessment of the team's interaction with the social, economic and cultural environment

The team has been successful in launching a biotechnology company on the basis of the discoveries of groups members. They filed 6 patents during the period under review. They have been very active in outreach activities for public awareness and knowledge transfer to high-school and elementary school students. They have also developed partnerships and consulting with biothechnology companies.

Assessment of the team's organisation and life

Sounds perfect.

Assessment of the team's involvement in training through research

Three students gained their PhDs during the last reporting period. The team is also comprised of two additional permanent staff scientists both of whom have published independent, senior author manuscripts. One former team member, now appointed at Institut Curie, Paris in 2010, is establishing a prominent reputation in the area of HIV and innate immunity.

Assessment of the strategy and the five-year plan

Investigations in three areas are summarised. 1) Restriction Factors: cDNA library expression and shRNA approaches are noted as strategies to identify nuclear pore complex (NPC) components important for infection by some SIVs, as well as the saturable restriction Ref2 of some viruses. High throughput technologies such as lentivirus shRNA libraries are available locally, and encouraging preliminary results showing rescued infectivity in the context of Ref2 restriction in Jurkat and U2OS cells have been obtained. This is a relatively minor interest of the group, but,

even though the field is competitive, it is possible for a talented scientist to make an important impact single-handedly. 2) Retrovirus Envelopes and Receptors: two areas will be explored in further details. First, the RBDs of BLV and PERV-B will be used to characterise the expression profile of the cognate receptors, potentially leading to the identification of the hithertofore unidentified receptors. Second, bioinformatic tools will be utilised to find potential endogenous RBDs in the human genome; should this be successful, the characterisation of the RBDs together with the profiling of their receptors will be pursued using established approaches. 3) Nutrient Transporters: the team is pioneering the application of retrovirus RBDs as diagnostic tools to track expression of their receptors, which are often nutrient transporters. The utility of the approach has been demonstrated for breast cancer tumours and there is much scope to derive panels of engineered RBDs with novel patterns of transporter recognition. This approach has benefits over "more standard" ones in that it is rapid, inexpensive and amenable to further development. This topic is also ripe for collaboration with various teams which may be interested in particular receptors; the track record of the team is one of successful collaboration, and this project is recognised as an area of scientific distinctiveness. Finally, a biotechnology company has been launched on the basis of this technology.

Conclusion

The foundation of the programme continues to be retrovirus biology. The principal focus of past and future activity is viral envelope glycoproteins and their cellular receptors. The team's plans reflect a good balance between analyses of genes/proteins that have already been identified, discovery of new genes, and the application of RBDs to more translational applications. The additional project on retrovirus restriction receives less resource, but has the potential to make valuable contributions to the field. Overall, this internationally recognized team is harmonious, collaborative, and receives external funding from a number of agencies.

- **Strengths and opportunities:**

Internationally recognised team, publications in prestigious journals, collaborative, diverse funding (national and international), industrial and clinical partnerships, translational research perspective

- **Weaknesses and threats:**

Smallish group, insufficient technical support, low numbers of PhD students, limited laboratory space, restrictive policies/laws on staff retention and recruitment.

- **Recommendations:**

The group is encouraged to increase its working force.

Team 14: Hematopoiesis and Immunotherapy

Name of team leader: Ms Naomi TAYLOR

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	
N2: Permanent EPST or EPIC researchers and similar positions	5	5
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	9	8

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs

The achievements of this group over the past five years have been in 4 related but distinct scientific areas within the hematopoietic system:

- Improvement of HSC therapy by thymus targeted approaches for immune deficiencies;

- Improving the induction of lymphopenia for anti tumour T cell therapy;

- Glucose transporter Glut1 in T cell function, differentiation and retroviral infection.

Glucose and other nutrient transporters in hematopoietic differentiation

The publication of this group has been outstanding over the evaluation period. They published, with the team leader as last author, one Cell paper and 4 further primary data papers in journals with impact factor >10 (Blood, PNAS). Additionally the 2 senior scientists in the group published each a paper in journals with impact factor from 5 to 7. With fourteen members in the team this is a very acceptable output over 5 years. Additionally three patents have been filed.

This compares favourably with successful laboratories in other countries and would attract funding at international level elsewhere. Indeed the funding record of the group is well above average in terms of number of awards and funds received, when compared to the other IGMM groups. The research interests are an exciting blend of basic/discovery and translational projects, the latter being underpinned by the team's active involvement in 2 clinical trials.

Assessment of the team's academic reputation and appeal

The team leader is well established as an international leader in her field. She has taken leadership in several international networks and has organised a number of high profile international meetings.

Moreover, the group is very well integrated in the research programmes at IGMM, with on-going fruitful collaborations (for example using invaluable reagents developed by another team at IGMM). The existing collaborations with prominent US laboratories help to the success of the team and have been fostered both through visits of the team leader herself as well as through exchanges of postdoctoral fellows.

Assessment of the team's interaction with the social, economic and cultural environment

The team has licensed two patents, has conducted research for the FDA and is involved in the EU consortium ATTACK2 that will carry out a muti-centre NY-ESO based T cell therapy for metastatic melanoma and gastro-oesophagal cancer.

Assessment of the team's organisation and life

The group is formed of 3 permanent senior staff scientists in addition to the team leader, 5 PhD students, 1 technician and 3 post-doctoral fellows. The staff scientists help to drive the different programs; this is also illustrated by the fact that they are senior authors on some of the major publications of the laboratory.

Assessment of the team's involvement in training through research

The team has trained 6 PhD students (completed) and 17 undergraduate students. The team leader and her team are running an MSc programme, and are involed in other undergraduate and graduate teaching.

Assessment of the strategy and the five-year plan

The future projects continue to address the established and distinctive areas that the team has worked on over the past five years, namely

(1) the intrathymic gene and stem cell targeting for T cell reconstitution (mouse models). The group will pursue the use of Zap70 mutant mice and intrathymic injection of progenitor T cells expressing the gene driven by various promoters. The survival of these cells will be followed with the final goal to apply these to human gene therapy.

(2) conditioning hematopoietic differentiation via nutrient transporters. The team will establish the cell surface "transportome" signatures for murine and human hematopoietic progenitor subsets and determine the role of different nutrient transporters and metabolic pathways in HSC expansion and differentiation.

(3) role of lymphopenic environment on T cell metabolism. The group will investigate how chemotherapy regimens alter the fate of adoptively transferred tumor specific T-cells and establish the role of metabolic changes triggered by chemotherapy and tumor progression on general and tumor specific T-cell fate.

(4) impact of glucose and glutamine metabolism on HIV infection in primary T cells. The team will study the role of the Glut1 glucose transporter in the infection of IL-7 and TCR activated CD4 T cells by X4 and R5HIV strains under physiological oxygen conditions and the role of ASCT-2 mediated glutamine transport in HIV-1 infectrion.

There is a focus on energy metabolism in the areas 2 to 4. The group benefits from outstanding reagents developed by another team at IGMM while also creating their own tools and methodologies to analyse metabolism and signalling in primary cells and in the context of hematopoeitic cell differentiation (Seahorse, phosphoflow, etc).

Conclusion

Even though the team's interests span an ambitious range of topics, it is apparent that the team leader is managing them expertly and is at "the top of the game". With the help of her staff scientists, the team will be able to continue publishing in top peer-reviewed journals. The panel felt that the team was one of the successful and international visible groups in the institute. The panel strongly recommends that the team leader applies for an ERC advanced grant as the main principal investigator.

- **Strengths and opportunities:**

Internationally recognised team;

Publications in prestigious journals;

Collaborative, diverse funding (national and international), industrial and clinical partnerships;

Translational research perspective.

- **Weaknesses and threats:**

Immune metabolism is a highly competitive field;

Loss of focus;

Lack of space for expanding the lab;

- **Recommendations:**

Stay more focused;

Apply for ERC grant as principal investigator.

Team 15: Metazoan Messenger RNA Metabolism and Splicos Cooperative Laboratory

Name of team leader: Mr Jamal TAZI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	8	5

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team's projects arise from their long-standing interests in alternative RNA splicing and its contributions to physiology and pathology, and in cell-encoded regulatory proteins most notably the SRSF proteins (e.g., SRSF6/SRp55). There is also a strong translational/ technology arm to the programm, and a drug discovery company has been established. A wide range of experimental systems is employed for the work, including cultured cells (including iPSCs), flies, mice and viruses. The team is collaborative, and publishes consistently in prestigious peer-reviewed journals (e.g., Cell, Nature Neuroscience, Nature Cell Biology, Nature Communications, PLoS Genetics). Some of the more recent highlights include: 1) recognising roles for alternative splicing factors in processes other than splicing, e.g., the interaction of SRSF6 with topoisomerase 1 and the suppression of competition between DNA replication and transcription; 2) discovering that splicing profiles change during the reprogramming of cells (fibroblasts) into iPSCs, and subsequent redifferentiation, and that MBNL1 and the forkhead protein RBFOX2 are important regulators: one important implication being that splicing alterations may be just as important as transcriptional changes for establishing and maintaining pluripotency (published in Nat Comm); 3) establishing a mouse model for the premature aging condition Hutchinson-Gilford Progeria Syndrome (HGPS), where alternative splicing of the lamin A pre-mRNA is disrupted by mutation and connections with energy metabolism have been recognised; 4) undertaking CLIP (cross-linking/ immunoprecipitation combined with deep sequencing) to define the RNA ligands for the stress granule protein G3BP, and finding preferential binding to introns and non-coding RNAs, as well as a retention of these introns in the cerebellum (relative to other parts of the brain). Coupled with this, viable G3BP-deficient mice have been studied, and perturbation to glutamate receptor activity noted (indicative of diminished neuronal plasticity); 5) exploring the manipulation of alternative splicing as a therapeutic avenue, in particular using indole derivatives: some encouraging results have been obtained in cultured cells with HIV-1, a virus that uses extensive alternative splicing to express its full complement of proteins. Recent updates on a lead compound, SPL-464, were presented; the mechanism of action appears to be via a cell-encoded micro-RNA and its modulation of a cellular splicing factor.

Assessment of the team's academic reputation and appeal

The team is recognised internationally for its contributions to the field of alternative splicing of both cellular and viral RNAs and its potential for pharmacologic targeting. They have established a large number of collaboration at the national and international, which resulted in publications. The team leader and team members have been invited regularly to international meetings. The team is member of the EURASNET netwok on alternative splicing and coordinator of a "Laboratoire Européen Associé" which includes one French and one German laboratory. Team members have organised 2 international meetings on Alternative splicing and disease and several workshops at national level. The team has recruited 3 staff CNRS scientists, 2 post-doctoral fellows, and several other scientists

Assessment of the team's interaction with the social, economic and cultural environment

The team leader suceeded in establishing a successful biotechnology company that has secured considerable funds to bring to clinical trials an HIV inhibitor. In addition, he created a common UMII-CNRS-Splicos laboratory at IGMM that pursues research on inhibitors of splicing.

Assessment of the team's organisation and life

The team includes permanent scientists who are supervising the different research projects of the team. One issue raised by the committee concerns the compatibility between PhD projects and the secrecy required for projects of a biotech company.

Assessment of the team's involvement in training through research

The team leader is a full professor at UMII and assumes major responsiblities at the level of graduate teaching. Six students gained their PhDs during the last reporting period. The team hosts two staff scientists, a CR1 and a CR2, and both have published first/ senior author research papers.

Assessment of the strategy and the five-year plan

The future plans of the team are organised into three themes. 1) Characterisation of alternative splicing patterns and the identification of cellular factors that regulate these processes. This work will be undertaken in a number of settings, including flies, invasive cancers and reprogrammed stem cells. The current approaches are descriptive in nature in that profiles of splicing will be defined, their alteration in response to cues (changes in cell state, altered expression of trans-acting factors, etc) addressed, and regulatory events recognised in the broadest sense. What is less obvious is the longer term vision: the rationale leans towards defining genome-wide patterns of splicing as opposed to seeking to understand the principles of alternative splicing, identify important regulatory proteins, elucidate the molecular details of how such regulators work, or identify key molecules in cellular processes whose regulation by alternative splicing underpins altered function. It might be more prudent to maintain more flexibility on experimental outlook, as there remains a great deal to be learnt about the molecular basis for alternative splicing, its regulation, and its relationship to other cellular processes such as (rates of) transcription. 2) Building mouse models to study pathologies where RNA processing and its regulation play central roles. Two models are discussed, HGPS/premature ageing where alternative splicing of lamin A RNA is important; and G3BP's role in the function (and dysfunction) of the brain, though this latter project will be terminated once the data have been published. The HGPS project has yielded interesting data, but the longer term aspirations for this project and whether the team is equipped to analyse in depth changes in metabolism, behaviour, neurodegeneration, and so forth are not made clear. 3) Pursuing pharmacologic interference of alternative splicing, as part of a close relationship with the biotechnology company, as a potential therapeutic for HIV, cancer, obesity, etc.

Conclusion

The group has made a number of exciting findings in recent years and momentum is good; however, the report is descriptive in places and delineation of more clearly defined future objectives, rationale and directions of travel would have been instructive. Overall, the team is collaborative, is publishing well and receives additional funding from commercial sources and research agencies.

- **Strengths and opportunities:**

Internationally recognised team, publications in prestigious journals, large size of team (currently 13 members), diverse funding (including commercial), industrial partnership.

- **Weaknesses and threats:**

Low numbers of PhD students in Montpellier, broad diversity of research projects, potential conflicts between commercial and academic research.

- **Recommendations:**

An effort should be made to elucidate the detailed molecular mechanisms that control alternative splicing and to identify key genes that affect the biology of cells and organisms by alteration in their alternative splicing. The effort to link the basic knowledge on splicing to biotechnological development is highly appreciated. However, an effort should be made to allow PhD students or post-docs who are part of the common laboratory to communicate and exchange freely their results.

Team 16: Transcription and Epigenomics in Devlopping T-Cells

Name of team leader: Mr Jean- Christophe ANDRAU

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions		1
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		4
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6		5

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		1

• Detailed assessments

Assessment of scientific quality and outputs

This is a newly formed group at IGMM, starting January 2014. The team leader previously worked semi-independently at the Marseille CIML Institute. The scientific emphasis of the group is the application of genomic analyses to characterise transcriptional processes associated with T cell development.

The team leader has a very strong track record in the transcription field as he has worked in a number of top transcription laboratories as a graduate student and postdoc and published a number of excellent papers in the field (Mol Cell, EMBO J, Nat Struct Mol Biol). In Marseille he has moved towards an independent position and has also collaborated with several excellent European laboratories. His team has studied T cell enhancer transcription and also nucleosomal organisation around promoters and enhancers. Finally they have worked on RNA polymerase II CTD modifications (especially Thr4 and Tyr1 phosphorylation). The work during the evaluation period has resulted in 12 publications with 9 with the team leader as a senior author, including 2 Nature Struct Mol Biol, 1 EMBO J, 1 Methods, and 1 Annual review Genet.

Assessment of the research team's academic reputation and appeal

The team leader has highly visible international position in the study of transcription and epigenetic (Associated Member of the European FP7 'Epigenesys' network, co-organizer of a joint EMBO/Epigenesys course on noncoding RNAs in 2014)

The project of the team regularly attracts funding by several organizations including ANR, FRM, FP7 funding.

The team has recruited 2 foreign post-doctoral fellows.

Assessment of the research team's integration in the unit's organisation and life

The team has just joined the structure. Perspectives are promising.

Assessment of the strategy and the five-year plan

The project at the IGMM is to perform more systematic genomic analyses of T-cell transcription at a range of developmental stages and to try to precisely correlate genomic/transcriptomic patterns with T cell development. The team will also plug into this approach analyses of RNA polymerase II CTD modification patterns as well as nucleosome density as affected by CpG island promoters. A danger with this research proposal is that it will at least initially be largely descriptive. The challenge will be to show by experimentation that particular promoter enhancer/polymerase features uncovered do directly play a role in T cell development, rather than occurring indirectly as a consequence of other molecular events. The research program is very ambitious and its feasibility is good despite its complexity. Additional human and economical resources would be advantageous.

Conclusion

The team leader has an high international visibility in the field. The excellent research project represents the natural continuation of the work done in the past few years. This situation guarantees the feasibility of the proposed experiments and promises very interesting results.

- **Strengths and opportunities:**

The team leader has a strong experience in RNA seq and other genome-wide approaches. The interactions with the other team of the IGMM could be a real opportunity for the development of an efficient bioinformatic platform dedicated to high-throughput sequencing analysis.

- **Weaknesses and threats:**

The team has not a sufficient critical mass to perform the ambitious program planed for next years. There is a tendency to develop too many projects at the same time, which might weaken the potential of the team. Similar genomic approaches are being carried out by numerous other labs internationally.

- **Recommendations:**

It is therefore important for this group to develop its own research "niche" so as to avoid being in competition with other larger, stronger laboratories.

The possibility to maintain existing collaborators specialized in bioinformatic is critical. In addition the team should incorporate additional scientists from CNRS or University in a near futrure.

5 • Conduct of the visit

Visit dates:

Start: January 20th, 12 a.m.

End: January 22nd, 3 p.m.

Visit site: IGMM

Institution: CNRS

Address: 1919, Route de Mende - 34293 Montpellier Cedex 5

Conduct or programme of visit:

The general presentation by the director will be public. *However, due to the limited capacity of the seminar room of IGMM, the first session (Monday 20th, 14h00-15h) will also be shown in the auditorium of the CNRS Regional Delegation (videoconference).*

The presentations by the groups will be "private" in the presence of the director. They will be followed by discussions with group leaders only (i.e. in the absence of the group and of the director).

Monday, January 20th

Morning:	Arrival of Committee Members
Late morning:	Visit of IGMM and Campus
12h00-13h15:	*Lunch (members of the Committee and the AERES Scientific Delegate)*
13h15-13h45:	Closed-door meeting: Committee Members and Scientific Delegate of AERES
13h45-14h00:	Presentation of AERES evaluation and Committee to IGMM by the Scientific Delegate of AERES and the Chairman of the Committee
14h00-15h00:	Presentation of the IGMM report and project by the director
	Presentation
	Discussion with director
15h00-16h35:	Presentations of 2 teams by group leaders
15h00-15h50:	Mr Edouard BERTRAND
	(presentation, discussion with group and alone)
15h50-16h35:	Mr Remy BORDONNÉ
	(presentation, discussion with group and alone)
16h35-17h00:	*Coffee Break (Committee and Group Leaders presenting on Monday)*
17h00-19h15:	Presentations of 3 teams by group leaders
17h00-17h45:	Ms Solange DESAGHER
	(presentation, discussion with group and alone)
17h45-18h30:	Mr Robert FEIL
	(presentation, discussion with group and alone)

18h30-19h15: Mr Daniel FISHER

(presentation, discussion with group and alone)

19h15-19h45: Debriefing of the first day (closed-door meeting of the Committee)

20h30: Private dinner of the Committee + AERES Scientific Delegate

Tuesday, January 21st

8h15-8h30: Arrival of Committee at IGMM

8h30-10h45: Presentations of 3 teams by group leaders

8h30-9h15: Mr Thierry FORNÉ

(presentation, discussion with group and alone)

9h15-10h00: Mr Michel HAHNE

(presentation, discussion with group and alone)

10h00-10h45: Ms Ula HIBNER

(presentation, discussion with group and alone)

10h45-11h10: *Coffee Break (Committee and Group Leaders presenting on Tuesday morning)*

11h10-12h00: Presentation of 1 team by group leader

11h10-12h00: Mr Eric KREMER

(presentation, discussion with group and alone)

12h00-12h45: Meeting with Supervisory bodies and Representative of CBS2 Doctoral School

12h00-12h30: Meeting with Supervisory Bodies (INSB, UM1 and UM2)

12h30-12h45: Meeting with the director of the Doctoral School

12h45-13h45: *Lunch (Buffet) Committee with Supervisory Bodies and director of the Doctoral School*

13h45-16h05: Presentations of 2 teams by group leaders

13h45-14h35: Mr Marc PIECHACZYK

(presentation, discussion with group and alone)

14h35-15h20: Ms Marta RADMAN-LIVAJA

(presentation, discussion with group and alone)

15h20-16h05: Mr Marc SITBON

(presentation, discussion with group and alone)

16h05-16h30: *Coffee Break (Committee and Group Leaders presenting on Tuesday afternoon)*

16h30-18h10: Presentations of 2 teams by group leaders

16h30-17h20: Ms Naomi TAYLOR

(presentation, discussion with group and alone)

17h20-18h10: Mr Jamal TAZI

(presentation, discussion with group and alone)

18h10-18h40: Meeting of the assembly of group leaders in the absence of the director

18h40-19h30: Debriefing of the second day (closed-door meeting of the Committee)

19h30-21h00: Working buffet: Committee with all group leaders and director

Wednesday, January 22nd

8h15-8h30:	Arrival of Committee at IGMM
8h30-10h00:	Presentation of new teams by group leaders
8h30-9h15:	Mr Etienne SCHWOB
	(presentation, discussion with group and alone)
9h15-10h00:	Mr Jean-Christophe ANDRAU
	(presentation, discussion with group and alone)
10h00-10h20:	*Coffee Break (Committee and Group Leaders presenting on Wednesday morning)*
10h20-11h20:	Meeting with personnel (3 sub-committees)
11h20-12h00:	Meeting of Committee with director
12h00-15h00:	Closed-door meeting of Committee and discussion of the final report (+ lunch)

6 • Supervising bodies' general comments

nouvelle université de Montpellier
un projet, une ambition

UNIVERSITÉ MONTPELLIER 2
SCIENCES ET TECHNIQUES

Le Président

Montpellier, le 28 mars 2014

M. Didier HOUSSIN
Président de l'AERES

M. Pierre GLAUDES
Directeur de la section des unités de recherche

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Affaire suivie par :
Ingrid CHANEFO,
Directrice de la Recherche et des Etudes Doctorales

Objet : Réponse de l'établissement support au rapport d'évaluation de l'unité IGMM – UMR 5535
Réf. : rapport d'évaluation S2PUR150008343

Messieurs

Je tiens à remercier le comité de visite pour la qualité de son rapport d'évaluation concernant l'unité de recherche IGMM - INSTITUT DE GENETIQUE MOLECULAIRE DE MONTPELLIER (UMR 5535), dirigée par Marc PIECHACZYK.

J'ai bien noté les remarques formulées par le comité de visite.

Nous souhaitons mettre en avant un point concernant une équipe « Fisher », pour laquelle les données prises en compte dans le rapport sont erronés et sous-estiment injustement la contribution majeure de ce groupe dans sa production scientifique et son réseau denses de collaborations, y compris internationales. Les éléments apportés par le directeur d'unité sont exclusivement factuels.

En tant que tutelle universitaire de cette unité de recherche, je ne formulerai aucune remarque supplémentaire

Je vous prie d'agréer, Messieurs, l'expression de mes salutations les plus respectueuses.

Le Président de l'Université Montpellier 2,

UNIVERSITÉ MONTPELLIER 2 ★ SCIENCES ET TECHNIQUES ★

Michel ROBERT

Pièce(s) jointe(s) :
Relevé des erreurs factuelles à rectifier dans le texte du rapport
Observations générales formulées par le directeur

IGMM accepts the HCERES committee's report as its stands.

It however wishes to correct several factual points concerning the Fisher group (Phosphorylation and Cell Cycle) to make clearer its leading role in its scientific output and more apparent its extensive network of collaborators, both of these aspects being underappreciated in the report.

During this evaluation period, Daniel Fisher's group published senior author manuscripts in the *Journal of Cell Science*, *Chemistry and Biology, Nucleic Acids Research*, *Oncogene*, *Cell Cycle*, *EMBO J* and *Molecular Cell* amongst others. In contrast to the statement in the HCERES report, the group of D. Fisher has collaborated extensively: EIGHT of the 11 manuscripts published during this period were performed in collaboration with external groups (the report stated that there were none). In 5 of the articles, D. Fisher collaborated with groups outside the IGMM but within Montpellier, attesting to his interactions with the Institut de Génomique Fonctionelle, Institut de Génétique Humaine, CREEC and Inserm Centre de Biochimie Structurale, the latter of which resulted in co-first authorship. Two manuscripts were performed in collaboration with French groups in Paris, Rennes, Lyon, Perpignan and Sophia Antopolis. Finally, 3 manuscripts were published in collaboration with groups outside France: University of Oxford, Sante Fe Institute and the University of Calgary. Beyond these published collaborations, Daniel Fisher has an extensive network of local, national and international collaborations that were presented during the evaluation visit.