IGBMC - Institut de génétique et de biologie moléculaire et cellulaire

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Institute of Genetics and Molecular and Cellular Biology

IGBMC

Under the supervision of the following institutions and research bodies:

University of Strasbourg

Centre National de la Recherche Scientifique

Institut National de la Santé et de la Recherche Médicale

October 2011

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

Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head

Pierre Glaudes

Unit

Name of unit:	Institute of Genetics and Molecular and Cellular Biology
Acronym of unit:	IGBMC
Label requested:	UMR CNRS/Unité INSERM
Present no.:	UMR 7104/U. 964
Name of Director (2009-2012):	Mr Olivier POURQUIÉ
Name of project leader (2013-2017):	Mr Olivier POURQUIÉ

Members of the committee of experts

Chair:	Ms Margaret BUCKINGHAM, Paris
EXPERTS:	Mr Markus AFFOLTER, Basel, Switzerland
	Ms Lucia BANCI, Sesto Fiorentino, Italy
	Mr Jean-Louis BESSEREAU, Paris (INSERM CSS representative)
	Mr Yves BOURNE, Marseille
	Ms Joan CONAWAY, Kansas City, USA
	Mr Alain EYCHENNE, Orsay (CoNRS representative)
	Mr Kenneth H. FISCHBECK, Bethesda, USA
	Mr Thierry FRÉBOURG, Rouen (CNU representative)
	Mr John GURDON, Cambridge, UK
	Mr Frank GROSVELD, Rotterdam, Netherlands
	Mr Pierre LÉOPOLD, Nice (INSERM CSS representative)
	Mr Achim LEUTZ, Berlin, Germany

Mr Beat LUTZ, Mainz, Germany

Ms Ursula LIEBL, Palaiseau (INSERM CSS representative)

Ms Jane MELLOR, Oxford, UK

Mr Cédric NOTREDAME, Barcelona, Spain

Mr Michael NILGES, Paris (CoNRS representative)

Mr Norbert PERRIMON, Cambridge, USA

Mr Hervé PRATS, Toulouse (INSERM CSS representative)

Ms Carina PRIP-BUUS, Paris (CoNRS representative)

Mr Hilger ROPERS, Berlin, Germany

Mr Guy ROULEAU, Montréal, Canada

Mr Michael SATTLER, Munich, Germany

Ms Sylvie SCHNEIDER-MAUNOURY, Paris (CoNRS representative)

Mr Daniel THOMAS, Compiègne, CNU

Mr Daniel. N. WILSON, Munich, Germany

Representatives present during the visit

Scientific Delegate representing AERES:

Mr Jean-Antoine LEPESANT

Representative(s) of the unit's supervising institutions and bodies:

Ms Dominique DAEGELEN, INSERM

Ms Martine DEFAIS, CNRS

Mr Serge POTIER, UDS

Report

1 • Introduction

Date and conduct of visit:

The AERES visit to the IGBMC, Strasbourg, took place on the afternoon of Monday October 17th, and continued throughout the day on the 18th and 19th. The visit began with presentations by the AERES co-ordinator who gave instructions to the Committee, and then, in the presence of all the team leaders, statutory scientists, heads of platforms and ITA delegates, explained the AERES evaluation process. The chair of the visiting committee, Margaret BUCKINGHAM, briefly welcomed the Committee and said a few words to the assembled representatives of the Institute. This was followed by a presentation by the Director of the IGBMC. He gave an overview of the Institute, in terms of its scientific research, organisation and sources of finance. The Committee then split into four sub-committees to evaluate individual research teams. This was necessary, because of the size of the Institute, in order to give each team leader 40-50 minutes, depending on the size of the team, in which to present their results and research programme and reply to questions. Four sub-committees reviewed the scientific programmes of the Institute as follows: 1) Developmental Biology and Stem Cells (15 teams) chaired by Norbert PERRIMON; (2) Functional Genomics and Cancer (13 teams) chaired by Joan CONAWAY; (3) Translational Medicine and Neurogenetics (10 teams) chaired by Guy ROULEAU; (4) Integrated Structural Biology (8 teams + 1 team proposition) chaired by Michael SATTLER. The lunch break provided an opportunity for informal meetings with team leaders and heads of the technology platforms. On the afternoon of October 18th, the sub-committees 3 and 4 who had finished their team reviews, together with the visiting Committee president, met with the ITA (Engineers, Technicians, Administrators) and then with the Statutory Scientists, who are not team leaders. Each session lasted about one hour and consisted of questions and discussions initiated by the personnel or visiting committee members. A lunch was organised by the representatives of the Tutelles who made short presentations to the Committee. In particular Eric WESTHOF (representing the University of Strasbourg), stressed the current problems with governance. Any free time in the afternoon was used for discussion of the evaluation within each sub-committee. At the end of the day, the visiting Committee met with the interim bureau, which consists of two members of each of the four programmes. This provided the necessary opportunities for the Committee to gauge the situation in the Institute. It took place in the absence of the director. The President asked the representatives to summarise the point of view of the members of each programme and this was followed by general discussion with the Committee. The members of the visiting committee, who had also experienced periods of institutional tension expressed sympathy and encouragement; the Committee questioned the bureau about the current very difficult situation and discussed potential ways forward. On the morning of the 19th, the Mouse Clinic (ICS) was presented by its director, followed by a presentation of the Instruct initiative and the Center for Structural Biology (CBI) by Bruno KLAHOLZ. The visiting Committee then divided into two subgroups to hear presentations by the personnel responsible for the 5 technical platforms. Each platform presentation was scheduled for 15 minutes, leaving time for only a few questions. At the end of the morning the visiting Committee met with the students and postdocs of the Institute who presented their community activities, followed by questions and discussion. In the afternoon, the sub-committees convened to discuss individual team evaluations. This was followed by a brief discussion with the full committee alone and then with the Director, when the scientific programmes, and particularly the management of the Institute, were discussed.

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

The IGBMC was founded seventeen years ago as a result of the fusion of two major research Units, one with an emphasis on gene function/transcriptional regulation directed by Pierre CHAMBON and the other focussed on structural biology directed by Dino MORAS. These entities remained as distinct Units within the Institute until 2007 when they were merged into a single Unit, under the Tutelles of the CNRS, INSERM and the University of Strasbourg. The IGBMC was directed by Pierre CHAMBON until his retirement in 2002, then by Jean-Louis MANDEL, Dino MORAS and Olivier POURQUIÉ since October, 2009.

The Institute initially benefitted from the financial support of Bristol-Myers Squibb both for the construction of the building and for functioning (about 3.5 million euros a year) including salaries, mainly for personnel working on platforms and in core facilities. When this major industrial support came to an end, a GIE (Groupement d'Intérêt Economique) was established with the three Tutelles as shareholders, to deal with the difficult problem of continuing staff support. This structure, called the CERBM (Centre Européen de Recherche en Biologie et en Médecine) is mainly financed on grants obtained by the research teams of the Institute and is under the responsibility of the Director of the IGBMC.

The Institute was established in a building, which is an impressive example of modern laboratory architecture, at Illkirch where there is a biotechnology park, just outside Strasbourg. The IGBMC site now has a number of scientific buildings, including the Institut Clinique de la Souris (ICS) and a building under construction which will house the Center for Structural Biology (CBI). The IGBMC, as its name implies, carries out biological research over a wide range of areas covering genetics, cell, developmental, molecular and structural biology. It is a very large structure with about 420 researchers, postdoctoral and PhD students working with 300 engineers, technicians and administrative staff, excluding the ICS (about a further 100). There are 46 research teams, grouped within 4 programmes: Integrated Structural Biology; Functional Genomics and Cancer; Development and Stem Cells; Translational Medicine and Neurogenetics. There are 6 technological platforms specialising in Structural Biology and Genomics, Bioinformatics, Microarrays and Deep Sequencing, Imaging, High throughout Cell based Screening and Proteomics/Mass Spectroscopy. There are also common services, such as that provided by the animal house or flow cytometry facility. These platforms work with research teams in the IGBMC and also external laboratories. The ICS and future CBI provide important infrastructures for the IGBMC.

Management team:

Given its size, the management of the IGBMC requires a team of dedicated professionals. There is a financial manager and administrative director who supervises the central administration, including human resources. The IGBMC Director is assisted by a director of scientific affairs, with experts in communication and grant funding/valorisation and a director for scientific operations and logistics, and supervision of the common services. A senior scientist and an engineer supervise Hygiene and Security the Informatics network of the Institute is supervised by an engineer and overseen by the Direction.

Unit workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	24	23	24
N2: EPST or EPIC researchers	81	78	77
N3: Other professors and researchers	4	5	5
N4: Engineers, technicians and administrative staff *on a permanent position	140	138	
N5: Engineers, technicians and administrative staff * on a non-permanent position	155		
N6: Postdoctoral students having spent at least 12 months in the unit	129		
N7: Doctoral students	134		
N8: PhD defended	132		
N9: Number of Habilitations to Direct Research (HDR) defended	13		
N10: People habilitated to direct research or similar	82	79	
TOTAL N1 to N7	**667**	**244**	**106**

2 • Assessment of the unit

Overall opinion on the unit:

The IGBMC is a major scientific centre, very well known and respected nationally and internationally. It has made and continues to deliver exceptional contributions in the fields of gene expression regulation and associated molecular structures, molecular genetics, genomics, development, cell biology, cancer and human genetics. Its research output is remarkable, with important scientific contributions as evidenced by the quality as well as the quantity of publications, many of which are in high profile journals. It attracts excellent students and young postdoctoral scientists, who constitute a dynamic international community, together with the permanent staff of the Institute. The team leaders and infrastructure platforms have been very successful in attracting major national and international grant support.

Strengths and opportunities:

The main strength of the Institute is its excellence in research. It has built along the years unique facilities for support to research projects, such as the "Institut Clinique de la Souris". The institute demonstrates its ability to remain continuously at the forefront of competitive research topics. The broad spectrum of subjects covered and the accompanying scientific and technological expertise add to its impact and attractiveness.

Weaknesses and risks:

The main weakness of the IGBMC centers on its problem of governance. The current atmosphere of mistrust and uncertainty is toxic to the conduct of research and threatens to undermine the Institute. In this context it is very important to maintain the unity of the IGBMC.

Interactions both within and between the previous Programmes/Departments are not optimal. Some of the scientific platforms require attention to ensure that they remain up to speed.

Recommendations:

The visiting Committee strongly recommends that the issue of governance be resolved rapidly. It concludes that rules of governance, with the implementation of a departmental structure are essential. The departmental heads, elected for a term of office by the relevant team leaders, should play a major role in the functioning of the Institute. At the departmental level their responsibilities, for example, for scientific animation and mentoring, should be clearly defined. At the level of the IGBMC, their participation in decision-making processes should be clearly stated in the new statute, so that the director alone cannot impose actions which are not approved by consensus. This new mode of collegial functioning will not materialise without the direct intervention of the Tutelles. It is vital for the IGBMC that the Tutelles concord on the new rules of governance, ratify this statute and closely oversee its application. In addition to addressing the immediate situation, this recommendation holds for the successful long-term governance of the IGBMC, which has evolved as a highly successful but complex large Institute.

It is the view of the visiting Committee that all the parties concerned, should do everything possible to restore the confidence and serenity of the Institute by adhering to this line of action.

3 • Detailed assessments

Assessment of scientific quality and production:

The IGBMC carries out research at the forefront of the biological sciences. Over 200 original scientific papers are published every year with 421 peer-reviewed papers as last or corresponding author from 2007 to mid-2011. The quality of this remarkable production is demonstrated by the fact that over 15% of these publications are in journals with high impact factors (> 12). Twelve IGBMC scientists rank in the top 1% of the most cited scientists in their respective fields.

Assessment of the unit's integration into its environment:

The IGBMC is actively involved in the valorisation of research, with 13 patents deposited since 2007. Its members are also involved in technology transfer, exemplified by PhenoPro, a spin off from the mouse clinic (ICS), which provides phenotyping services to industrial partners. Benefits will be re-invested in research at the ICS and to provide funds for creating a professional chair in the area of translational medicine, physiology and behaviour. In general, the technological platforms of the IGBMC are open to external use, including clients from industry. This is important in establishing industrial interfaces and for the financial support of the platforms. Other initiatives include a planned academic-industry partnership with Sanofi-Aventis to use their platform for the development of new candidate drugs. The IGBMC is in close contact with the society created by the University of Strasbourg for the acceleration of technology transfer and plans to recruit, through Labex funding, an on-site "IP Scout" who will help the teams to identify and exploit findings of economic interest. The Institute participates in public outreach initiatives such as the Fête de la Science and proposes to further promote the interface with the public by increasing the number of press releases and communications and improving the Web site.

The IGBMC has long standing contractual relations with major French associations such as the AFM, ARC, the Ligue contre le Cancer, or the Fondation pour la Recherche Médicale. Not only do teams of the Institute receive financial support, but IGBMC scientists are also members of their scientific boards. The EU is also an on-going source of research contracts for research teams in the Institute as well as for the major infrastructures such as the ICS and now also the CBI.

The IGBMC has been very successful in obtaining external funding, which reflects the quality and topical interest of the scientific research. In addition to national and international grants from these sources, many teams in the Institute have obtained competitive ANR grants from the French Science Ministry, 7 of the recently recruited young group leaders received ATIP/Avenir grants, and 6 principal investigators have been awarded prestigious ERC grants at both the junior and senior level. Other sources of international grants, as well as the EU, include the HFSP, NIH and DARPA. Excluding the ICS, external funding from the EU constitutes 14% of their current budget with 5% from other international sources. Grants from charitable associations represent another 15%. The Institute has successfully submitted applications within the national AVENIR programme. They have obtained a Laboratory of Excellence (Labex) award (co-ordinator O. POURQUIÉ), as well as major grants for infrastructure under the Phenomin (co-ordinator Y. HERAULT) and FRISBI (co-ordinator B. KLAHOLZ) programmes and participate in the France Génomique project (I. DAVIDSON).

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

IGBMC team leaders are recognised international scientists, invited to speak in conferences round the world, and in 2011, alone, 5 international meetings were organised by IGBMC researchers. 31 members of the IGBMC have received prestigious national (21, including CNRS medals, prizes from INSERM and the Academy of Sciences, the Schlumberger award) and international (5, including the Gairdner prize) awards. The Institute has had a strong international reputation for many years and continues to attract excellent researchers, at all levels. After P. CHAMBON's retirement in 2002, a number of well known team leaders left. However since then, the Institute has successfully recruited 11 excellent new team leaders, many of whom have arrived in the IGBMC since the last AERES evaluation. This influx of new young PIs is particularly high in the Developmental Biology and Stem Cells programme, which was previously at a low ebb, largely thanks to its

former director, M. LABOUESSE, together with the Institute's previous directors. Since O. POURQUIÉ's arrival, an additional group working at the frontier between physics and biology has been recruited. Like other leading centers, the IGBMC attracts large numbers of excellent postdocs from around the world. There are currently 167 postdocs, 133 PhD, and 23 master's degree students. The Institutes runs an international PhD programme, affiliated with the University of Strasbourg, which attracts many applicants (180 in 2010).

Research teams in the IGBMC are involved in collaborative projects within France exemplified by ANR joint grants or the Canceropole initiative, where a group leader in the IGBMC co-ordinated a strategic axis on tumour invasion. There are also collaborations with the hospital and the medical faculty of the University, particularly with teams in the Translational Medicine and Neurogenetics programme. The mouse clinic (ICS) is a major partner in post-genomic mouse programmes in France, (ex. CELPHEDIA, ROCAD) and the CBI will host FRISBI (French infrastructure for Integrated Structural Biology). This is a French axis of the EU INSTRUCT network. The ICS is also a node for EU programmes on mouse phenotyping, such as INFRAFRONTER and its predecessors. IGBMC scientists participate in 14 EU networks, in areas ranging from epigenetics to structural approaches to drug development. Within Europe, the Institute has close collaborations with the Karlsruhe Institute for Technology and participates in regional networks with Institutes in Germany and Switzerland. In addition to Europe, IGBMC scientists have long standing collaborations with US researchers and several are participants in NIH funded networks. Teams in the Institute are also members of world-wide consortia such as SYSGENET, or IMPC in the case of mouse clinic.

Assessment of the unit's governance and life:

The IGBMC has greatly increased in size since the time when it was founded under the inspiring leadership of Pierre CHAMBON. After his retirement in 2002 it continued as a community led by his successors who were major scientific figures appointed from within the Institute. Olivier POURQUIÉ's external appointment as Director in 2009, received wide support from within the Institute and outside. By this time, the Institute was organised in departments, but did not have rules of governance, which would provide an operating framework for the new director. Olivier POURQUIÉ decided to transform the departments into more flexible research programmes with a similar scientific contour which, however, did not appear to have resulted in more scientific interaction. Increasing opposition from some of these, led him to dissolve the programmes, replaced by an interim bureau with two representatives from each of the previous departments/programmes. At the time of the committee's visit the IGBMC was in a state of conflict. Resistance to changes imposed by the director, his style of governance and methods of communication, have led a number of team leaders to contest his leadership. Interviews conducted by each sub-committee gave each team leader the opportunity to comment on the situation. It is clear that there is a general anxiety, which is having a de-stabilising effect on all the personnel of the IGBMC. However opinions differ about the Director's capacity to lead the Institute forward. Many team leaders in Integrated Structural Biology and Functional Genomics and Cancer are negative, tending now to be of the opinion that the situation can only be righted if he steps down as director, whereas most of the PIs in the other two programmes continue to be supportive. Even within the two programmes where the majority of PIs are negative, this view is not unanimous. In general, newly appointed young group leaders are positive about the current Director. This in itself tends to be perceived as an unfortunate cleavage between generations.

It is clear that the current atmosphere of mistrust and uncertainty is toxic and that it is essential to re-establish the calm required for concentration on research. It is probable that dismissal of the Director would be badly perceived by the wider scientific community, to the discredit of the IGBMC and French life sciences in general. It would also make it difficult to find another high-level scientist to accept the job. Attempts to resolve the conflict and establish a new framework for governance are underway. This became apparent in the discussion with the interim bureau where members initially expressed conflicting opinions, but subsequently were open to constructive discussion. Guidelines had been proposed by the scientific advisory board (SAB) based on the regulatory structure of other large European Institutes and the SAB president has discussed these recommendations, more recently, with the bureau and the director. It is the view of the visiting committee that every effort should be made to draw up rules of governance. For an Institute of the size of the IGBMC, it is essential to have a well-structured departmental system where department heads, chosen by the corresponding team leaders, have an important role in the functioning of the IGBMC. Decisions should not be taken by the Director alone, but by consensus with the heads of Department. Establishment of rules of governance is not only important in the current situation, but also for the IGBMC in the long term. In the immediate future, it will be important that the Tutelles take an active part in ensuring that functional departments are in place. The Director, who had no previous experience of

directing an Institute, has acknowledged publically that he has made mistakes and has expressed his willingness to implement a new governance structure. However he and the IGBMC will need guidance and again the Tutelles should be proactive. Given the polarisation of opinion between programmes/departments, there is a risk that Integrated Structural Biology, as in the past, would prefer to be an independent Unit. In the view of the visiting committee a great strength of the IGBMC is that it includes a wide range of biological disciplines and any fragmentation of this should be avoided.

In the visiting committee's meetings with different categories of personnel, questions of management and communication were discussed. The committee was informed that a laboratory council for the IGBMC, with their representatives, existed, but that prompt diffusion of the minutes was a problem. Particularly at present, this is unfortunate since communication is an issue. In the meeting with the ITA, the impression of anxiety, linked to the current problems of governance, was compounded by the situation in the mouse clinic, where many of the technical staff with short-term contracts, are in a precarious position because of the financial difficulties encountered by the ICS. It was clear that there are problems in human resource management, with resentment about sudden changes in job attributions and lack of respect for the individuals. This particularly affects ITA attached to platforms and infrastructure administered under the GIE. Recently the Direction appointed a personnel manager (DRH) to try to improve this aspect. The postdocs and students are also well aware of the tensions within the Institute, although their main preoccupations center on their immediate research environment. In general, they very much appreciate the scientific and technical opportunities offered by the IGBMC. With the support of the Direction, they run a dynamic association. Further comments, which stemmed from the meeting with postdocs and students, are made in the Section for Assessment of Training. In the meeting with scientists (58) who have permanent positions, but are not team leaders, it was clear that they were in favour of a departmental structure. They play an important role in the scientific life of the Institute, including the supervision of students. These senior scientists encounter problems of recognition; it seems surprising that they cannot replace the PI at meetings, if he/she agrees, and that they do not have more control over research grants that they have been awarded. In addition to the line of communication, which should be provided by a functional laboratory council for the IGBMC, they had created an internal "info" journal, and this initiative merits on-going support.

The IGBMC has an active policy for external communication with the general public and is also conscious of the importance of the interface with the press. A communications officer is attached to the scientific administration.

As discussed previously, the IGBMC is an outstanding center for scientific research. This status necessarily involves successful initiatives for the stimulation of scientific activity and the development of emerging areas of research. This is exemplified by the founding of the CBI, the recruitment of young research teams at the frontier between biology and physics or indeed by the innovative Labex project.

Members of the IGBMC are also involved in educational activities, both with the University of Strasbourg and internationally (see Section on Training). The Institute is implicated in the structuring of regional research, both in relation to the University and other institutions in Strasbourg, to the Illkirch site and also in the context of neighbouring institutions in Switzerland or Germany (see section on the Integration of the Unit in its environment).

Assessment of the strategy and 5-year project:

The individual research teams have clear scientific projects, which in almost all cases have been favourably evaluated (see below, section 4).

Comments on the programmes/departments are as follows:

Development and Stem Cells (DSC)

The 15 groups within the Development and Stem Cells Department address various questions in cell biology, developmental biology, stem cell biology and morphogenesis and utilize various model organisms, yeast, Drosophila, zebrafish, worm, chicken and the mouse. The diversity of questions under scrutiny, such as the control of stem cell maintenance, cell fate reprogramming or mechanisms that control cell shape changes during morphogenesis provides a stimulating intellectual environment, especially important for students and postdocs. Further, as a whole, the various groups apply an impressive repertoire of state-of-the-art methods in imaging, genetics, cell biology, genomics, proteomics and biophysics. As such the Department provides a

rich intellectual and technical environment that should promote exciting interdisciplinary and cross-organism collaborations. The Department should be encouraged to think about ways to capitalize on their extraordinary resources and talents. For example, interactions between groups would be enhanced by weekly Departmental seminars where two students present their work.

Functional Genomics and Cancer Biology (FGCB)

Although there is a fair amount of overlap in research focus among the groups, those who entered from the previous Cancer Biology department in particular feel that they are not fully integrated into the program and would appreciate increased opportunities to interact in both formal and informal settings with other colleagues in the current Functional Genomics and Cancer Biology Program. The committee felt that in general, members of the Functional Genomics and Cancer Biology program from both the previous Cancer Biology and Functional Genomics/Transcription departments would benefit from more interaction. The committee strongly encourages members of this group to make every effort to enhance their interactions, including establishment of regular departmental seminars / retreats, as such activities seem likely to allow them to share expertise, make the most of potential synergies, and improve collaborative opportunities. The committee also notes that the research in Functional Genomics and Cancer Biology is increasingly dependent on sophisticated proteomics and genomics approaches that generate large and complex datasets and accordingly require high-level bioinformatics support. It will be important that the Institute appropriately address needs for bioinformatics expertise and solutions to bioinformatic management problems, including data processing, storage and effective data-mining.

Integrated Structural Biology (ISB)

The former ISB unit is a strong pillar of the IGBMC which is a unique place in Europe and world-wide in providing an excellent research environment to stimulate synergies and collaborations combining structural, molecular and cell biology to address important questions in basic biology. Thanks to the vision of its previous director, the ISB is a key player in national and international research networks, e.g. FRISBI, INSTRUCT that help to support and further extend the research infrastructures at IGBMC. The creation of the CBI is an important strategic decision that should be strongly supported and implemented and hopefully help to integrate research at IGBMC. This center will pioneer science in Europe by combining high-.powered technology with creative and innovative research. The proposal to continue and further build on the excellent research on transcriptional and translational regulation is strongly recommended. It appears sensible that the unit moves into new areas by extending their research towards structural studies of co-activators and chromatin regulating complexes. Given the scientific excellence and success of research on translational regulation this area should be considered for further strengthening within the ISB programme/department and within IGBMC as a whole. The research projects greatly benefit by the existing and further developing expertise in integrated structural biology techniques and will offer new interactions with the other programmes/departments at IGBMC, including with new teams that have arrived recently. The ISB should further build on their potential to exploit integrated structural biology by combining the existing strong expertise in crystallography, electron microscopy and NMR, with imaging and other complementary techniques. The up-coming retirements of prominent and highly recognized scientists, D. MORAS and A. PODJARNY, poses substantial challenges. The institute should ensure that these expertises are continued by young researchers of the highest potential.

Translational Medicine and Neurogenetics (TMN)

The Translational Medicine and Neurogenetics department includes some of the key groups, which, historically, have contributed to the renown of the IGBMC. This department has evolved in different directions, leading to a situation where no single subject, perhaps with the exception of ataxia, has reached a critical mass to lead the field. Future recruitment is needed to ensure that this department remains at the cutting edge of science. Eight groups work in either neurosciences (aneuploidy, addiction) or in neurogenetics (ataxia, intellectual deficiency, repeat diseases). It would make sense to evaluate the kinds of recruitment that might strengthen the department by bridging the interests of various groups and building on areas of focus, such as repeat disorders, ataxia and intellectual disability. In the field of metabolism, significant recruitment would be needed to strengthen the single (excellent) group. This may not be the ideal choice for the future, unless several recruitments are possible. It is unfortunate that the genetics section of the department, like a number of other laboratories in France, has fallen behind with respect to the current revolution in this field engendered by high throughput sequencing. However they should be able to catch up by focusing on the areas where they have significant strengths, such as those mentioned previously.

Technical platforms and infrastructures

The technical platforms and infrastructures were also reviewed by the visiting committee (see at the end of section 4). In this context, plans to restructure the informatics services of the Institute should be implemented.

The Director of the IGBMC announces his intention to continue to recruit teams in the area of biology/physics and to develop stem cell research in the Institute. These initiatives certainly merit support. However it is important that, with the future directors of departments, a wider scientific strategy is developed, integrating suggestions on the present report.

The allocation of means follows the established and well-proven practice of the Institute, where resources allocated to the IGBMC are mainly used for common services (charges are made for use of platform facilities) and also for new recruitments, whereas grants awarded to individuals are used for their research effort. The GIE is currently under financial review, but the visiting committee had the impression that its management structure and decision making in relation to the IGBMC requires clarification.

Originality and risk taking is exemplified by the scientific projects of the teams and the collaborative ventures discussed previously.

Assessment of the unit's involvement in training:

The IGBMC has a close synergy with the University of Strasbourg, which is one of the three Tutelles. The new Center for Integrated Biology (CBI) building, which will house state of the art technologies for protein analysis and structure determination, financed by the Région Alsace, will belong to the University. There are 23 professors or assistant professors with appointments in the University of Strasbourg and 81 full time researchers in the Institute, with 3 other scientists with professorial appointments (ex. Collège de France). These staff is actively involved in teaching. 82 of the research scientists have an HDR and 132 PhD theses have been defended since 2007. Master's degree students are also trained in IGBMC labs. There are current plans to set up an MD/PhD programme co-ordinated by a member of the Integrated Structural Biology Programme and also master degree programmes in Cellular Physics, piloted by members of the Development and Stem Cells Programme with colleagues in the University and a new master's degree in Structural Biology, Bioinformatics and Biotechnology co-ordinated by members of the Integrated Structural Biology Programme, again as a joint venture between IGBMC scientists and the University. The international PhD programme, which is greatly in demand, will be able to offer more places, supported by Labex funds. At an undergraduate level it is proposed that the IGBMC develop an international summer research programme.

The visiting Committee met with the students and postdocs and was impressed by the dynamic association (SPA) that they run in the IGBMC. The SPA, thanks to a core of motivated individuals, organises scientific (ex. poster sessions) and non-scientific social activities, as well as a website, which are important for the integration of new students or postdocs, with a special effort made for foreigners. In discussion with them, it appeared that different programmes within the Institute were more or less active in ensuring annual retreats, regular student seminars etc. Most internal seminars were given by postdocs and students. Within the University of Strasbourg, students are regularly followed, but it emerged that more formal supervision within the IGBMC should be implemented. Although the Institute makes an effort to help, administrative hurdles, particularly for International students, were a source of anxiety. It was not clear to what extent the IGBMC had a policy to encourage students once they had obtained a PhD degree, to experience research in other Institutes. Some postdocs had continued in the same laboratory, which was not necessarily ideal for their CV. For students and especially postdocs a major concern, understandably, was career possibilities. They would benefit from more advice and an alumni association would also be helpful. Inequalities in postdoc salaries according to the funding sources (French private or public sector, different international fellowships), and also problems with insurance and a lack of advance payments, aggravated in the case of short-term contracts, were also invoked. In such a large Institute, students and postdocs depend, of course, on their immediate supervisor, but beyond the research team, a departmental structure with a director who is responsible for animation of joint scientific activities and provides some informal mentoring is required. The direction of the IGBMC encourages the SPA and tries to help, particularly international students, however this pan-Institute activity should be complementary to initiatives in the smaller departmental community. At this level, the career opportunities and future developments of students and postdocs should be easier to monitor.

4 • Team-by-team analysis

DEVELOPMENT AND STEM CELLS (DSC) PROGRAMME

Team DSC-1: Single cell Biophysics

Team leader: Gilles CHARVIN

Workforce:

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

Assessment of scientific quality and production:

This is a recently established group by a newly independent investigator who has published in good impact journals during his post-doctoral studies at the Rockefeller University (PLoS Biol, PNAS). The team uses physical and mathematical tools to understand growth, proliferation and senescence in isolated cells. The development of innovative microfluidic devices allows the team to monitor the full lifetime division program of single mother yeast cells and therefore to question the mechanism of cell senescence. The influence of stress response, cell metabolism and genetic determinism will be studied using this experimental approach.

A second separate project of the team aims at understanding the cell cycle changes induced by stress in isolated yeast cells. The combined use of fluorescent markers of cell cycle phase and stress together with the use of microfluidic chambers allowing monitoring yeast cells and applying defined stresses (temperature, oxydants) will set a new stage for these studies. The next step will be to apply the microfluidic techniques to the study of mammalian cells. This would considerably increase the impact of the current research.

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

The team leader has been successful in attracting start-up funds for the lab, although to a modest level (one ANR grant as a coordinator with one additional partner, i.e. 60 k€/year). This does not provide a possibility for rapid recruitments in the coming years. One application for an HSFP grant is pending. It is not known whether the PI has applied for French starting grants like Avenir/ATIP.

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

The PI was appointed to the IGBMC at the end of 2010, and has assembled a team that includes two postdoctoral fellows with expertise in biology and one master student with training in physics. The very high impact publications of the PI have not established yet a strong visibility. He was an invited speaker at a satellite meeting (called "Future approaches in life microscopy") of the EMBL Imaging conference. This is certainly due to the very recent establishment of the team. The PI demonstrates a strong dynamism and has established a number of local (teams DSC-10 and DSC-14), national (Lyon) and international (Montreal) collaborations.

Assessment of the strategy and 5-year project:

The PI proposes two main projects for the lab, both relying on mastery of microfluidic technology and of the yeast biological model. Questions raised are of high fundamental interest. They should allow exploration of related questions in mammalian cells in the near future. The proposed projects testify to the autonomy of the team and are not simply collaborations established on the ground of physical and mathematical knowledge. Given the small size of the group, one possible risk is dispersion through collaborations. The group leader should continue finding the right balance between autonomous projects and collaborative work.

Conclusion:

Strengths and opportunities:

The team leader has successfully begun to establish an innovative research program. The expertise of the team is very strong in the domain of microfluidic technology, which provides the team with a great potential to deliver new insight into fundamental aspects of cell division and senescence.

Weaknesses and risks:

The PI should be encouraged to focus on these biological questions and to seek advice from experts when necessary.

Recommendations:

The recruitment of the team serves the general strategy of the institute to develop biophysical approaches as well as mathematical modelling. Nevertheless, the group is still small and should avoid the risk of dispersing its limited strength in a large number of collaborations. Funding of the team should be reinforced by obtaining a starting grant (ATIP/Avenir or ANR JC).

Team DSC-2: Roles of retinoic acid in nervous system development and Physiology

Team leader: Pascal DOLLÉ

Workforce :

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	2	2	2
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *on a permanent position	1	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	4		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**11**	**5**	**4**

Assessment of scientific quality and production:

This well-established group has a long-standing interest in the retinoic acid (RA) signalling pathway. It has used mouse models as well as in ovo experiments in chicken to understand the respective functions of individual components of this signalling pathway during development and in the adult, with a focus on the brain. During the period under review, their major achievements were to identify a crosstalk between RA, FGF and Shh signalling during early neurogenesis, to show that Rdh10, an enzyme that catalyzes the retinol-to-retinaldehyde transformation, has an essential function during mouse embryogenesis, and to identify a control by RA on affective behaviours in adult mice. They have published well: 15 publications where team members are first or last, among which 1 Neuron, 1 PNAS and 1 Development, and many collaborative publications. They also got two patents. While one can regret some dispersion in the processes studied, the results obtained by this group provided significant new insights into the function of the RA pathway in the developing and adult brain.

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

The group has a good level of funding. During the period under review they were partners in two European consortiums: Evi-genoret and Eurexpress. They have secured funding until the end of 2015 with a recent ANR grant.

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

This is a relatively large group (12 people, 4 staff scientists) with a good connection to both the Hospital and the University of Strasbourg, the PI and another group members being physicians and University teachers (PU-PH/MCU-PH).

A young scientist in the group published independently and took charge of the adult brain function and behaviour project. He set up locally devices for behavioural assays in collaboration with the "Institut Clinique de la Souris". The group is well known and highly respected in the field of RA signalling during development. They have written reviews (4 in the last five years, one in Nature Reviews Genet). They were invited to 10 international conferences and received several prizes and awards. The PI is an ISI Highly Cited researcher.

Assessment of the strategy and 5-year project:

In the line of the previous interests of the group, their projects are oriented toward the function of the RA signalling pathway in the mouse brain, both during development and in the adult. The group proposes to study pathways during stem cell/precursor populations in the embryonic forebrain using neurosphere cultures, functional studies in mice and transcriptomic analyses. In the adult mouse, they will pursue their study of the role of the RA signalling pathway in the physiopathology of the dopaminergic system and in affective behaviours. This project is a follow-up of the previous work of the group and is based on many tools already available in the lab, such as null and conditional mutant mice for different components of the pathway, using various Cre driver mouse lines. The committee felt that the project lacked an in-depth analysis of the RA signalling pathway and suffered from some dispersion of the processes studied.

Conclusion:

Overall appreciation:

This is a good, well-installed group, which follows-up on one of the traditional themes of scientific strengths of the IGBMC: the detailed functional analysis of the retinoic acid pathway. There are several dynamic young scientists in the group.

Strengths and opportunities:

The group has international recognition and a good past publication record. Several young staff scientists in the group are very active and are able to drive their own research projects.

Weaknesses and threats:

The PI has a tendency to disperse on the study of different embryologic processes and, probably in consequence, the projects lack an in-depth analysis of RA action at the molecular level. This may lower the impact of their work and, given the competitive environment of the IGBMC, prevent them from recruiting very good PhD students and post-docs in the future.

Recommendations:

The PI may want to focus on selected, innovative projects and try to go more in-depth in the understanding of the function and mode of action of the RA signalling pathway at the molecular and systemic levels.

Team DSC-3: Integrin function and signaling in tissue morphogenesis, integrity and homeostasis

Team leader: Elisabeth GEORGES-LABOUESSE

Workforce:

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

Assessment of scientific quality and production:

The group is rather small (apparently by choice) and the productivity is not overwhelming. However, the group has produced a number of publications in journals with significant impact factors and does solid science of high quality. Their work on the role of integrina6b4 in the intestine is of particular interest and has been recently published (Eur J Cell Biol.) with another manuscript in preparation. Furthermore, their mouse model has helped others to decipher the role of integrina6 in extravasation, which produced a highly visible paper in Nature Medicine.

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

Funding for the next period should be secured, most of the grants finish in 2011.

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

This research group is well embedded in the IGBMC and promising collaborations have been set up with team DSC-9, with students moving freely between the groups.

Assessment of the strategy and 5-year project:

While continuing to work on the role of integrins in intestinal physiology, a new ambitious project has been set up with team DSC-9. In analogy to genetic suppressor and enhancer screens in C. elegans, a partial KO of plectin in cultured cells will be screened for interactors in a scratch assay using siRNAs (candidate approach, with an eventual larger screen). The strength of the approach is the interaction with the C. elegans community within team DSC-9, which is also interested in mechanotransduction. The particular set-up of the cell culture screen carries a number of risks, but if successful could give a lot of insight into mechanotransduction, both in C. elegans (provide candidates) and in cultured cells.

Conclusion:

Strengths and opportunities:

This small research group is now moving more into mechanotransduction, a topic which is along one of the research avenues the IGBMC would like to go in the future. Strategically smart collaborations have been set up and it is expected that the group will continue to produce in a manner similar to past years.

Weaknesses and risks:

No obvious weaknesses detected

Recommendations:

Emphasis should be put on trying to link potential siRNA interactors to function in or outside the Plectin pathway, using a variety of approaches (biochemical and cellular interaction assays, etc.).

Team DSC-4: Retinoic acid signaling pathways driving spermatogonia ontogenesis and differentiation

Team leaders: Manuel MARK / Norbert GHYSELINCK

Workforce

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

Assessment of scientific quality and production:

This group led by two PI has been working for many years on retinoic acid (RA) signalling. They use mouse mutants to understand the role of this pathway in different developmental processes and in the adult. In the last 4 years, they have focussed their projects on the function of RA receptors and of some of their target genes at different stages of spermatogenesis and in different cell types such as Sertoli cells and spermatogonia. By analyzing the transcriptome of RARa mutant testes, they have also identified an interaction between the RA and Wnt-bcatenin pathways. This work has led to the publication of 5 original papers in journals with high impact factors (PNAS, J Cell Science, Reproduction). Apart from these main projects, they also contributed to a number of collaborative projects, leading to 17 other publications, and one of the PIs published two comprehensive method papers describing procedures for post-mortem tissue collection and for histopathological investigations in mice. Overall the scientific activity of the group in the past 5 years has been satisfactory.

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

The PIs were able to secure a significant amount of funding, including ANR funding which runs until 2014. They have filed two patents.

Both PIs have heavy duties outside the group: One of them is responsible for the Hygiene and Security of the whole institute (ACMO), which takes him 50% of his time, and the other is a University professor, which implies heavy teaching duty.

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

The group is of medium size with two permanent scientists only (the two PIs), three students and post-docs and several technicians.

The PIs are invited to give national and occasional international conferences and have a number of collaborations in France and abroad. Their RA mutants are a valuable resource. In the last 5 years they have been able to attract 3 post-docs (including 2 from abroad) and PhD students.

Assessment of the strategy and 5-year project:

The project focuses on the function and molecular pathway of RA signalling in the testis. The group aims at identifying sources and sinks of RA in the seminiferous epithelium and at reassessing RA involvement in meiosis. To this end, they will perform conditional inactivation in 4 cell types, Sertoli, spermatogonia, spermatocytes and Leydig cells, of Raldh, RAR or RXR genes, a strategy for which they already have all the required mouse lines. They will also use a pharmacological approach to inactivate the RA antagonists of the Cyp26 family. They will perform transcriptome analyses to identify genes regulated by RA. The project is labour intensive, involving a lot of mouse lines, with double and triple conditional knock-outs. The committee approves the decision of the PIs to focus their projects on spermatogenesis, but feels that the projects would benefit from diversifying the approaches and trying to address new biological questions (other than the involvement of RA signalling) in this well-defined developmental system.

Conclusion:

Overall opinion on the team:

This group is well known and respected in the field of RA signalling. Focussing their work on spermatogenesis should allow them to go deeper into the molecular dissection of the RA pathway in this system. In the future they should envisage diversifying their approaches and tackling other signalling and/or regulatory pathways implicated in this interesting developmental system.

Strengths and opportunities:

Over the years the two PIs have acquired an extensive expertise in mouse histopathology and phenotyping and have accumulated a unique collection of genetic tools to study the function of the RA pathway in mice. The project benefits from the IGBMC mouse facility and the proximity of the mouse clinic.

The decision of the PIs to focus their projects on spermatogenesis should allow the group to go deeper into the understanding of the RA pathway in this system.

Weaknesses and risks:

A threat is that the two experienced and permanent scientists in the group have heavy duties outside the lab. This risks having a negative impact on the success of the group.

Although this could be seen as strength, they also tend to have a too RA-centric approach.

Recommendations:

Having focussed their work on spermatogenesis, the group should now try to investigate wider biological questions, as well as RA involvement, and thus to obtain a broader understanding of this developmental system.

The committee acknowledges the important contribution of N. Ghyselinck to the life of the IGBMC. However, they feel that, in such a big institute, an engineer's position should be devoted to the supervision of Hygiene and Security.

Team DSC-5: Cellular and molecular mechanisms of nervous system differentiation

Team leader: Angela GIANGRANDE

Workforce:

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	1	1	1
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *on a permanent position	1	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	4		
N7: Doctoral students	3		
N8: PhD defended	4		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**10**	**2**	**1**

Assessment of scientific quality and production:

Ms GIANGRANDE studies cell differentiation in the nervous system and the process of collective cell migration. A number of years ago, she identified a single transcription factor, glide/GCM that is both necessary and sufficient for the generation of glia in Drosophila. The current focus of the lab is to determine how the level of GCM is precisely regulated and to identify its targets. An intriguing finding is the observation that GCM in addition to its DNA binding activity can act as an RNA binding protein. In addition, genetic screens have identified a role for the Polycomb group in the plasticity of aging neural stem cells. An emerging project in the lab is the study of collective cell migration of glial cells in the fly wing. Using live imaging and UV-mediated cell destruction, the group has beautifully demonstrated the requirement for cell pioneers and the role of cell interactions for correct glial migration. The publication level of the group for the last five years is very good, with a number of articles in highly regarded journals in the fields of Development and Neurosciences, and one in PNAS.

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

The team has achieved a good level of funding until 2012 that it now needs to renew.

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

The group could be interacting more with others at the IGBMC. We note the lack of interaction with the only other Drosophila group at IGBMC. The interaction with the neurobiology group appears minimal as well.

Ms. GIANGRANDE is a recognized leader in the field. She participates in numerous meetings and is invited to give talks. Her group is obviously very attractive for PhD students and post-docs.

Assessment of the strategy and 5-year project:

Ms GIANGRANDE's projects aim at identifying Glide partners and direct targets and the role of RNA metabolism in the Glide pathway. She also aims at addressing the evolutionary role of Glide in the mouse immune system in collaboration with immunologists at other centers. Another part of her projects concerns the mechanisms underlying collective migration of glial cells along axons.

The long-term plans are interesting and sound. It will be particularly important for Mr GIANGRANDE to figure out how Glide regulates downstream targets.

Conclusion:

Strengths and opportunities:

Overall, Ms GIANGRANDE's group addresses fundamental problems in neurobiology and cell biology. The publications are of high quality and the group is very good, well supported and dynamic.

The group has a good international visibility, and the different parts of her projects are all promising.

Weaknesses and risks:

The PI is the only permanent researcher in the group. While this is not a real problem given the ability of the PI to attract post-docs, it may be interesting in the future to recruit another staff scientist.

Recommendations:

The interaction of the group with others at the IGBMC could be strengthened by internal collaborations.

Team DSC-6: Differentiation and physiopathology of endocrine cells in the pancreas and intestine

Team leader: Gérard GRADWOHL

Workforce :

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

Assessment of scientific quality and production:

This group uses the mouse system to study the molecular and cellular mechanisms controlling the differentiation of neuroendocrine cells in the pancreas and the intestine. The PI discovered the neurogenin 3 gene (Ngn3) and studies its role in pancreatic islet progenitor formation. The projects of the lab aim at characterizing specific effectors downstream of Ngn3, like the Rfx6 transcription factor, or the Glial-derived neurotrophic factors and their receptors. The team also proposes to study the pathophysiology of Ngn3 mutations using mouse models. Lastly, the mechanism of intestinal neuroedocrine cell formation will be investigated, since it utilizes some of the mechanisms observed for pancreas islet cell differentiation. This constitutes the most innovative part of the overall project. The PI has been quite productive since his appointment as a group leader in 2008 (Development 2010, J Clin Invest, 2010 and several papers in collaboration). Overall, the team leader's track record is very good.

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

The group leader has been successful in attracting start-up funds for the lab (currently, an ANR grant as a coordinator and a FRM équipe grant).

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

The team has reached a reasonable size (8 persons: 1 staff scientist, 1 postdoc, 3 students, 2 technicians). The group leader has a good track of invitations to meetings, attesting a strong recognition in the field. He is part of an NIH consortium on beta cell Biology, providing a solid collaborative environment for his research. The PI has also developed active international and national collaborations with specific labs (Brussel; London; Philadelphia; Nice). Overall, the PI is well connected in the field, which is a decisive condition for the development of cutting edge research in such a fast evolving and competitive field. The PI is a member of several national and US grant panels and is a reviewer for main journals in his field of research (Development, Genes & Dev, Dev. Biol., Diabetes, J. Clin. Invest. , etc.).

Assessment of the strategy and 5-year project:

The proposed projects on pancreas islet cells are ambitious and will be developed in a competitive environment. It seems that the team has found a niche with the study of intestinal neuroendocrine cell that should provide a less competitive framework for future research.

Conclusion:

Strengths and opportunities:

The PI has developed an independent line of research over the last 5 years, for which he has gained international recognition. The group has strong connections with the main actors of its field, which should allow them to pursue competitive work. The project is clearly outlined and the questions are sound and should provide an interesting outcome.

Weaknesses and risks:

This field of research is very competitive and the PI should pay attention to developing original lines of research on the side of the main competition track, like the study of the intestinal neuroendocrine cells for which he has good expertise.

Recommendations:

The PI should ensure that publications are kept at cutting edge level to maintain a strong visibility in his field.

The size of the group is probably limiting given the importance and competitiveness of the proposed aims.

Team DSC-7: Genetic and molecular analysis of early neurogenesis in Drosophila melanogaster

Team leader: Pascal HEITZLER

Workforce :

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

Assessment of scientific quality and production:

Mr. HEITZLER leads a very small group working on sensory patterning in Drosophila, a classic model to study cell-cell interactions and stereotyped patterning of neuronal architecture. His genetic studies over the years have led him to develop a sophisticated model of gene regulation that involves transcription factors that bind to the enhancer of proneural genes. His work on the dLMO protein emphasizes the cooperation between promoter and enhancer elements in this process. In recent years, he focused on the regulation of dLMO level by miRNAs, leading him to uncover the antagonistic relationships between two miRNAs (9a and 79). This regulatory network is a beautiful example of the role of miRNA in establishing a feedback loop regulating the activity of key members of the Notch pathway. The work is relevant to mechanisms in mammals as the transcription factors involved, and possibly the miR regulatory network, are conserved between Drosophila and the hematopoietic system. The group's publication record during the period of review is reasonable considering the size of the group but overall a bit low.

Assessment of the research team's integration into its environment, its reputation and drawing power:

The group is very isolated and does not interact with the only other Drosophila group at IGBMC.Mr. HEITZLER is a talented geneticist who has developed excellent tools to dissect the genetics of an important evolutionary regulatory circuit. His expertise is in genetics and, as shown for example by his recent use of the PacMan system, he applies the most updated tools. However, in recent years his team has lost attractiveness. The PI has not succeeded in recruiting students and postdocs and his group has been reduced to a critically small size.

Assessment of the strategy and 5-year project:

Mr HEITZLER's project follows up on his previous work. He will pursue the careful dissection of the network of transcription factors leading to the regulation of proneural gene expression. He will also further analyse miRNA function in proneural cluster formation, in particular in the Notch pathway feedback loop. In parallel, Mr HEITZLER aims at exploring miRNA function on LMO2 expression in malignant lymphomas, in collaboration with a group in Lyon. This last project is of broad interest but its feasibility can be questioned, given the extremely small size of the group.

Conclusion:

Overall opinion on the team:

Moving forward, the group is unfortunately facing significant issues. These include: 1. the size of the group as it currently only consists of two technicians; 2. the sense that Mr. HEITZLER will remain mostly a geneticist at core and will not diversify his repertoire of methods to solve the problems that he is studying; 3. the isolation of the group at the IGBMC; and 4. the poor record of grant funding.

Strengths and opportunities:

The committee acknowledges Mr HEITZLER's excellent past activity as a Drosophila geneticist, but feels that he is too isolated in his current environment at IGBMC. Mr HEITZLER is a talented geneticist who has brought significant contribution to the understanding of the spatial regulation of proneural cluster formation in Drosophila. His experience and know-how would be extremely useful in a group using Drosophila genetics.

Weaknesses and risks:

The group is facing significant issues, including its small size, its isolation within IGBMC, and the obvious difficulty of the PI to attract students and post-docs and to secure funding.

Recommendations:

The committee recommends Mr HEITZLER to actively search for a group, within or outside IGBMC, in which he will have the opportunity to insert and pursue his activity as a Drosophila geneticist while using his experience and know-how to help other scientists in their projects.

Team DSC-8: Understanding the cellular and molecular basis of cell plasticity in vivo

Team leader: Sophie JARRIAULT

Workforce :

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

Assessment of scientific quality and production:

The central theme of the research project of Ms JARRIAULT is to analyse the particular case of a natural switch in cell-type from one differentiation state to another entirely unrelated one. There is widespread current interest in the extent to which the normal strong stability of cell differentiation can be over-ridden experimentally. One way of achieving this is by the widely recognized procedure called induced pluripotency stem cell formation. This involves the overexpression of defined transcription factors. However, it takes place in a very small proportion of cells over a long period of time. This makes it very difficult to analyse the mechanism of the iPS route of cell differentiation reversal. Another way of achieving so-called "nuclear reprogramming" is to make use of mechanisms by which this process can occur without the addition of any genes, factors or other substances. One such route is the special case being followed by the group of Ms JARRIAULT.

In this case, use is made of the defined cell lineage of the nematode C. elegans. A particular cell, named the Y rectal cell is able to undergo transdetermination to become a PDA motor neuron. This is a

remarkable case of transdifferentiation, in which there is no cell division. A cell of epithelial type switches to become a nerve cell. This process occurs in normal development and offers a special opportunity to work out the mechanisms involved. A special merit of this system is that the cell-type switch can be seen in vivo in live animals; it is a highly reproducible process, which takes place in a limited time (of about ten hours). Ms JARRIAULT embarked on this project while still working as a postdoc in New York and has concentrated her research on this problem since joining the IGBMC. She has achieved a number of publications in highly-regarded journals; one such is in Development this year. She also has published papers in the journals Genetics and PNAS. It has taken some time to prepare the necessary mutations for this work, which benefits greatly from the genetic advantages of C. elegans. Recent work is in the form of a manuscript currently under consideration. Ms JARRIAULT has the advantage that this particular example of a natural transdifferentiation was established as a project by her and, in its present state, appears to be unique to her laboratory.

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

Ms JARRIAULT has already been awarded substantial research grants during the years 2006-2009, among which a CNRS ATIP funding in 2006 and an ATIP PLUS extension in 2009. She is in receipt of funding continuing through 2012, 2013 and 2014.

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

Ms JARRIAULT has received several recognitions including the CNRS ATIP, a Young Investigator Award from the EuroSyStem and a scientific Prize from FRM Alsace. The research group of Ms JARRIAULT appears to be well organized and to be able to attract highly-qualified postdoctoral and graduate students.

Assessment of the strategy and 5-year project:

As a strategy and project for the next five years, Ms JARRIAULT plans to identify the molecular networks that bring about the rectal-to-neural transdifferentiation in the nematode. What is special about the Y cell compared to the other five rectal cells? How does the transformation take place? The mechanisms that emerge may elucidate processes involved in other examples of transdifferentiation. Three specific aims are identified. The first is to extend a genetic screen for mutants, several of which have already been found. The second aim makes use of the finding that the Y cell expresses the Notch receptor while neighbouring rectal cells do not. A pulse of Notch signalling makes a Y cell competent to change identity. The hope is to identify signalling pathways and downstream genes required to make a Y-cell competent to be reprogrammed. A third aim takes advantage of a mutant FP15, in which a Y cell can initiate but not complete this transformation to a PDA cell. These various strategies have a good chance of producing valuable results even though each part of the programme is subject to the risk that unforeseen difficulties could arise.

Conclusion:

Overall opinion on the team:

The overall impression is of a well-planned programme of investigation into a remarkable phenomenon.

Strengths and opportunities:

This is a young, dynamic group with an excellent research project. All aspects of the proposal are well focussed on the major primary observation and have a good chance, between them, of achieving a molecular understanding of how this particular transdetermination event takes place.

Weaknesses and risks:

During the period under review, the group has launched several genetic screens and obtained tools required for their projects, which takes time, and thus they have not yet brought all their results to fruition, in the form of publications.

Recommendations:

In order to remain attractive for post-docs and students in the competitive environment of the IGBMC, the group will have to publish their results without delay and at the highest possible level.

Team DSC-9: Forces and signal in tissue morphogenesis

Team leader: Michel LABOUESSE

Workforce :

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

Assessment of scientific quality and production:

Mr. Michel LABOUESSE´s work has generally been considered to be of excellent quality in his research field. Using C. elegans as a model system, his group has successfully combined genetic and reverse genetic (RNAi) approaches with protein interaction screens and EM tomography to address questions related to mechanotransduction, lumen formation and cuticle formation, with the major aim behind these studies being to better understand the processes of tissue morphogenesis.

In the past five years, his work has received considerable visibility, to which his recent publications in Curr Biol and Nature obviously contribute. He has also written a number of reviews on topics related to mechanobiology and morphogenesis and is a leader in this field. More recently, he also started a collaboration with physicists from the Ecole Normale Supérieure Paris to model the process of elongation during C. elegans development. This shows that he aims at a higher-level understanding of the morphogenesis process and is building a solid foundation for his future research.

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

The work on mechanosensation and mechanostablilzation is well funded by the ANR and now by an ERC grant, which will help the group to remain competitive.

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

Mr. Michel LABOUESSE is very well integrated into the IGBMC where he takes ample advantage of the excellent expertise available in the imaging facility. He was head of department and contributed to successful recruitments to build up developmental biology. He is also active with regard to student affaires, a job which is invaluable if well done.

He has been able to attract good people, which allowed him to be competitive in the past. The increase of groups in the Development and Stem Cell section of the IGBMC should increase visibility in this field and therefore facilitate recruitment to basic research on model organisms, particularly for a group at the interface with biology/physics, which is currently seen as an upcoming area of research.

Assessment of the strategy and 5-year project:

Major efforts will be invested in linking hemidesmosomes to mechanotransduction and ultimately tissue morphogenesis. Important aims are the identification of the primary hemidesmosomal mechanosensor, the development of in vivo tension biosensors and the characterization of resistance forces. In addition, collaboration with team DSC-3 aims at a better description of vertebrate hemidesmosome function. This project might well be quite successful (maybe different screening procedures will have to be taken), since it should result in a synergistic interplay between research done in the two different systems.

Mr. Michel LABOUESSE proposes to work on a number of other, novel topics in the next few years (lumen formation, trafficking in polarized cells, …). These topics are well chosen and use the strength of the C. elegans system at its best.

It is expected that the visibility of the group will be even further increased over the next few years. In addition, since there are now a number of groups at the IGBMC, which study the role of forces in development, the visibility of the entire Institute in this emerging field will definitely increase. The group will certainly also profit from the recent recruitment of physicists and the multidisciplinary organisation of the Institute. Most importantly, Mr. Michel LABOUESSE's initiative (together with team DSC-11 leader) to set up a new Master2 program at the interface between Physics and Biology will certainly help to increase recruitment to his group; considering the many interesting and challenging projects, an increase would certainly be certainly a smart move.

Conclusion:

Overall opinion on the team:

This team has the opportunity to further increase its visibility considerably in the next few years. The projects outlined for the future are ambitious but feasible and well thought out.

Team DSC-10: Development of muscle and vertebrae

Team leader: Olivier POURQUIÉ

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *on a permanent position	4	4	
N5: Engineers, technicians and administrative staff * on a non-permanent position	5		
N6: Postdoctoral students having spent at least 12 months in the unit	8		
N7: Doctoral students	4		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**23**	**6**	**2**

Assessment of scientific quality and production:

Mr Olivier POURQUIÉ is a major scientific figure. His identification of the molecular oscillator that drives the rhythmic segmentation process of somitogenesis has been hailed as one of the major discoveries in the field of developmental biology during the last century. Since moving to the IGBMC in 2009, his laboratory has continued to make major progress in understanding the segmentation clock. A genomic analysis between vertebrate species shows the conservation of oscillations in the Notch, Wnt and Fgf signalling pathways, with striking plasticity in the genes employed within these pathways. Microarray analyses also revealed an unexpected segregation of metabolic processes. Bilateral symmetry during somitogenesis in the face of left/right signalling was thought to depend on retinoic acid signalling and this team has now made important advances in understanding this mechanism. Axis elongation is intimately linked to the process of somitogenesis and they have recently examined cell behaviour in this context, with a high profile publication in Nature in 2010 on this subject. In addition to fundamental research on animal models, the PI is also engaged in genetic studies on congenital scoliosis in humans. This work, initiated in the USA, is now continuing in France.

The PI has an outstanding publication record, with papers in Development and in Nature, in the last two years, which partly result from work performed in the IGBMC. He is also the author of recent reviews as well as co-author in a collaborative project published in Nature in 2010.

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

Mr POURQUIÉ's laboratory is now well established in the IGBMC where it is a major asset for the reputation of developmental biology at the Institute. In addition to his high impact basic research, Mr POURQUIÉ's work on congenital scoliosis is of biomedical and social importance. On the economic front, he has recently founded a biotech company. Since coming to France, he has been very successful in attracting funding for his laboratory, with support from the ANR and AFM, for example, and a prestigious ERC advanced grant.

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

In addition to the ERC advanced award, Mr. Olivier POURQUIÉ received the Grand Prix Alliance/Institut de France in 2011. He is editor in chief of Development, an important international journal in this field. He is a frequent invited speaker at Institutes worldwide and at international conferences, where his laboratory members also participate. His large research group at the IGBMC now has 25 members. The success and wide appreciation of Mr POURQUIÉ's work has attracted many postdocs both nationally and internationally as well as PhD students, who have joined his laboratory at the IGBMC. An INSERM CR1 scientist has also integrated his group.

He has established collaborations with laboratories in the USA, Germany, Belgium and the UK, as well as in France. He is co-founder and president of an international consortium for vertebral anomalies and scoliosis (ICVAS).

Assessment of the strategy and 5-year project:

Among the future directions of his work, he will continue to focus on the segmentation clock pacemaker. Although the signal molecules Wnt, FGF and Notch are involved, these do not appear to be primarily responsible for the oscillation observed. An important aim is to be able to observe synchronized oscillations in vitro. This could lead to a biochemical dissection of the pacemaker of the clock. In parallel it is proposed to analyse the segmentation clock in vivo. It is hoped to be able to identify drugs that can modify the oscillation period in a dose-dependent manner. Other work in the laboratory aims to pursue the analysis of left-right symmetry of somite formation in which retinoic acid is involved. All of these experimental directions proposed are appropriate to analysing the remarkable phenomenon of oscillatory segmentation. Having pioneered this field, Mr POURQUIÉ and his colleagues remain in the forefront of work analysing this remarkable phenomenon. This is now coupled to work on the molecular regulation of axis elongation, with very interesting indications of how Hox genes regulate this process, which will be pursued.

In a more recent line of research, Mr POURQUIÉ aims to find a way of differentiating embryonic stem cells into the paraxial mesoderm from which somites are formed. For this they use a posterior mesoderm marker, Msgn1, marked with Venus YFP. This could open a way to the identification of a pacemaker for the segmentation clock oscillator. The aim is also to obtain efficient protocols for making somite derivatives such as skeletal muscle. This could lead to the generation of iPS cells from dystrophic patients in which the causative mutation could be genetically corrected, with potential therapeutic applications.

Conclusion:

Strengths and opportunities:

In conclusion, this is an excellent group noted for its original discoveries and widely appreciated for the direction of their research. Strength is certainly there and opportunities are clearly envisaged.

Weaknesses and risks:

There is no obvious weakness or threat to the success of the projects.

Recommendations:

The necessary resources seem clearly to be available at the IGBMC and a long-term investment in this research will be required and is clearly justifiable. Much original thinking and experimental risk is required.

Team DSC-11: Cell physics

Team leader: Daniel RIVELINE

Workforce :

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

Assessment of scientific quality and production:

Independent PI since 1999, Mr. Daniel RIVELINE has joined the IGBMC in 2010 after spending three years as a visiting professor at Rockefeller University. To better understand the physics underlying biological systems, this team tackles questions related to shape transformation in individual cells, monolayers and tissues and tries to understand the underlying physical principles. This team is also part of the Institute of Science and Supramolecular Engineering (ISIS) at the UdS, which is an advantage for interdisciplinary research of this type. The publication record has been solid over the years although not overwhelming.

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

Most importantly, Mr. Daniel RIVELINE´s initiative (together with team DSC-9 leader) to set up a new Master2 program at the interface between Physics and Biology is an excellent move to increase the future attractiveness of the IGBMC and the participating research groups.

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

Mr. Daniel RIVELINE has already integrated very well into the IGBMC and is in close contact with many groups, including teams DSC-9, DSC-10 and DSC-14 and others.

Again, the initiative to set up a new Master2 program at the interface between Physics and Biology will certainly help to increase the visibility of his group. His citation record is clearly in an upward trend, and since the integration of physics with biology is an important step to be taken in future years, he is in a good position to have impact. Collaborating with teams DSC-9 and DSC-10 is an excellent initiative in this context.

Assessment of the strategy and 5-year project:

The projects proposed for the next years include two major lines of research: 1) Cell fluctuations in single cells and in monolayers and 2) Force distributions in developing embryos. In both cases, it will be important to test some of the conclusions in in vivo settings, and some of these experiments are planned with team DSC-10. Daniel Riveline appears to be very open for collaborations with biologists, and the environment of the IGBMC with numerous groups interested in forces (teams DSC-9, DSC-10 and DSC-14 just to name a few) provides numerous occasions for this.

Conclusion:

Overall opinion on the team:

The arrival of Mr. Daniel RIVELINE at the IGBMC is very timely and promises to pay off for both parties in the future. The successful implementation of a new master program at the intersection between physics and biology is a major step in the right direction and will help to attract interested students.

Team DSC-12: Cell cycle and ubiquitin signaling

Team leader: Izabela SUMARA

Workforce:

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

Assessment of scientific quality and production:

This is a recently established group (October 2010) by a newly independent investigator who has already conducted (semi-?) independent research as a senior scientist at the ETH in Zurich. Previous work of the PI has shown the importance of Cul3-E3 ubiquitination pathways in controlling the sub-cellular localization of important cell cycle regulators, therefore controlling cell cycle transitions. The proposed project is in line with previous work of the PI and concerns the study of ubiquitin signaling for the control of cell cycle transitions in mammalian cells.

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

The research of this young team has already been consolidated by an ATIP/AVENIR funding (2011-2013), and a SANOFI-AVA grant (180K€, 3 years).

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

The PI was appointed to the IGBMC at the end of 2010, and has assembled a team that includes two PhD students, one postdoctoral fellow and one technician. The PI has already published several papers as

corresponding author before her appointment as a group leader at the IGBMC, testifying of her independence in elaborating and conducting her research projects. The PI demonstrates a strong dynamism with many communications at meetings and has established several international collaborations (Zurich; Lausanne; Miltenyi Biotec; Dundee; Toronto).

Assessment of the strategy and 5-year project:

The project is organized around 3 main aims: (i) understanding the role of cul3-mediated ubiquitination in controlling cell division and chromosome stability. This relies principally on a better characterization of the Cul3 machinery (substrate adaptors), the identification of Cul3 function in microtubule dynamics, and the identification of downstream components of the pathway, using high throughput RNAi screens and live video microscopy analysis. (ii) identification of new Cul3 substrates using the result of an already performed high throughput protein microarray assay. The function of several candidates isolated in the screen will be further studied. New biochemical screens will be performed (shotgun mass spectrometry after immunoprecipitation with susbtrate specific adaptors). (iii) Analysis of other UPS components required for mitosis by RNAi screen and video microscopy.

This is an ambitious and extensive project on the function of UPS in mitosis, requiring strong experimental implication. The group is still small and it is difficult to envisage that only 2 students and one postdoctoral fellow can carry out such extensive work. The recruitment of other lab members will have to be done rapidly in order to reinforce the ongoing projects.

Conclusion:

Strengths and opportunities:

Ms. I. SUMARA is a dynamic PI conducting an extensive project for which she has already good expertise and recognition. The research is cutting edge and should provide new insights into the refined mechanisms of protein modification by the UPS in controlling cell cycle transitions. The techniques proposed are classic but well mastered by the PI, as well as supported by in house facilities in the Institute.

Weaknesses and risks:

The manpower of the team is still limited and not fully adequate with the ambition of the proposed projects.

Recommendations:

New team members should be recruited soon to reinforce the team.

Team DSC-13: Epignetics and cell fate in early mammalian development

Team leader: Maria-Elena TORRES-PADILLA

Workforce :

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

Assessment of scientific quality and production:

Ms TORRES-PADILLA had a highly successful period of work as a postdoc. She discovered that the overexpression of Carm1, an enzyme that places an arginine on histone H3, can significantly change cell fate when overexpressed in one of the four mouse blastomeres. Benefitting from the considerable expertise and experience gained while working with early mouse embryos, Ms TORRES-PADILLA plans to study how changes in cell potency are controlled by chromatin-mediated changes in gene regulation. Her work on the arginine methylation of histone H3 (through an H3 arginine methyltransferase CARM1) had a substantial impact on the field of early mouse development because it is the only case, so far, where an epigenetic modification can change a very early mouse cell fate. Ms TORRES-PADILLA's publication record over the last few years has been excellent. Of 27 accepted publications, 20 have been with her as first or corresponding author. Notably, in the last few years she has had papers published in Genes and Development, Nature Structural Molecular Biology, Nature Cell Biology and in Molecular and Cell Biology. This is a remarkable record for only two and a half years.

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

The group has attracted substantial funding with three large grants finishing in the years 2011, 2012 and 2013.

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

Ms TORRES-PADILLA is collaborating successfully within France (Institut Curie, Paris) as well as in the IGBMC Institute. Her collaborations seem very appropriate since the expertise of her collaborators complements her own abilities She has been invited extensively to speak at chromatin and developmental meetings, and many of her invitations come from laboratories of exceptionally high standing. She interacts very closely with her colleagues and students, forming therefore a small but very successful group.

Ms TORRES-PADILLA has received very considerable recognition and attracted excellent students.

Assessment of the strategy and 5-year project:

Ms TORRES-PADILLA's future work is designed to explore mechanisms of selective gene repression or activation in early mouse development. There are three stated aims. The first is to examine the position of genes within the three-dimensional space of embryonic nuclei. This is a fashionable topic and many laboratories consider that intra-nuclear location could be of special importance. It is planned to experimentally change the positioning of Nanog within an early embryo nucleus. The second aim is to attempt to induce heterochromatin gene repression in embryo nuclei by overexpressing various factors such as HP1a, linker histone H1, etc. Heterochromatin formation at repeated loci will be particularly looked at. A concern about this experimental approach is that it might lead to global repression, making it hard to be sure of the effects on individual genes. However, Ms TORRES-PADILLA has the interesting idea of using the Zinc finger technology to localize repression.

The first of these projects is risky because it is not yet certain that the intra-nuclear localization of genes is causally connected with their expression. The other two directions of work seem particularly interesting and exceptionally worthwhile. With Ms TORRES-PADILLA knowledge of cell fate as well as chromatin modification this seems an excellent research programme. If it is possible to localize gene repression through the Zinc finger approach this would provide an invaluable opportunity for gene-specific analysis. Altogether this seems an excellent programme for a highly successful group.

Conclusion:

Overall opinion on the team:

Ms TORRES-PADILLA is an outstanding young investigator who has already made a major mark in her field. Furthermore, her future plans fit exceptionally well with her experience and her technical ability. These are strengths and opportunities in this project, which does not have obvious weaknesses or threats.

Team DSC-14: Mecano-genetics interplays and embryonic morphogenesis

Team leader: Julien VERMOT

Workforce:

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

Assessment of scientific quality and production:

Mr. Julien VERMOT has been successful both during his PhD at the IGBMC as well as during his postdoctoral stay in Pasadena (USA). He has already published some 25 papers, and many of them are rather well cited.

As a postdoc, he started to work on mechanical stress, flow and hydrodynamics in the zebrafish model using novel and innovative high-resolution light microscopy approaches. He successfully investigated the role of local flow during valvulogenesis in the embryonic heart as well as the role of flow forces generated by beating cilia during otholith formation and signed the resulting papers as first author (PLoS Biology) and last author (Dev. Cell), respectively. The quality of his science is excellent, and so is the production in the past years, including since his arrival at the IGBMC in 2009, from where he published the Dev Cell paper in 2011.

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

Mr. Julien VERMOT has already secured substantial funding for the next years and his group is certainly attractive for incoming students and postdocs.

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

In the short time since his arrival, this PI has integrated extremely well into the IGBMC and the technical platform groups. Within the institute, his lab has already started collaborations with team DSC-6 as well as with team TMN-7 and discussion is also intense with the incoming physicists. Julien Vermot's advice and help is also very much appreciated by the leaders of the imaging facility and his interactions with the facility will be crucial for the future development of the latter. Julien Vermot could act as part of the "scientific steering committee" to help to ensure that the facility will provide the best possible environment for both the scientists that use it as well as for the people who work there.

Assessment of the strategy and 5-year project:

The major interest of this team in the near future concentrates on the mechano-genetic interplay during embryonic morphogenesis, building on the valvulogenesis story, and on the role of cilia in general (he identified cilia on most endothelial cells!). No need to say that the role of blood flow during vascular development is an important field, both with regard to basic as well as biomedical research. His research aims are ambitious (identification of the mechanosensitive pathways at work during angiogenesis and valvulogenesis, screenable tools for cardiomyopathies, etc.) but his studies are likely to make a major impact in a rather competitive field.

Conclusion:

Overall opinion on the team:

Mr. Julien VERMOT is an outstanding and promising young investigator with clear aims for the future. In this fruitful environment, he will very likely succeed and establish his group firmly in the field in the next five years.

Team DSC-15: Primordial germ cells (PGC) ontogeny and pluripotency

Team leader: Stéphane VIVILLE

Workforce:

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

Assessment of scientific quality and production:

The scientific research of this team centers on primordial germ cells, focussing on spermatogonia. This includes work in the mouse model on genes that are implicated in the properties of these cells and work in human genetics to identify genes that are responsible for infertility. Based on a bioinformatics search the group had identified Tex19-1 and Tex19-2 in primordial germ cells and in the early mouse embryo where their expression pattern resembles that of Oct4. They have gone on to make single and double mouse mutants. The Tex19-1 mutant phenotype was first described by a group in Edinburgh, but Stéphane Viville and colleagues have a double Tex19-1/2 mutant, which has a fully penetrant phenotype. Preliminary results point to potentially interesting effects on reprogramming and transposon regulation in primordial germ cells, as well as placental defects. A second gene, SCS2, which belongs to the large family of deubiquitinase enzymes has also been selected for analysis and a mouse mutant is being generated, with the help of the ICS. These genes encode proteins of unknown function and little progress has been made so far in understanding Tex19. On the human genetics front this team has identified genes implicated in globozoospermia. A third activity of the laboratory has centered on the production of human ES cell lines. They have successfully derived lines

from embryos affected with monogenic disease and are now also working to produce human and mouse iPS lines.

The publication output of the laboratory is rather limited for the size of the group, with only one main paper on Tex19 in Stem Cells in 2008, and two papers in the American Journal of Human Genetics in 2007 and 2011 out of 8 peer-reviewed articles in international journals as corresponding author. They are also collaborators on other papers in the fields of human genetics and infertility.

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

This work on human infertility is clearly of social importance. In this context the team has successfully raised funds both nationally and internationally. Its biobanking activities for human pluripotent cells, to be transferred to the medical faculty, also represent an important contribution; this work has received major support from the AFM.

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

The PI is known for his work on human infertility and on human ES cells; he has been an invited speaker at national and international conferences on these subjects. He is an elected member of the European Society of Human Reproduction and Embryology, which he helped to found, and is co-ordinator within this society of the special interest group on reproductive genetics. Within France he has been a member of committees of the Agence de BioMédecine and the AFM. As a professor in the medical faculty of the University of Strasbourg, he has played an active role in teaching. In 2007, he received an award from the Minister of Education. His research laboratory, in addition to two staff scientists, is mainly composed of PhD students and ITA, with very limited international attractiveness. He is involved in collaborations/networks on the human genetics of infertility and on pluripotent stem cell lines.

Assessment of the strategy and 5-year project:

The biobanking activity will be transferred to the medical faculty, where it will continue to expand. He will also pursue his research on the human genetics of infertility, with on-going work on globospermia. His projects on Tex19 and SCS-2 it will involve phenotypic analysis of mutants. However the major challenge is to determine the function of these proteins. This includes strategies for looking at DNA targets and protein partners. Despite the expertise present in the IGBMC, the committee was not convinced, given the lack of progress to date, that these projects would advance significantly beyond a descriptive stage.

Conclusion:

Overall opinion on the team:

Overall, the research on the human genetics of infertility is moderately satisfactory and his biobanking activities provide a resource both of cell lines and expertise.

The work on the regulation of primordial germ cell properties, through the study of Tex19 and SCS2 has not been very productive and is unlikely to have important impact.

Team FGC-1: Hematopoiesis and leukemogenesis in the mouse.

Team leader: Susan CHAN / Philippe KASTNER

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	1	1	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	5		
N8: PhD defended	5		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**10**	**4**	**3**

Assessment of scientific quality and production:

The research of the KASTNER/CHAN team is entirely focussed around the Ikaros family of zinc finger transcription factors and their role in hematopoietic development with an emphasis on the lymphoid system (T and B cells) and dendriditic cells. The Ikaros family has five members (Ikaros, Helios, Aiolos, Eos and Pegasus) and the group has gone a long way to collect or generate a number of genetic tools in the mouse to study the role of these factors, including a floxed Ikaros mouse, an Ikaros hypomorph and a Helios null mouse. The generation of floxed Aiolos and Helios alleles are in progress. The group uses genomic methods and technology in combination with the mouse mutants to develop hypothesis driven questions in a highly competitive area of research. The work has resulted in a number of papers in journals such as J. Exp. Med., Blood, MCB or J. Immun. on the role of Ikaros and Helios in T cell and HSC development/ maintenance and the role of Ikaros in B cell class switching. Perhaps most interesting is the role of Ikaros in the control of the Notch pathway and T- cell acute leukemia (T-ALL). Ikaros suppresses the Notch pathway and mutant mice

develop T cell acute lymphoblastic lymphoma/leukemia (T-ALL). Ikaros re-expression in leukemic cells inhibits proliferation and down-regulates Notch target genes by binding on the promoter of HES1. These observations are likely to be extended to virtually all Notch target genes, as suggested by their recent ChIP-seq experiments.

They have published 6 papers in good (IF 5-10) to very good (IF 10-15) journals (J. Immunol., Mol.Cell.Biol., Blood, J. Exp. Med.) as last/corresponding authors and an additional 8 collaborative publications with some in excellent journals (Cell, Cell Stem Cell, Development…) and clearly have significant impact in the hematopoietic/leukemia field, but fall short of being real international leaders in this field.

In addition they supervised 5 PhD's.

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

The team has been very successful in raising funds (> 2 M€ during the 2007-2012 period) through competitive grant applications at the national level either as coordinators or as partners (INCa, ANR, LNCC (équipe labellisée), ARC), and they are partners in an EU FP7 ITN that was obtained in early 2011.

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

Ms Susan CHAN has received the 2011 J.M. Le Goff prize of the French Academy of Sciences. There have been no invitations to international meetings and 2 invitations to French symposia.

The team recruited one staff scientist at INSERM (2007) and is presently composed of 3 staff scientists, 2 post-doc and 5 PhD students of both French and foreign origin.

The team does have a number of strong and fruitful national and international collaborations. The two co-leaders are members of Scientific Committees of French Charities (ARC, LNCC, FdF). M. P. KASTNER is the scientific consultant of the IGBMC microarray facility (label IBISA), while Ms S. CHAN is the scientific consultant of the IGBMC flow cytometry facility. She is also in charge of the Immunology phenotyping at ICS.

Assessment of the strategy and 5-year project:

The team addresses a number of important questions and proposes to continue their current work. The additional focus on dendritic cells appears appropriate. It is based on the Ikaros family of proteins/genes. However the team invested a lot in mouse mutants. Thus the committee recommends that the team should much better characterize the transcription factors (and their co-operating or antagonistic partners) at the biochemical level to maximize the interpretation of the data they will obtain from their models.

Conclusion:

Strengths and opportunities:

The team develops excellent mouse models, has good collaborations and a significant impact in the lymphogenesis/leukemia field.

Weaknesses and threats:

There is insufficient biochemical insight into the Ikaros factors and relevant co-operating or antagonizing factors. There also appears to be a lack of communication with other groups in the new department of Functional Genomics and Cancer, which houses a number of groups that could provide very useful advice in the functional genomics and biochemistry area.

Recommendations

To improve communications with other groups in the department.

To strengthen/widen the biochemical characterisation of the Ikaros factors and co-operating or antagonizing factors to allow more insight into the regulatory network in which these factors participate.

Team FGC-2: Transcriptional regulatory networks and signaling in cancer

Team leader: Irwin DAVIDSON

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	3	3	3
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	0	0	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	4		
N8: PhD defended	4		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**11**	**3**	**3**

Assessment of scientific quality and production:

The previous work of the team focused on the general transcription factor TFIID and its associated factors, in particular TAF4. Mouse mutants were generated and the function of TAF4 was studied in embryonic differentiation, tissue differentiation and function in epidermal keratinocytes, ovary and testis. This work has been published and the group has begun to refocus on the function of transcription factors that were discovered in conjunction with research on TAF4.

Two novel retinoic acid receptor binding elements were identified and studied in detail through biochemical/biophysical techniques (isothermal titration, band-shift) and biological assays (ES cell differentiation) on a genome wide level.

Another focus of the laboratory is the bHLH transcription factor MITF and its role in melanoma where the metastatic stage differs from the primary state by a switch in the levels of MITF (down) and Pou3F2 (up). They identified the interaction partners of MITF and determined the genomic binding sites of MITF and the change in expression profile when MITF is downregulated by siMITF. Important findings are that MITF partially takes over E2F functions downstream of Raf/Pou3F2 signaling and binds to co-factors involved in DNA

replication, mitosis, gene silencing, and DNA damage response. Sumoylation of MITF is suggested to determine its interactome and genomic binding sites. Interacting proteins include the TRIM family of transcriptional repressors and proteins of the NURF and SWI/SNF remodeling complexes. TRIM proteins/complexes are under further scrutiny and were found to play a major role in murine hepatoma formation.

While the multiple directions of the group's research initially appear quite broad, the individual approaches and projects are in fact tightly linked at a mechanistic level.

The group leader has published 11 articles as corresponding author during the evaluation period, several of them in very good journals (PNAS, Development, MCB, Oncogene, Biol Reprod) and 11 papers as co-author. (NAR, Oncogene, MCB, JBC) and 5 peer reviewed reviews.

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

The team showed a very good ability to raise funds (> 2.3 M€ during the 2007-2012 period) and developed very productive collaborations

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

The work of the team has significant impact on the understanding of basic transcription and mechanisms that link TFIID to signal dependent development and tumorigenesis. The team is internationally highly recognized for the work on TAFs and has been able to raise considerable funding for their research. It should also be noted that the group leader has played an important role in bringing novel "omics" techniques into the Institute.

Also highlighting the impact of the team's work, the team leader has received a good number of invitations to speak at international (7) and national (3) meetings.

The team is well balanced with 4 Post Doctoral researchers and 4 PhD Students.

Assessment of the strategy and 5-year project:

The team will continue on RA-response, MITF and related research on TAF4 and associated factors. A matter of concern is that the multiplicity of projects may lead to competitive disadvantages, however, the committee also considers this as a transition period and re-orientation phase.

Conclusion:

Strengths and opportunities:

The team has very good national and good international visibility with robust international collaborations. There is a connection between basic mechanisms and disease. The connection between projects is good.

Weaknesses and threats:

The team develops multiple projects in highly competitive fields.

Recommendations:

The committee has some concerns about the proposed work in the melanoma project, focused around the TRIM proteins and targets and in particular the role of retrotransposon non-coding RNAs. This is not a very large group, and given the large amount of work proposed in a number of different areas, it will be important to prioritize carefully to maximize the ability to maintain research on all topics at an internationally competitive level.

Team FGC-3: Genome expression and repair

Team leader: Jean-Marc EGLY / Frédéric COIN

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	3	3	3
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	4	4	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	4		
N7: Doctoral students	9		
N8: PhD defended	7		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**20**	**7**	**3**

Assessment of scientific quality and production:

The team has a longstanding and outstanding research record in exploring the molecular functions of the transcription and DNA repair complex TFIIH. The group is famous for their work and continues to unravel complex TFIIH functions by exploring defects caused by human mutations in TFIIH components or in TFIIH associated co-factor complexes or interacting transcription and DNA repair machinery. The research of the group unites genetic, molecular genetic, and biochemical approaches not only to unravel the genetic connections but also to explore the underlying mechanisms and thus to disclose potential pharmacological targets. Their approach is extraordinarily successful and provides an admirable paradigm for how basic science can impact on clinical science and vice versa.

The team publishes its work with group leaders as corresponding or senior authors in the leading journals, including multiple publications in Science, Molecular Cell, EMBO J, Nature Struct. Biol/Neuroscience, and others; and also as collaborative work (Mol. Cell; PLos genetics, EMBO J). The two group leaders make a remarkably effective team in which both make essential contributions to the research

program, with F. Coin having primary responsibility for aspects of the work addressing mechanisms and regulation of nucleotide excision DNA repair.

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

The fund raising is very high (> 4.3 M€ during the 2007-2012 period). The team maintains a number of very productive collaborations.

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

The work of the team has an outstanding impact on uncovering the function and pathological consequences of mutations in the basic transcription machinery. The work is also of the highest clinical relevance and thus directly impacts on human health and disease.

The more senior group leader, Mr. J-M EGLY, has been invited to speak at many international and national meetings (17) and is the recipient of many prestigious prizes and awards. He also serves on advisory panels for the ERC and INSERM, and he has significant leadership roles in both private and French national research organizations including INSERM.

Mr. F. COIN is at a significantly earlier stage in his career but is developing a national and international reputation on his own as evidenced by his authorship of invited reviews, by editorial responsibilities, and by service on review panels for the ARC and ANR. The committee believes it would be beneficial for the team if he were able to enhance his visibility further by presenting the team's work at national/international meetings and, where appropriate, with independent publications.

The team attracts a large number of international scientists and PhD students.

Assessment of the strategy and 5-year project:

The team will continue their extremely successful studies. The results are highly relevant to basic and clinically applied research. The group comes up with novel connections (e.g. between TFIIH and Mediator) and their biochemical resources/knowledge permit the integration and experimental validation of medical consequences of recurrent human mutations that lead to complex diseases.

Conclusion:

Strengths and opportunities:

The team has an outstanding international recognition. They are leaders in the field with highly productive international collaborations. There is a very good connection between basic mechanisms, disease, and clinical targets. The sub-projects are very coherent. The junior group leader exhibits a very high level of scientific maturity and capability compared to others at his stage of career development.

Weaknesses and threats:

The committee feels that it may be challenging for the junior group leader to live up to the expectations and to develop an independent scientific identity and, ultimately, to maintain the group's effort at the current level of international leadership.

Recommendations:

This is an impressively outstanding and distinguished project. The group should be congratulated for their work. The Institute and Department leaderships is encouraged to support development of the more junior group leader's career and to ensure that he has appropriate resources, including office space, needed for success as a group leader.

Team FGC-4 : From nuclear receptor to novel paradigm for cancer therapy action

Team leader: Hinrich GRONEMEYER

Workforce:

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

Assessment of scientific quality and production:

This team has a longstanding interest in (i) the structure, mechanism of action, and regulation of nuclear receptors and (ii) of TRAIL-mediated tumor selective apoptosis. Their work over the past four years has provided novel insights into molecular mechanisms by which ligands affect the structure, activity, and coregulator interactions of retinoic acid and retinoid x receptor family members in retinoic acid signaling. They have also published, or have submitted, a series of papers describing approaches for modulating TRAIL signaling in cancer therapeutics. Their recent evidence that (i) CBP methylation by CARM1 regulates CBP activity and is needed for estrogen-induced CBP recruitment to target genes and (ii) differentially methylated CBP species exhibit distinct patterns of recruitment to different ER-activated genes is significant in that it has revealed an unexpected level of complexity in CBP function in ER signaling, and led to the proposal of a "meHAT" code in gene regulation. The team's development of reagents as well as improved methods and bioinformatics tools for genome-wide studies should be of considerable use in experiments to explore this hypothesis further in their own group as well as the larger community. Their efforts to develop therapeutic strategies targeting nuclear receptor and apoptotic signaling have implications for human health.

The importance of the group's findings is reflected in a series of high-impact publications in excellent journals. Among these are 21 articles as corresponding author, including 1 Nature Methods (2011), 1 Genes & Dev (2011), 1 Cancer Cell (2009), and 1 PNAS (2007); 11 peer-reviewed reviews, and 11 publications within the frame of collaborations.

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

The group has a very strong ability to raise research funding through competitive grants, having attracted substantial funding alone or as part of national or large-scale European consortia (ANR, INCa, LNCC, FRM, and EU grants,), most of them as coordinator. The group leader presently coordinates 1 ANR and 1 INCa programs.

The group filed 3 patents during the evaluation period.

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

Also attesting to the significance of their findings is recognition of the team leader by invitations to speak at national and international meetings and to serve on multiple editorial boards. The team leader is recipient of several national prizes.

Assessment of the strategy and 5-year project:

The group has a long history of productive, significant findings, and it is likely that novel information about the function and regulation of CBP/p300 methylation, nuclear receptor function, and tumor-selective apoptosis mediated by TRAIL signaling will emerge from the proposed systems / genomic analyses. In the report the research plans are described in outline form with little indication of rationale or priorities, although concern about this issue was alleviated somewhat by discussion during the committee's meeting with the group leader. Careful consideration of how the results of the planned research can be taken to the next level to illuminate mechanism and to drive development of cancer therapeutics would be beneficial; however, in light of the past success of this group in applying approaches ranging from structural biology to genomics to gain mechanistic insight, this is somewhat less of a concern than it might otherwise be.

Conclusion:

Summary:

This is a strong research team with a long history of significant contributions, a strong publication record, and an excellent ability to raise funds through competitive grants. The research addresses important questions, and the team is expected to continue to gain insights with basic science and translational implications.

Strengths and opportunities:

(1) Established team leader with national / international reputation. (2) Long history of significant contributions to understanding nuclear receptor function, mechanism of agonist / antagonist action. (3) Combination of basic and translational research. (4) Emphasis on genome-wide studies takes advantage of methods and bioinformatic tools developed in the group.

Weaknesses and threats:

Although the planned systems and genomics analyses will undoubtedly yield considerable useful information, there was little indication of priorities or how the proposed work fits into the larger context of the field, nor was there much discussion with the committee of how this information will be taken to the next level to dissect the underlying mechanisms. The work on non-coding RNAs is a relatively new direction for this group and is in a highly competitive area.

Recommendations:

Overall the research program addresses important problems and is likely to yield advances that are of fundamental scientific as well as technological significance. However, the group's research addresses many problems, and they are encouraged to focus on those areas where they can be expected to make the most unique contributions at an internationally competitive level.

Team FGC-5 : Chromatin and epigenetic regulation

Team leader: Ali HAMICHE

Workforce:

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

Assessment of scientific quality and production:

The group is new to the IGBMC, having joined the Institute from Villejuif in March 2008. The group is focused on an important and understudied area of chromatin biology, namely, the question of how histone variants influence various aspects of cell biology. They use tagging and overexpression to identify proteins associated with variant histones in order to understand how they are deposited, regulated and how they function. The group has expertise in ubiquitylation and PARylation, the DNA damage response, and many aspects of cell biology. Their work combines biochemistry and structural determination with standard molecular biology techniques.

The group has made a number of important contributions to this field including the identification of DAXX as a H3.3 chaperone and co-discovery of HJURP as a histone chaperone important for centromeric localization / deposition of the histone H3 variant CENP-A. They have also identified a novel kinase in the centromeric CENP-A complex that phosphorylates both CENP-A (on Ser7) and the HJURP protein. Attesting to its functional significance, loss of the kinase activity leads to multinucleate cells and mitotic errors.

They have also characterized an H2AZ-associated protein from a protein complex and made the intriguing observation that a factor called p30 recruits the p400/Tip60 chromatin remodelling complex to H2AZ and is associated with the eviction of H2AZ from a promoter that is associated with loss of RNA polymerase II. The strategy is excellent for a new group establishing themselves, as it is focused but has the potential to provide new and exciting results as a basis for future work. These are important questions and this is reflected in two excellent papers from the group in 2010. The team leader has a number of collaborative papers with groups in the IGBMC and with a long-term collaborator external to the institute. In addition, there is one good paper from the 2 permanent staff in his group, presumably work done prior to starting with the Hamiche group. The committee hopes these staff members will integrate fully into the efforts of the laboratory, as this will enhance the whole man power.

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

The group is well funded from all French funding agencies with a range of collaborative projects as a partner and coordinator.

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

The PI is well integrated into the Institute with a number of successful and productive collaborations. The group appears to be well integrated and supportive of the PI.

The group leader is teaching, attending national and European meetings, and contributing to funding panels. He has been awarded the "Prix Scientifique du Comité Alsace de la FRM 2010".

Assessment of the strategy and 5-year project:

The research plan was well presented and overall has good potential for success. The team uses highly original approaches exploiting the platforms and services at their disposal at IGBMC. Projects to explore further the structures and functions of CENP-A-associated proteins and H2AZ assembly and exchange complexes are logical extensions of prior work and are well within their area of expertise. The group also has evidence for developmentally regulated chaperones and for a role for histone variants and their chaperones in spermatogenesis. There are plans for a number of experiments in mice to examine biological functions of the different forms of histone H3.3 variants using knock-out and knock-ins of these variants as well as to isolate and characterize chaperones isolated from MEFs derived from these lines. The committee appreciated the importance of the planned genome-wide location analysis of variant histones but had some concern that the team leader may not have adequately considered controls essential for unambiguous interpretation of these experiments.

Conclusion:

Overall opinion on the team:

The team has made an excellent start at the IGBMC. The group is doing novel work in a competitive field with some success.

Strengths and opportunities:

The team has novel factors required for histone variant deposition, placing the team in a strong competitive position for future work. It also has strong collaborations within the IGBMC and outside which will enhance the expertise and strong base the group has established. The team is exploiting the platforms at IGBMC in order to maximise the output. The PI is a very good biochemist with a large and supportive group.

Weaknesses and threats:

Genomic analyses and studies using mouse models represent a relatively new direction for this team and thus may fall outside its area of greatest expertise.

Recommendations:

It will be important to ensure that the PI maintains critical and objective oversight of the data generated and its interpretation; continued collaboration and consultation with colleagues with more experience with approaches outside of the core biochemical expertise will be important. The team leader should try to enhance his international visibility further by submitting abstracts for platform presentations at international meetings in the field. He should also encourage his graduate and post-doctoral students to attend at least one international meeting during their time with him.

Team FGC-6: Genetic dissection of nuclear receptor signaling in the mouse

Team leader: Daniel METZGER / Pierre CHAMBON

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researcher	3	3	2
N3: Other professors and researchers	1	1	1
N4: Engineers, technicians and administrative staff *****on a permanent position	2	2	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	4		
N6: Postdoctoral students having spent at least 12 months in the unit	4		
N7: Doctoral students	4		
N8: PhD defended	5		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	4	4	
TOTAL N1 to N7	**18**	**6**	**3**

Assessment of scientific quality and production:

This is an outstanding group of ~ 20 scientists co-directed by Mr. Daniel METZGER and Mr. Pierre CHAMBON who work as a team with both making important contributions to the direction of the group. The research in the past four years has been highly original, exceptionally productive, and represents a model for the effective use of cleverly designed conditional knockouts in mice. One major line of research exploits mouse models that mimic atopic disease (atopic dermatitis and asthma) to gain insights into the etiology of this prevalent disorder; growing out of these studies are very exciting new results that identify a novel mechanism for negative regulation of gene expression by direct binding of glucocorticoid receptor to previously uncharacterized negative response elements and suggest new strategies to screen for compounds that might bypass side-effects of glucocorticoid therapy. Their analyses of androgen signaling in skeletal muscles demonstrate surprising, muscle-specific differences in the consequences of AR deletion and have implications for approaches used to identify compounds that modulate androgen signaling, while studies on p160 family coregulators have provided novel insights into the interplay between different members of this family in energy homeostasis. Finally, the development of a new mouse model for prostate cancer as well as

new Cre-ER derivatives responsive to synthetic ligands should open up further opportunities for highly productive research.

The team has produced a large number of papers (>80), has many national and international collaborations and is very effective in raising national and international funds.

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

There are internationally recognized leaders in the field of nuclear receptors and their roles in signal transduction and endocrinology.

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

They have developed a powerful set of genetic tools that are of great utility not only to their own group but also to researchers around the world. They have established a network of national and international collaborations, the effectiveness of which is highlighted by the extensive list of collaborative publications in addition to those that are primarily from the IGBMC group.

Both Mr. CHAMBON and Mr. METZGER have been awarded a number of prizes. Mr. CHAMBON received the Koch award, the Gairdner award and the Bougine Cancer Prize and two Honorary Doctorates, while Mr. METZGER was awarded the Prix Janine Courrier, Grand Prix Jules Martin and the CNRS silver medal. Both are regularly invited to speak at international meetings.

Assessment of the strategy and 5-year project:

The research plan is very clearly described and justified, and it builds logically on prior work from this group. The proposed research is very ambitious in scope; however, given the group's history of highly productive, innovative, and important research, there is every reason to believe that substantial new insights with potential to advance human health and basic science will emerge.

Conclusion:

Overall opinion on the team:

Mr. D. METZGER and Mr. P. CHAMBON are a superb team of group leaders. The research program is innovative, productive, and is addressing problems with great importance for understanding fundamental problems in gene regulation and physiology and with significant implications for human disease and therapeutics.

Strengths and opportunities

Established group leaders with international reputations. Outstanding use of mouse genetics coupled with molecular biology/biochemistry to address important problems. Novel research tools. History of highly productive, high impact research. Well-funded, with a strong track record of recruiting very good young scientists as postdocs and PhD students.

Weaknesses and threats

No major concerns.

Recommendations

The team is to be congratulated on an outstanding research program and merits continued strong support.

Team FGC-7: Molecular biology of B cells

Team leader: Bernardo REINA-SAN-MARTIN

Workforce:

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

Assessment of scientific quality and production:

The group studies molecular mechanisms that determine antibody diversity, in particular somatic hypermutation that is induced by cytidine deaminase in a locally restricted fashion. Within the institute the group collaborates with team FGC-1 on isotype switching and there are several other international collaborations on NHEJ reaction and transcription coupled AID function.

The group has published several papers in top journals: two publications in Journal of Experimental Medicine with the group leader as last author and 11 other publications with the group leader as co-author (Journal of Experimental Medicine, 2 papers in Cell, Molecular Cell, Immunity, Mol Cell Biol and Oncogene) reflect the productivity and originality of the scientific approach. The group is very well integrated in the IGBMC (collaborations with teams FGC-8 and FGC-12) and has set up several international collaborations.

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

The group leader has demonstrated a good ability to raise funds (> 1.3 M€ during the 2007-2012 period) all from competitive funding.

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

The group leader was recognized with the Schlumberger Foundation prize in 2010 and the Prix FRM-Alsace in 2009 and has been asked to speak at national and international conferences, including Cold Spring Harbor and Keystone Meetings, and at Rockefeller University. He has attracted 4 PhD students and 2 postdoctoral fellows, and he is a member of the PhD Program Steering Committee. Finally, the group has established and is benefiting from highly synergistic collaborations within IGBMC.

Assessment of the strategy and 5-year project:

The work is rated as highly relevant and promising. Of particular importance is the finding of AID associated proteins and development of an interesting model for AID targeting. An interesting collaboration has been set up to study the proteome of DNA repair foci, taking advantage of the innovative approaches of the team FGC-12. The committee appreciated the ambition and the originality of this program, although some doubts were raised as to whether the planned 3C approach involving mediator/cohesin could safely distinguish transcriptional from structural effects - although a mouse model is available that may help to resolve this.

Conclusion:

Overall opinion on the team:

The committee appreciated the amount and the significance of the work performed by this young team to address an important problem, namely, mechanisms that determine antibody diversity. The work was acknowledged in effective collaborative studies and in recent publications.in J. Exp. Med. (2009 & 2011).

Strengths and opportunities

(1) Important scientific project with relevance to chromosome translocation and cancer (lymphoma) formation. (2) Interesting protein complex identification. (3) Mouse model available. (4) Very good national and good international visibility. (5) Fruitful collaborations.

Weaknesses and threats

(1) Field is highly competitive. (2) Results of 3C experiments to study DNA looping and the contribution of Mediator/Cohesin may be difficult to interpret unambigously.

Recommendations

The team is encouraged to develop active local or outside collaborations with bioinformaticists and others with appropriate expertise to ensure that data derived from the planned analyses of the proteome of DNA repair foci and the 3C experiments can be fully exploited. In addition, the team may benefit from further diversifying its collaborations within the department and IGBMC.

Team : FGC-8 Molecular and cellular biology of breast cancer

Team leader: Marie-Christine RIO and Catherine Laure TOMASETTO

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	3	3	3
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	2	1	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	4		
N8: PhD defended	3		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	**11**	**5**	**4**

Assessment of scientific quality and production:

The work of the team is focused on a sub-selection of genes that had been identified previously to be deregulated/overexpressed in breast cancer. The team concentrates on a few gene products that were rationalized to play a role in breast cancer heterogeneity and in the tumor microenvironment. They used KO mice to study the stromal cell-associated role of the MMP11 metalloproteinase and the tumor-associated estrogen receptor target gene TFF1 in the metastatic process. Previous and ongoing work showed TFF1 as a superior biomarker in pregnancy associated breast cancer and this marker is now in clinical use. The team showed a connection between fat cell expression of MMP11, metabolic functions of MMP11, and crosstalk between adipogenic and tumor tissue. Bioassays and a mouse model to examine the MMP11 connection and tumor metabolism have been established.

The team also investigated the function of HER2 co-amplified genes in HER2-positive breast cancer (MLN51, TRAF4, STARD3). Current and future research includes MLN51 that is a component of the exon junction complex. The team showed MLN51 association with a novel unclear territory and suggests a

connection between mRNA metabolism and cancer. Another protein, STARD3, connects to lipid metabolism and plasma membrane functions that may be linked to altered cell surface receptor signaling.

Altogether, the two group leaders have published 6 articles as corresponding authors during the evaluation period, 5 of them in good journals (IF 5-7)(Oncogene ; J. Cell Science ; Int. J. Cancer ; PloS One). They also published 15 collaborative papers in journals including Gastroenterology; Oncogene; FASEB J.; Am. J. Pathol.; J. Biol. Chem., and 7 reviews.

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

The team is internationally highly recognized for their biological/cell biological results and has been able to raise considerable funding for their research (> 2 M€ during the 2007-2012 period) as coordinators through competitive grant applications at the national level (INCa, LNCC (équipe labellisée), ARC). Both group leaders display strong integration at the regional and national levels, including scientific/administrative responsibilities and teaching. One of the PI is the coordinator of Axis IV of Canceropole Grand-Est/INCa (23 labs) and the President of the Scientific Council of the Committee "Interrégional du Grand-Est" of LNCC". The other PI is a member of INSERM CSS4 committee. The two co-leaders are members of Scientific Committees of French Charities (ARC, FdF, LNCC).

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

The work of the team has significant impact on clinical aspects of breast cancer diagnosis and advances the understanding of tumor stroma interactions. The team leaders had several invitations at regional (7), national (6) and international (11) meetings during the period under review.

12 post-docs and students have been recruited during the evaluation period, most of them from France.

The team developed very productive collaborations (15 publications) with both French and foreign partners, but there is little integration/collaboration within the IGBMC, and the group would benefit from more scientific interactions with other groups in the FGC and DSC Departments.

Assessment of the strategy and 5-year project:

The team will continue on the recent projects related to the role of stromal adipocytes in metastatic process, the contribution of the RNA binding complex in the deregulation of genes in breast cancer and the potential link between cholesterol trafficking and cancer (SARD3). The team concentrates mostly on the metabolic axis, however one may wonder how the crosstalk with other tumor-prone cell types, such as monocytes, will be integrated to develop a more complete model of tumor stroma interactions. Although the work is of high quality, there appears to be little overlap between the three major topics, and concerns have been raised as to the feasibility of maintaining internationally competitive research programs on each of several topics as diverse as lipid metabolism, splicing, and tumor-stroma interactions. The group is encouraged to improve contextual work or to concentrate on distinct aspects.

Conclusion:

Strengths and opportunities:

(1) Good national and good international visibility. (2) Fruitful collaborations. (3) The team has been reinforced by the arrival of one young staff scientist from INSERM and one MD from the Faculty of Medicine of Strasbourg.

Weaknesses and threats

(1) The team is running multiple projects in highly competitive fields. (2) Interesting candidate gene products but multiple projects have little obvious connection.

Recommendations

Although the quantitative output of publications is high, the team may benefit from refocusing on fewer subjects with an emphasis on gaining deeper and more general mechanistic insights and on increasing the impact of individual publications.

Team : FGC-9 Nuclear retinoic acid receptors phosphorylation and cross-talk with signaling pathways

Team leader: Cécile ROCHETTE-EGLY

Workforce:

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

Assessment of scientific quality and production:

This team has a long-lasting expertise in the field of nuclear retinoic acid receptors and their regulation by post-translational modifications. Pioneer studies from this team have demonstrated that phosphorylation triggered by different intracellular pathways plays a crucial role in the stability, conformation, recruitment of partners and transcriptional activity of these receptors. During the evaluation period, the team pursued these studies and made several interesting observations (EMBO J. 2009). They showed that retinoic acid not only acts directly through the transcriptional activity of its receptors, but also drives rapid non-genomic events leading to the activation of protein kinase cascades such as p38/MSK1, which in turn regulate the activity of RARs and their co-activators such as SRC-3, through phosphorylation. The team also showed that phosphorylation impacts on the interaction of RARs with DNA, co-regulators, and the ubiquitin/proteasome system, through conformational changes. This part of the work benefited from fruitful collaborations with teams ISB-2 and ISB-3.

The team published 6 articles with the PI as corresponding author during the evaluation period in good journals (IF 5-10)(EMBO J.; Oncogene; Mol.Biol.Evol.; FASEB J.; J.Biol.Chem.). The team also published 5 articles within the frame of collaborations (Nature Med.; Mol.Cell.Biol.; Cancer Res.) and 5 peer-reviewed reviews. This represents a good publication level considering the size of the team. 3 PhDs defended.

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

The group has a very good ability to raise funds (> 1.2 M€ during the 2007-2012 period) through competitive grant applications at the national level either as coordinators or as partners (INCa, ANR, ARC, FRM). The PI is the scientific head of the cell culture facilities at IGBMC.

The PI organized an EMBO Workshop in September 2011. She also served as a panel committee member for several French agencies (AERES, ANR, INCa and ARC) during the evaluation period.

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

Attesting to the impact of the team's research, the group leader has been awarded the Prix Marguerite Delahautemaison (FRM, 2009); she has also received 4 invitations to speak at international conferences (USA,Germany, Italy) and two invitations to national conferences. In addition, 4 communications from members of the team have been selected for oral presentations at international meetings.

On average, the team is composed of 2 post-docs and 2 PhD students from both France and abroad. No other staff scientist than the PI.

The team leader is currently coordinating three running grants (ARC, ANR, INCa) and has good national collaborations but none with foreign partners.

Assessment of the strategy and 5-year project:

The team is moving from molecular biology toward developmental studies, cell differentiation/proliferation, and cancer. The future project will develop along two axes: RAR phosphorylation in development and cancer. The role of RAR phosphorylation during development will be assessed using Zebrafish and differentiation of mouse ES cells as models. The second axis will aim at correlating the phosphorylation profile of RARs in various breast cancer cells with intracellular distribution, retinoic acid response and target gene expression, using top-notch mass-spec equipment available at IGBMC.

The projects are well funded and will take advantage of collaborations within IGBMC and outside to get more expertise on new experimental approaches (structural biology, mass spectrometry, bioinformatics, clinical access…).

Conclusion:

Overall opinion on the team:

The team has made recent interesting and innovative findings, such as the new evidence for non-genomic functions of retinoic acid receptors. Its projects are original and relevant.

Strengths and opportunities

(1) A well-established, internationally recognized research program in the field of retinoic acid receptors combined with an ideal scientific environment at IGBMC. (2) An effective collaboration with researchers in the Structural Biology Department results in significant mechanistic insights into the RAR regulation by phosphorylation. (3) Well-funded research team.

Weaknesses and threats

The team is somewhat small with only the PI as staff scientist, one permanent engineer, and on average 2 post-doctoral fellows and 2 PhD students.

Recommendations

New evidence from this team for non-genomic functions of RARs is novel and potentially very exciting. The committee strongly encourages the PI to continue efforts to develop tools to test rigorously the physiological relevance of these observations.

Team : FGC-10 Protein Networks and Complexes Regulating Eukaryotic mRNA Decay

Team leader: Bertrand SERAPHIN

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	2	2	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	3		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**11**	**4**	**2**

Assessment of scientific quality and production:

The team leader was recruited to IGBMC in September 2009 after a successful period at the CGM in Gif-sur-Yvette with a well-established group, from which several collaborators moved with him. The team has made important contributions to our understanding of the nature and functions of protein complexes that contribute to RNA decay. Their investigations into the exosome defined the subunit responsible for the exosome endonuclease activity and identified a previously unrecognised endonuclease activity. This work is important as it challenges current thinking about the nature and identity of exosome activities. Other work from the group over the past few years has provided important insights into mechanisms and regulation of deadenylation, deadenylases, decapping enzymes and other key players in RNA quality control pathways. The quality of the research is evidenced by the numerous publications in outstanding to very good journals (e.g. Nature, NSMB, EMBO J., NAR, JBC, Structure, RNA etc.). The team's interesting work on methods for expression, purification and analysis of multi-protein complexes should help to advance their own work and studies in the larger community.

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

The team has productive national and international collaborations and has attracted significant funding through EU integrated projects or network of excellence grants. Currently, there is one large grant from the ANR, funding from the LNCLC for 2011-2013 and two fellowships to support post-docs in the lab.

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

The team leader has been recognised by invitations to speak at Universities or Research Institutes and scientific meetings, both nationally and internationally, has received a silver medal from the CNRS and was elected to EMBO membership.

Assessment of the strategy and 5-year project:

The proposed research is clearly described and well-thought out. The experiments, for the main part, build on extensive data obtained by this group and are thus logical extensions of their current research; however, the research also includes more exploratory directions that will in turn help to build new hypotheses and drive the research into the next stage. Given the strong focus of this group on mechanisms and regulation of RNA degradation, they are in a strong position to sort out functions of the enigmatic elongator complex and the poorly understood Ccr4/Not1 complex. The work to set up new assays for mRNA decay will allow the study of RNA decay events genome wide and will be an important advance for the development of the field. Plans for projects that allow integration and collaboration with other groups in the IGBMC working with neurological diseases are judicious.

Conclusion:

Overall opinion on the team:

The achievements of the team are excellent. The group leader has built a strong research group and programme.

Strengths and opportunities

RNA decay is an understudied area in which control of gene expression can be mediated and thus is an important problem. This group has a long history of productivity in this area and is well set up for a productive future. NMD is a good model for more general RNA decay. The work effectively combines molecular biology and functional studies with strong structural biology. Their approach offers the potential for a systems–type approach to studying the dynamic networks involved in RNA turnover.

Weaknesses and threats

A potential weakness lies in the sheer breadth of the projects proposed and the potential difficulty in maintaining funding to support the large group and wide range of projects.

Recommendations

The group should be careful to set priorities that will allow them to focus on those areas most likely to produce novel and innovative results and to make the most of the environment at the IGBMC.

Team : FGC-11 Functional epigenetics and chromatin regulation

Team leader: Robert SCHNEIDER

Workforce:

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

Assessment of scientific quality and production:

Note : This is a new team that has very recently been recruited to the IGBMC (October 2011). Accordingly, the committee believes it is too early to assign a rating for each criterium; however, the committee believes this group has made an outstanding beginning and very highly rates for the potential of the group leader and the project.

Until October 2011, Mr. Robert SCHNEIDER was a group leader at the MPI in Freiburg and is currently moving his group to the IGBMC. The majority of his group has moved with him. The group is focused on discovering and understanding the role of post-translational modifications to histone proteins, notably on those in the nucleosome core, on histone H1 variants, and on the C-terminal region of H2A. The group pioneered the study of new core histone modifications with their work on K64 methylation and have gone on to characterise several novel modification using a careful and well controlled approach. They have recently started studying new chromatin associated proteins such as DEK, an oncoprotein with a role in silencing

through HP1. The move to IGBMC and access to the platforms and groups will be instrumental in enhancing their understanding of the role of these modifications in development and cancer.

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

The group leader actively participates in the organisation of meetings, in teaching and training, and general administration. He has obtained generous funding, including an ERC starting grant and is a coordinator or partner on a number of other grants.

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

The problems addressed by the team are important ones, and this is reflected by the high profile publications in journals such as NSMB, Genes & Dev, and PLoS Genetics as corresponding author and some very significant publications in collaboration. The group leader has been recipient of a number of awards previously. He actively and productively collaborates with groups in Europe, Asia and the USA. He is regularly invited to give seminars and participate in national and international conferences.

Assessment of the strategy and 5-year project:

The proposed work builds on very strong foundations and will play to the strengths of the IGBMC. Of particular note is the new direction to study the role of novel histone modifications in tumourigenesis, which has potential to lead to new therapeutic applications. The panel was particularly impressed with the clearly thought out strategy and the very well controlled experimental data the group produces.

Conclusion:

This is a very promising young team with a growing international reputation and carefully thought out and well-designed experimental strategies to address important problems.

Team : FGC-12 Cell biology of genome integrity

Team leader: Evi SOUTOGLOU

Workforce:

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

Assessment of scientific quality and production:

Note: Given that this team has only recently been established as an independent research group, the committee feels it is too early to assign a rating for each criterium. However, the committee believes this group has made an outstanding beginning and very highly rates it for the potential of both the group leader and the project.

The team leader was recruited to the CNRS in 2009 with a CR1 position and selected by the CNRS-ATIP program to start her own research group at IGBMC (joined the Institute in February 2009). The team is studying the role of chromatin and nuclear architecture in double strand break (DSB) DNA repair. To this end, the PI previously developed an elegant cell system in which a DSB can be induced at a defined genomic site (lacO/ISceI/tetO array system), in order to follow in real time the recruitment of the DNA repair machinery and the fate of damaged DNA in living cells (Nat.Cell Biol.; 2007). This allowed her to investigate the role of the repair factor MDC1 in chromatin decondensation and to study the dynamics of RNA pol II transcription in

response to DSB by ChIP experiments. The team also recently identified new chromatin-associated proteins involved in DSB repair through siRNA screens combined with high throughput cell imaging. The research developed in this team directly impacts on our understanding of the mechanisms involved in chromosomal translocations that occur in cancer cells.

It is too early to evaluate the impact of the results obtained since establishment of the IGBMC team, although a manuscript has been accepted in Nat Struct Mol Biol. During her previous post-doc period, the group leader published two major papers in Nat Cell Biol. (2007) and Science (2008). Of note she is corresponding author of the Science paper. She also published several reviews in excellent journals since 2007 (Trends Cell Biol., Nat Rev Mol Cell Biol., Curr Opin Genet Dev., Cell Cycle).

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

The team shows a very good ability to raise funds: the newly recruited young group leader already obtained several grants as coordinator, reaching a total of 1.2 M€ since 2009 (ATIP, HSFP, EU, INCa, ANR). It is too early to evaluate her ability to participate in international or national scientific networks or to establish stable collaborations with foreign partners.

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

The team leader is already establishing an international reputation as evidenced by a number of awards, including an HFSP career development award (2009), Prix Olga Sain, LNCC (2010). She was also invited to speak at the 3rd EMBO meeting in Vienna (2011). The team is showing a good ability to recruit post-docs and students from France and abroad, having already recruited 2 foreign post-docs, 2 PhD students and 2 engineers/technicians.

Assessment of the strategy and 5-year project:

Following selection of the most robust hits, the team will further analyze the role of the novel chromatin-associated proteins, identified through the siRNA screens, in DNA repair and DNA damage response. The role of MDC1 in chromatin decondensation will be also further explored. In addition, the team proposes to exploit the successful approach of the lacO/I-SceI/tetO array system to study the impact of nuclear architecture and organization in DNA damage response. Finally, the team will use state of the art experimental approaches such as PICh (proteomics of isolated chromatin segments) to determine the proteome of DNA repair foci, and live cell imaging to visualize the formation of chromosomal translocations. These smart, cutting edge projects are very well designed and very clearly described.

Conclusion:

Overall opinion on the team:

This is a very promising young team, with a focused research program addressing important problems. The team has already obtained strong financial support.

Strengths and opportunities

1. An outstanding young team leader with an excellent record of achievement as a post-doctoral fellow. 2. Innovative projects highly relevant to the "Functional Genomics and Cancer" Department. 3. Ability to recruit international students and postdocs.

Weaknesses and threats

No significant weaknesses identified.

Recommendations

The heads of the Institute and of the Department should make strong efforts to support this team and to ensure its smooth integration into the "Functional Genomics and Cancer" Department.

Team : FGC-13 Chromatin modifications and regulation of gene expression during differentiation

Team leader: Laszlo TORA

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	1	1	1
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	1	1	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	5		
N7: Doctoral students	5		
N8: PhD defended	5		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**14**	**3**	**2**

Assessment of scientific quality and production:

The team has a long-standing interest in the mechanisms responsible for regulating transcription of protein-coding genes in vertebrates, with a focus on the roles of components of the general transcription factor TFIID in this process. More recently, the research program has broadened to include studies on the Gcn5/PCAF-containing chromatin modifying complexes SAGA, which includes proteins originally identified as TAF subunits of TFIID, and ATAC, which shares subunits with SAGA and is a logical outgrowth of the group's earlier work. The program not only provides novel insights into basic transcription mechanisms but also contributes to understanding human disease, as mutations in TFIID and SAGA subunits are associated with various cancers and with the neurodegenerative disease spinocerebellar ataxia.

In one particularly intriguing line of research the team has obtained evidence that transcription factors long thought to be generally required for all transcription are in some cases dispensable and/or replaced by other factors. This includes the unexpected and highly significant finding that TFIID is needed for

initial gene activation in hepatocytes, but is dispensable for maintaining on-going gene transcription, as well as the demonstration that an oocyte-specific form of the general transcription factor TBP, TBP2, has an essential role in female germ cell development in mice and can replace TBP during oocyte maturation. In addition, the team has been among the leaders in defining structure and function of the human and Drosophila SAGA and ATAC complexes, and their work has provided significant new insights into the roles of these factors in gene regulation via different signal transduction pathways. Among their major contributions was the demonstration that in metazoa a SAGA-associated deubiquitinating enzyme removes ubiquitin from histones H2B and H2A, is needed for optimal nuclear receptor activity, and affects heterochromatin silencing. Finally, they have a history of taking on challenging projects that could be regarded as at the periphery of their expertise and bringing them to a successful completion. As an example, they have in press an interesting story on how collisions between transcription and replication complexes contribute to fragile site instability.

The importance of the team's findings is reflected in some 30 publications in excellent journals (including 4 Molecular Cell, 1 Genes Dev., 2 EMBO Journal, and 2 EMBO Reports).

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

The group is well funded, and it collaborates extensively with other excellent labs at IGBMC and elsewhere, both within France and internationally.

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

The reputation of the team is reflected by 7 invited reviews, and by numerous invitations to speak at international and national meetings.

Assessment of the strategy and 5-year project:

The proposed projects have high potential to generate significant new insights. The projects are focused on several main areas: (i) studying the roles of TBP family members and associated proteins; (ii) analysis of the SAGA and HAT complexes. The collaborative work with team DSC-13 and the ICS to sort out the biological functions of TBP2 and to define the biochemical properties of TBP2 containing complexes (if they exist) is particularly exciting. If successful the proposed structure/function studies have the potential to provide the most detailed understanding to date of the structure and assembly of TFIID and TAF-containing complexes. The wide-ranging studies on SAGA and ATAC extend from biochemical reconstitution to genomic (gene expression and chromatin IP) analyses of their roles in normal and cancer cells and during differentiation, and, given the group's expertise in these areas, promise to be productive. Given the substantial amount of effort involved in the major projects, it will be important to consider whether the proposals to extend the analyses to additional HAT coactivators risk dilution of the group's efforts.

Conclusion:

Overall opinion on the team:

This is an outstanding team that is addressing problems of central importance in the field of gene regualation.

Strengths and opportunities

(1) Established team leader with strong track record and an international reputation. (2) Strong collaborations within IGBMC and with other scientists who will provide essential technological expertise. (3) Willing to take on challenging and in some cases very long term projects, and, importantly, a history of succeeding. (4) Most of the proposed research builds logically on prior studies from the group. (5) Potential to make significant contributions to understanding the structures and functions of key transcriptional regulators and to define molecular mechanisms by which mutations in components of these regulators contribute to disease.

Weaknesses and threats

(1) Minimal description of alternative approaches or potential problems in report – a concern mitigated by discussion during the review indicating that the group leader has considered these issues. (2) Ambitious research goals with minimal discussion of how the various directions are prioritized. (3) Some risk that the groups' efforts will be diluted by taking on too many disparate projects.

Recommendations

Going forward it will be important for this group to make sure that they put resources toward those areas where they have the greatest opportunities to make unique contributions.

Team : FGC-14 Molecular and cellular biology of cancer

Team leader: Bohdan WASYLYK

Workforce:

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

Assessment of scientific quality and production:

The team leader has a longstanding record of high-level research in the Institute starting with a number of important contributions in the field of regulation of transcription, which has shifted toward studies on "mis"regulation and cancer. The research group currently aims to understand biological pathways involved in a number of cancers, in particular the genomics of head and neck squamous cell carcinoma (HNSCC), involvement of TTLL12 in chromosome ploidy in prostate cancer, and cancer pathways connected to the RAS/Elk3 signaling cascade in conjunction with hypoxic response. The output of the group in all three areas has been good with a number of publications and/or patent applications. The HNSCC project is primarily concerned with the question of how metastasis develops and what markers would predict a favourable vs poor prognosis, the latter of which includes the work on HPV infected tumors. The group uses a number of “omics” techniques, of which a genome wide miRNA analysis and methylome are in progress. The group is well funded in this area, has access to sufficient and well-characterized tumor samples and maintains or is in the process of setting up several international collaborations.

The prostate cancer project is centred on TTLL12, which is expressed highly in proliferating prostate cells and increases in cancer cells, in particular in metastatic cancer cell lines. The protein is part of 14 known proteins involved in the post-translational modification of tubulin and hence the biology of microtubules. The latter are a well-known target in cancer treatment and the goal of the work is to find more specific and less toxic therapeutics through the study of factors like TTLL12. The group has shown that the inhibition or overexpression of TTLL12 affects microtubules and cell growth in cultured cells through changes in the level of nitrotyrosine in microtubules. A screen of a 10000 compound library has identified two lead inhibitors, which the group proposes to take further in future. The group has built up a good position in this area in Europe and has attracted adequate funding for the project.

The RAS/Elk3 project is the most promising of the 3 endeavours of this group. This project is a long term, focused research effort based on initial discoveries made by this team, including the initial discovery of Elk3 and its roles in Ras signaling, angiogenesis and hypoxia. The relationship between Elk3 and hypoxia was uncovered during the past review period and reported in a series of very nice papers in MCB, Oncogene, and JBC. The research group is internationally recognised in this area, has attracted substantial funding and has set up a number of collaborations. This work is the most original and in particular the role of Elk3 as a component of the hypoxic response is very interesting and adds a new dimension to a field that is traditionally centred around HIF1. Elk3 is regulated by three hydroxylases (PHDs) and responds differently to normoxia and hypoxia than HIF1, although the two pathways (Elk3 and HIF1) are linked intricately. The output of this project has been very good.

During the review period the group published 9 first/last author papers, 9 co-author papers, in good journals (but none in the highest impact journals), 1 review article and filed 3 patent applications.

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

The group leader has been successful in raising funds (approx 1 M€ during the 2007-2012 period) through competitive grant applications at the national and international levels either as coordinator or as a partner (INCA, ARC, LNCLC, EU).

The team has a number of strong and fruitful national and international collaborations.

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

Attesting to the respect with which he is held in the scientific community, the group leader has been elected to EMBO membership, he has many national and international collaborations, he is a regular speaker at international meetings, and has many advisory/reviewer roles. The team presently consists of the team leader, 1 international post-doc, 1 international PhD student, 2 PhD students and one technician. The group had been larger (e.g it had 5 international postdocs, delivered 6 PhDs and one MSc and was supported by two extra techs), but its space allocation has been cut substantially, and the number of personnel associated with the group has decreased significantly as well.

Assessment of the strategy and 5-year project:

The group leader indicated that the team has suffered significantly from the recent cuts and accompanying upheaval, but the worst appears to be over. Nevertheless the team presented good progress in all three research projects and the international standing of the group is good. The future proposals are a continuation of the current projects and address a number of important questions. In principle the proposal for each area is feasible and thoroughly thought through, but in light of the recent decrease in the size of the group and its space allotment, it is doubtful whether the group could remain competitive in all three areas. The most original and cutting edge project appears to be the Elk3 hypoxia project. When questioned by committee members about the priorities assigned to the various directions described in the written report and oral presentation, the group leader indicated that all or nearly all of the group's effort is currently focused on this latter project.

Conclusion:

Overall opinion on the team:

This is a small group with a long history of significant contributions to the transcription and cancer biology fields. The team has promising projects with potential to provide novel insights.

Strengths and opportunities:

There was considerably more evidence of focused effort and thoughtful use of resources / personnel during the discussion with the committee than in the written report. The committee recognizes the novelty of the contributions that the team has made to understand the Elk3/HIF nexus and is most enthusiastic about this area of research.

Weaknesses and threats:

The group is currently very small considering the breadth of proposed projects, and there is a significant danger of spreading the research efforts too broadly. It may prove difficult to obtain the large research grants needed to drive forward some of the proposed research.

Recommendation:

The group should very carefully consider which aspect of the research can be most effectively pursued with a relatively small research group and focus on that area.

Integrated Structural Biology (ISB) Programme

Team : ISB-1 Structural biology of epigenetic targets

Team leader: Jean CAVARELLI

Workforce:

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

Assessment of scientific quality and production:

The main research activities of the team are in the area of epigenetic effectors linked to diseases including cancers. The team has focused on a class of three major biological targets: protein arginine methyltransferases, histone chaperones and histone deacetylases. The scientific questions addressed are to decipher at the molecular level the mechanisms governing epigenetic processes with the characterization and structural analysis of functional complexes and the search for /discovery of novel epigenetic drugs. During the last 5 years the team has solved a number of novel structures in this field, including those of the coactivator-associated arginine methyltransferase 1 (CARM1), often as complexes with cofactors, inhibitors and/or peptide mimics, of the histone chaperone Spt6 also in complex with the conserved domain Iws1, and the histone deacetylase HDAC8 with or without an inhibitor. The team is involved in numerous collaborations with the IGBMC, ESBS and IBMC staff. Highlights of these collaborations are the mapping of the nucleotide binding site of kinases, the first structure of a full-length papillomavirus E6 protein and the structure of the Tfb5-Tfb2 complex and ligand-binding domain of the retinoic receptor RXR. Since 2007 the team has published 25 articles in internationally peer-reviewed journals of which 10 are from the team (first and/or

last author: 2 EMBO J) and important co-author papers (1 Nat Struct Mol Biol, 2 Mol Cell Biol and 1 Nat Methods), indicating a very good to excellent productivity. Major contributions are the structures of the CARM1 domain and the Iws1/SPt6 complex.

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

The team is deeply involved in educational activities including teaching and training and has successfully collaborated with other teams at IGBMC. The team is also involved in the development of the future center of integrative biology and will contribute to the success of the INSTRUCT and FRISBI programs at IGBMC with the development of state-of-the-art techniques and methods in molecular biology and X-ray crystallography.

The team led by Mr CAVARELLI is a partner of the FP7 EU project Settrend and has also attracted 11 other research contracts (4 as a coordinator) from various sources including 2 ARC (coordinator) 4 ANR (1 as a coordinator).

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

The team is involved in a number of national and international collaborations, and several of these have led to excellent publications, indicating that these collaborations are very successful. 1 PhD student defended a thesis during the period and the team has attracted 6 PhD students and 4 postdocs. The team has thus shown a strong attractiveness, as also evidenced by the number of collaborations in France, Europe and the US.

Assessment of the strategy and 5-year project:

The proposed activities of the research team are well focused on a particular class of epigenetic targets and build on the initial developments made during the past period in this field. A future strength of the team will be to focus on the same classes of epigenetic targets associated to a limited number of collaborative projects with particular emphasis on the benefit of the scientific challenge for the team. For the next period the team aims to focus and further develop their very successful research projects in this area. The scientific questions pursued by the team are not only highly relevant for new biological/biochemical insights, but also of great interest from a biomedical perspective with potential implications in cancer.

Conclusion:

Overall opinion on the team:

The team has made excellent contributions to structural biology and shows an excellent balance between the educational and research activities. The group shows a very good productivity and the work carried out over the last period has positioned the team among the leading groups in the structural study of epigenetic effectors.

Strengths and opportunities:

Strong aspects of the group are their excellent contributions and strong leadership in the field. They exploit multidisciplinary approaches with a large panel of methods and techniques that are available in-house and/or developed by the team. The members are strongly involved in educational activities at the local and European level.

Weaknesses and risks:

Some attention should be given to the somewhat too wide range of projects considering the limited number of permanent team members. Also, the group should aim to increase their participation in international conferences, preferably as invited speakers.

Recommendations:

The team should carefully consider and exploit integrated approaches that are available in-house in application to their biomedical targets and use them to provide complementary information to the traditional structural biology techniques employed by the team.

Team : ISB-2 Biocomputing

Team leader: Annick DEJAEGERE

Workforce:

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

Assessment of scientific quality and production:

Research from this group is of high quality, in particular when one takes into account the small size of the group, and the fact that the PI spends at least half of her time teaching. There are 7 publications as corresponding author, based on group projects, most of them either in very good journals (2 JBC), or in highly respected journals in the field (2 Proteins, 1 J Comp Chem, 1 J Mol Biol). A further 8 publications involve collaborations where the group brought its expertise to the project, 2 of them in PLoS One and J Med Chem. In addition, two software packages were developed, which are licensed to the pharmaceutical industry. The group has a very complete activity in computational molecular biology, ranging from force field development over electrostatics calculations, calculations of dynamics with detailed and simplified models, free energy calculations, to its involvement in integrative structural biology approaches.

The fact that software developments of the group are licensed to the pharmaceutical industry underscores their importance and relevance also to biomedical research. The tools will become available publicly after a short period of exclusive use by the pharmaceutical industry.

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

The funding that the group has attracted is very good, in a difficult context. Funding from the ANR has become extremely competitive, and it is in general difficult to obtain funding for methodological research. It is therefore unnecessarily difficult for small groups to obtain funding. In addition to public funding the group has been able to obtain support from industry, and competitive support for computing from the national high performance computing centres.

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

The work of the group is highly regarded on a national and international level. It is well integrated in the environment and indeed provides key expertise in the context of integrative structural biology. This is underlined by several collaborations within the department.

The number of PhD students and postdocs is high, again considering the small size of the group (two tenured scientists, one of them with a heavy teaching load) and the limitations in France on the number of graduate students (one graduate student per HDR, giving the possibility to exceed this number only for overlaps between graduate students to provide continuity). This indicates that the team is attractive for students and postdocs. The team has several international collaborations (e.g., one with UCSF). Team members are regularly invited to national and international meetings.

Assessment of the strategy and 5-year project:

The project for the next five years aims at a continuation of the challenging and successful work in the last 5 years. Methodological developments (to construct large complexes from hybrid data; to study allosteric mechanisms; to interpret results from ultrafast spectroscopy) will be used for high-level in-house collaborative projects (to determine the structure of TFIID; to study the structure and function of nuclear receptors). This underlines the critical role of the group in the integrative structural biology department: the group's development and expertise are crucial to make sense of much of the work going on in other groups in the department. The demand for collaborations in-house seems to exceed the capacity of the group.

It seems that computing at IGBMC is not well organised, with the group not having ready access to the in-house computer cluster. However, the group does very well with the high performance computing centres in France, where it regularly obtains computer time in competitive calls.

Conclusion:

Strengths and opportunities:

In particular considering the small size of the group, the production, attractiveness and impact of the group are very good. Work by the group is highly respected in the field. Recent work and future developments put it at the centre of integrative structural biology.

Weaknesses and risks:

As for other groups, the main threat comes from the present managerial situation at the institute.

Recommendations:

The committee encourages the group to follow its plan for the next five years and maintain a balance between methodological developments and applications to challenging problems. The size of the group is not sub-critical, but the fact that some collaborations cannot be done for lack of personnel indicates that the hiring of an additional tenured member for this group should be given high priority.

Team : ISB-3 Biomolecular Nuclear Magnetic Resonance

Team leader: Bruno KIEFFER

Workforce:

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

Assessment of scientific quality and production:

The scientific activity of the team addresses several aspects of the application of NMR to the characterization of biological molecules, from structure determination in solution, to biomolecules interactions and recognition to dynamical properties, to the modelling of the features of intrinsically disordered proteins (IDPs). The group has access to three NMR spectrometers (500, 600 and the newly acquired 700MHz). Its scientific production is very good in terms of quality and number of publications, also taking into account the heavy teaching duties of the team leader.

Within its research work (8 publications in J. Mol. Biol, Biochemistry, Nucleic Acids Res. , Biopolymer, J. Phys. Chem. B, EMBO rep., CR Chimie corresponded by the group), the team has developed some innovative approaches particularly for the characterization of IDPs and for the integration of Mass Spectrometry data with NMR data. Another 10 publications have been produced through collaboration with other IGBMC teams or with scientists from other institutions, also at international level. In addition to

publications, the group members have also produced a patent, software tools, and edited a book, in addition to a number of communications to conferences and workshops.

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

The team leader and the other members of the team have been able to attract a high level of funding, with successful grant applications to various French funding institutions. The team is involved in the development of software products and holds a patent.

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

The team is composed of the team leader Mr. Bruno KIEFFER, a MCU, two staff scientists (plus another in the past), a technician and few PhD students and post Docs.

The interactions and collaborations of this team with other groups at IGBMC are extensive and have continued over the years, as the group provides unique competences. Their expertise is essential for several studies performed at IGBMC and complementary to the techniques and approaches used by the other teams.

The group has attracted very good funding from competitive national grants (ANR). Team members have been invited to present their results at mainly national meetings in addition to one international conference. Some of the team members are with the team for several years.

Assessment of the strategy and 5-year project:

The plan for the next five years is well developed and challenging, addressing key and innovative aspects in the conformational and dynamical characterization of biomolecules in solution by NMR. It is articulated both towards methodological advancements (combination of NMR and EPR techniques) as well as to relevant systems such as intrinsically disordered proteins. It has original components, even if some aspects need to be further detailed.

Conclusion:

Strengths and opportunities:

The team, despite its small size, has a key and strategic role in IGBMC, as it is the only one to apply NMR techniques and experiments for the characterization of biomolecules and to make available this expertise to other IGBMC teams through either collaborations or as a service.

Weaknesses and risks:

The main weakness is the size of the group and the lack of support and personnel from the IGBMC. There are too few permanent personnel members and the uncertainty in perspectives leaves the team members insecure about their future, thus creating a non-optimal environment to perform research at its best.

Recommendations:

It is recommended that the team attracts new members that can expand and complement the existing know-how and that higher international visibility is pursued, for example, by presenting their research at international conferences.

Team : ISB-4 Large complexes involved in gene expression

Team leader: Bruno KLAHOLZ

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	2	3	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff ***on a permanent position	1	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position	2		
N6: Postdoctoral students having spent at least 12 months in the unit	4		
N7: Doctoral students	3		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**13**	**5**	**3**

Assessment of scientific quality and production:

This group uses predominantly electron microscopy (EM) methodologies to provide structural insight into large complexes involved in gene expression. Single particle cryo-EM studies of ribosome complexes by this group (in collaboration with groups from the IGBMC and IBMC) have resulted in high-impact publications in Cell (2007) and Nature (2008). But there has been a gap in the publication record since then. This may be due to the time invested in developing state-of-the-art methodologies for EM data acquisition and processing, as well as cryo-tomography, essential for future projects. Although a number of projects are nearing publication, it is unclear to the committee whether all team members will obtain first author publications during their PhD and Post-doc periods.

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

The team has been extremely successful in obtaining funding from internationally competitive external sources, notably an ERC starting grant and funds within the context of FRISBI and INSTRUCT. The

group is well integrated nationally and internationally, being instrumental in the set-up of the FRISBI and INSTRUCT infrastructures that will be located at the CBI.

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

The group is very well integrated, with evidence of previous successful collaborations as well as new projects developing with multiple groups within the department.

A reflection of the excellent reputation of the team is the large number of awards and prizes received, such as the EMBO young investigator award and CNRS bronze medal to the PI. Additionally, the importance of the methodological development and results from the team is reflected by the multiple invitations to speak at conferences and methodological workshops, such as the EMBO course on image processing and cryo-EM.

Assessment of the strategy and 5-year project:

The future research builds upon the success of past projects on translation, but also includes multiple new directions concerning nuclear receptors, co-regulators and nucleosome complexes. The latter are based predominantly upon the hard work of the last years to establish cryo-tomography within the department, as well as cryo-EM on relatively small complexes, such as receptors and chromatin remodelers. These are challenging projects, but also provide the basis for many future perspectives to assemble and study larger complexes.

Conclusion:

Strengths and opportunities:

The group has excellent international visibility, has obtained generous funding and is very well integrated into the IGBMC. It has established a number of state-of-the-art EM methodologies within the integrated structural biology platform.

Weaknesses and risks:

Present exploitation of the platform did not generate yet results and publications.

Recommendations:

The group is encouraged not to lose focus by addressing too many diverse biological problems, each requiring new methodologies.

A special care should be taken to ascertain regular and appropriate authorship for PhD students and post-doctoral fellows.

Team : ISB-5 Expression of genetic information

Team leader: Dino MORAS

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	6	3	3
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	2	1	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	2		
N6: Postdoctoral students having spent at least 12 months in the unit	5		
N7: Doctoral students	3		
N8: PhD defended	8		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	5	3	
TOTAL N1 to N7	**18**	**4**	**3**

Assessment of scientific quality and production:

The MORAS's team is internationally renowned for structural and mechanistic studies of eukaryotic transcriptional regulation, with two key areas being transcription initiation (TFIIH) and nuclear receptors. Impressive results were obtained in recent years. A number of scientific highlights that also implement and illustrate the strategy of the department are integrated structural analyses of heterodimeric nuclear receptors by combining crystallography with Small Angle X-ray and Neutron Scattering data, FRET and EM. Novel insight into TFIIH came from combining structural and biochemical analysis with functional genomics data from an in-house collaboration. The scientific excellence of the group is documented with publications in international top journals (26 as corresponding authors, including NSMB, EMBO J, and 33 in collaboration, 7 review articles) and their recognition for integrated structural biology of challenging macromolecular complexes.

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

The group has strongly contributed to shaping the ISB department and is an important player in various national and international projects, such as past SPINE2-COMPLEXES and ongoing FRISBI and INSTRUCT, where they contribute and benefit from advanced technologies for protein expression and structural biology.

The group attracts substantial competitive external funding, including 10 ANR grants during the review period.

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

The team is very well connected within the institute, with important and fruitful collaborations with groups in all the other departments of IGBMC that are documented in joint publications. The PI is regularly an invited speaker at international conferences, and two senior associates mainly visible at a national level. The team members are well connected and involved in various international collaborations and are important partners in European research networks.

Assessment of the strategy and 5-year project:

The future plan to focus research on transcriptional regulation involving TFIIH and NHR and thereby also developing and implementing novel integrated structural biology approaches is very sensible. It complements research on translation in other groups and exploits existing strengths of the group and the department in complementary structural biology techniques. This fits perfectly to the strategy and research goals of the Center for integrative biology (CBI) and further strengthens the links with FRISBI and INSTRUCT.

Conclusion:

Strengths and opportunities:

The research of this team is at the heart of the ISB and contributes greatly to the international reputation of IGBMC by excellent research published in top international journals and excellent integration into international funding networks (SPINE2, INSTRUCT). The team is extremely well connected within IGBMC, nationally and internationally. It played a leading and key role in the strategic development of the ISB unit, the IGBMC and the establishment of the CBI.

Weaknesses and risks:

No weaknesses identified

Recommendations:

The lead position of the group should be maintained in the future by appropriate support and integration in the future research strategy of the IGBMC. The proposal that the two senior associates should co-direct the team in the future should be considered only as an interim solution. It is strongly recommended that a high profile, internationally visible researcher will be searched/appointed as successor of Mr. Dino MORAS in the future.

Team : ISB-6 Evolutionary inference in biological networks

Team leader: Olivier POCH

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	3	3	3
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	1	1	1
N4: Engineers, technicians and administrative staff *****on a permanent position	3	3	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	3		
N8: PhD defended	6		
N9: Number of Habilitations to Direct Research (HDR) defended	2		
N10: People habilitated to direct research or similar	4	4	
TOTAL N1 to N7	**14**	**9**	**6**

Assessment of scientific quality and production:

Research from the POCH's group is of very high quality, and the group has shown a remarkable productivity with more than 70 publications in the last years. Some of this work is already heavily cited. The team is involved in the development of highly visible methods, including the latest Clustal Omega designed to deal with very large datasets. This important software is already installed in most major research centres in the world, a clear reflection of the worldwide impact that the work of this team has. Most biologists in the world have used one (or more) of the tools developed by this team over the last 5 years.

The team spends a lot of its resources in developing "low level" tools (low level referring to basic research tools, as opposed to integrated pipelines). Such tools, which include benchmark suites (like BaliBase) and alignment computation procedures (Alexys), are difficult to publish in very high impact journals, but are crucial for the development of science. The team is doing superbly well at making these tools public, and at publishing them in the best journals for that type of research. The committee encourages them to keep doing so at the same high level, even if such developments do not necessarily lead to publications in the most visible journals, visibility being achieved through citations. The overall usefulness of

this work is evidenced by the large number of collaborations the group has with teams within the institute and beyond.

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

The level of funding is very good, with 5 ANR grants secured over the last 5 years, another indication of the high quality of the work done by this group.

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

Apart from its worldwide recognition, the bioinformatics team is obviously a key player in an exceptionally well-integrated environment. The strong background in structural biology results in a number of important collaborations, and the development of many integrative methods. A major contribution of the team to the whole program is its strong interest in the bio-medical aspect of bio-informatics, resulting in a lot of added value to the collaborations. This interest may increase dramatically the horizontal integration of research at IGBMC by bridging the large gap between structure analysis and pathological phenotypes. This key contribution of bioinformatics has been mentioned by most groups in the program and is exceptionally well served by this team.

The report does not indicate the number of non-French scientists who were attracted in this team. Yet, judging from the number of masters and PhD students, the team is certainly a very attractive research environment. Its members have had long standing collaborations with worldwide top institutions (EMBL, Davis, UC–Dublin). The members are also frequently invited to international conference.

Assessment of the strategy and 5-year project:

The future research for the next 5 years is a well-balanced proposal between basic methodological development and large-scale data integration. It builds nicely on the know-how of the team while extending towards ambitious biological questions. The authors have understood well that the current pace of data production will prompt a new wave of data integration, required to make sure that new technology best benefits from new results. The project is original in the sense that it proposes a realistic framework for the use of evolutionary data in a very applied context. The idea is not entirely new, but this group is one of the few in Europe that may be able to carry out this task in a way that may be relevant for the entire biological community.

Conclusion:

Strengths and opportunities:

The group is one of the major players in bioinformatics in France and Europe. The future research plans represent a well-balanced proposal between basic methodological development and large-scale data integration. It builds nicely on the existing know-how of the team while extending towards ambitious but relevant biological questions.

Weaknesses and risks:

The only concern is the computational infrastructure at IGBMC. At this point, it is unclear whether this group (and the whole institute) receive sufficient computational support, and if that support is well enough integrated across the various groups and platforms so as to guarantee that the best use can be made of genomic and structural data.

Recommendations:

The group is strongly encouraged to pursue the proposed research.

Team : ISB-7 Action and inhibition studies of pharmaceutical targets

Team leader: Alberto PODJARNY

Workforce:

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

This team is proposed as a new group to be headed by Mr. A PODJARNY and to emerge through the fusion of two in-house existing sub-teams coordinated by two senior scientists. This restructuring is motivated by the future retirement of team ISB-5 leader and an expected refocusing of the scientific topics tackled by the two scientists during the last period.

Assessment of scientific quality and production:

The team headed by Mr. A PODJARNY has developed two main research projects covering a new quantum model of the catalytic mechanism and inhibition of aldose reductase by ultra-high resolution X-ray crystallography and the structural studies of a prototypic anti-freeze protein by neutron crystallographic techniques with the use of fully perdeuterated crystals. On his side, the other PI has deciphered the structure of full length HIV-1 integrase in the absence and presence of DNA by electron microscopy, a pioneering work compared to other partial structures of integrase available. During the past period both partners have published, respectively, 15 and 8 papers in peer-reviewed journals, of which 5 (1 PNAS) and 2 (1 EMBO J) originated from their own projects and 10 (1 JACS) and 6 as co-authors. This represents very good productivity. Major contributions are the structures of the antifreeze protein and the HIV-1 integrase.

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

The two senior scientists have demonstrated their capability to support their research by competitive external grants (15 total), including 1 HFSP and 3 ANR grants as partners.

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

The team is very well integrated with its contribution to the future center of integrative biology with the development of various methodological aspects.

Both partners interact significantly with other teams at IGBMC, in particular the team ISB-5. Thanks to his leadership in crystallography, A Podjarny benefits from an excellent visibility and has a very good capacity to attract pharmaceutical-based projects to carry out structure-based drug design studies. Both senior scientists showed very good participation in international meetings with 15 and 3 as invited speakers. 2 PhD students and 3 postdocs will be members of the team.

Assessment of the strategy and 5-year project:

The newly merged team proposes to focus on three main research themes. While one project will be the continuation of the on-going studies on the retroviral integrase superfamily with the combination of high, medium and low resolution structural data and in vitro and in cellulo functional data, the two other projects will be dedicated to the structural studies of the tumor marker AKR1B10, a member of cytosolic aldo-keto reductase, and the mechanism of fatty acid release in cardiac FABP by neutron diffraction. A new joint project will focus on the molecular mechanisms of the important Hsp70-Hsp90 co-chaperone machine regulation in apoptosis. The team also plans to further pursue various methodological developments and to study other protein-ligand complexes in the context of industrial contracts.

The projects proposed appear as a somewhat arbitrary collection of topics that in part are a continuation of previous successful research of the two senior scientists. The project that benefits mostly from the complementary expertise of the two groups (Hsp70/Hsp90) is very challenging, highly risky and competitive. The potential for success of this project was not clear from the report and presentations. Overall, at present the potential of the joined team in exploiting their very different but at the same time very complementary expertise did not become clear and deserves careful attention in the future.

Conclusion:

Overall opinion on the team:

The proposed team originates from the fusion of two sub-teams with complementary expertise in structural biology and biochemistry. The past productivity is very good to excellent and the various projects capitalize on the combined expertise of each partner to study structure-function relationships of various pharmaceutical targets leading to a positive impact on the feasibility of the joint project.

Strengths and opportunities:

Strengths of the team are excellent expertise in structural biology with world leadership in ultra-high resolution and neutron crystallography, the potential of two senior scientists with complementary expertise to tackle difficult and risky projects, and a strong involvement and commitment in education and training.

Weaknesses and risks:

The merging of the two groups faces threats: on one hand it appears that some of the individual projects incur high workload exceeding available capacities, while a convincing and promising joint project that combines the complementary expertises is lacking.

Recommendations:

It will be important for this new team to carefully reconsider and develop a strong unifying, collaborative project and to better capitalize on synergies and integration into the exceptional IGBMC environment. Strong integrative projects will also help to secure appropriate financial support by external grants. The joint team should initiate more internal collaborations to develop integrated projects that combine functional studies and structural biology. Whether such available expertise and intellectual skills should focus on the study of pharmaceutical targets needs to be carefully considered.

Team : ISB-8 Architecture of nucleoprotein systems by 3-D electron microscopy

Team leader: Patrick SCHULTZ

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	3	3	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	2		
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	1		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**10**	**6**	**3**

Assessment of scientific quality and production:

The team is one of the leaders in the field using cryo-electron microscopy to investigate the 3D architecture of complexes involved in transcriptional regulation, with recent highlights being studies of TFIID/DNA and the SCA7/SAGA complex. The group's findings provide important fundamental insight into the initiation of transcription. The team has been very productive within the past 5 years (40 publications) with some studies in top-ranking journals (Nature, EMBO J).

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

The team has been very successful in attracting external funding, including from European Union, such as FP7 and Marie Curie.

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

The team is well integrated within the department with a number of collaborations addressing different multi-subunit complexes using integrated structural biology approaches that have resulted in joint

IGBMC publications. Indeed, assignment of subunits within the complexes benefits from a collaborative multi-interdisciplinary approach within the ISB.

The excellent profile of the group is evident from numerous invitations to present at international conferences and to lecture at international workshops. While the group has attracted a number of talented scientists and technicians, only a few PhD students have joined the group. The research of the team is well integrated within national and international networks, such as FRISBI and INSTRUCT.

Assessment of the strategy and 5-year project:

The scientific strategy for the future is a well-balanced mix of new projects as well as projects that build upon already established results. The plan to address studies of endogenous TFIID is clearly challenging but the group has the required expertise and skills to tackle this topic and the research may give very novel insight. It is also sensible that the group in the future plans to study the link between TFIID and chromatin regulators, as this is of high biological significance and will exploit existing expertise and strengthen interactions with the biology groups. The combined analysis of in vitro and in vivo approaches to dissect these multi-subunit complexes, such as TFIID, is very complementary and should be strongly supported.

Conclusion:

Strengths and opportunities:

The team has an excellent track record, both in terms of methods development and scientific out-put, and will play an important role for the future success of the CBI. The research projects are well integrated into the ISB unit and address important fundamental problems.

Weaknesses and risks:

No weaknesses detected.

Recommendations:

The team addresses a large and diverse array of projects and some consideration and prioritization is recommended to bring the most feasible projects to fruition. Also it will be advisable that the group reaches out to further integration of EM data with complementary techniques such as imaging/FRET and small angle scattering.

Team : ISB-9 Ribosomes

Team leader: Marat YUSUPOV

Workforce:

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

Assessment of scientific quality and production:

This group uses X-ray crystallography to gain mechanistic insight into the fundamental process of translation in both bacteria and eukaryotes. There are few groups in the world that can crystallize and determine structures of ribonucleoprotein complexes as large as the ribosome, and this team is at the forefront of this field. The research team continues to make landmark contributions, the most recent being the report of the first crystal structure of a eukaryotic 80S ribosome at high resolution in the journal Science. It is clearly evident that all members of the team make valuable contributions to the team and are awarded with top-ranked publications. Indeed, the large number of high-impact publications in top-ranked international journals (Nature, Science, Cell and NSMB) directly reflects the high standards and quality of research in the group – a trend that will clearly continue in the future.

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

The team has been successful in acquiring external funding.

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

Strong collaborations with other groups at the IGBMC have led to high impact publications. However it is recognized that projects addressing translational control have decreased within the department in the past years. It would be beneficial to strengthen this area within the Integrated Structural Biology department, building around the continued success of this research group. Although the group has good external funding, it remains relatively modest in size. Given the large number of exciting projects, it would appear that some expansion may be beneficial, especially to support the most challenging and therefore long-term projects.

The high profile recognition and impact of the group results is clearly evident from the large number of invitations to international conferences (19) as well as the recent award of the Gregori Aminoff prize for crystallography from the Royal Swedish Academy of Sciences. The group has continually attracted extremely talented post-docs from abroad and all efforts should be made to support their future development at the IGBMC.

Assessment of the strategy and 5-year project:

Clear medium- and long-term strategies exist that comprise a balanced mix of projects based on the current available bacterial and yeast crystal structures. In addition, more challenging and higher risk projects are proposed that would represent landmark breakthroughs and maintain this group at the forefront of the field.

Conclusion:

Strengths and opportunities:

This is a talented team of top-class scientists performing high-impact, basic research, which would be competitive with any group at any institute worldwide.

Weaknesses and risks:

No weaknesses identified.

Recommendations:

The integrated structural biology department should consider strengthening research around the translational theme of this team to capitalize on their continued successes. The committee is supportive of the new focus to utilize the currently available crystals for addressing mechanism of action of antibiotic and anticancer drugs.

Translational Medicine and Neurogenetics (TMN) programme

Team : TMN-1 Physiopathology of RNA gain-of function diseases

Team leader: Nicolas CHARLET-BERGUERAND

Workforce:

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

Assessment of scientific quality and production:

The team has made recently very important contributions to research on myotonic dystrophy, fragile X-associated ataxia syndrome (FXTAS), and related disorders such as myotonic dystrophies (DM) type 1 and 2, caused by mRNA gain of function. Specifically for DM1 they have identified abnormal splicing of Bin1 as responsible for part of the myopathy and abnormal processing of Mir-1 as possibly involved in the cardiac arrhythmias seen in this disease. For DM2 there is preliminary evidence that the DM2 repeat sequesters many of the same proteins as the DM1 repeat, plus another protein Fox1, which may explain why DM2 repeats lead to a milder disease despite being larger than DM1 repeats. For the period under review the team has published three papers describing these findings with the team leader as senior author in high impact journals (Nat Med, Nat Struct Mol Biol, EMBO J). These studies implicate BIN1 and miR-1 in the myopathy and cardiac arrhythmia, respectively, of myotonic dystrophy, and SAM68 in FXTAS. The team leader has also been co-author on 4 other papers since 2007.

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

Funding of the team has been very good. It has received competitive funding from several sources, including ANR and AFM.

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

No recent prizes or awards are listed but Mr. CHARLET is still relatively new to the field, and he is not yet fully integrated into the international research community. However, he has started to make important contacts and form partnerships and collaborations with others in the field. He has participated in international meetings related to the diseases on which he is working. It would be good for him to further pursue these interactions, as he should do well in this area.

Assessment of the strategy and 5-year project:

This is an exciting project, and the investigator is well equipped to pursue it. The research plan is excellent. The team will continue to characterize the skeletal muscle and cardiac muscle specific pathogenic mechanisms in DM1. They also propose to create new mouse models for DM1 that will have significant muscle disease using AAV viral delivery to muscle. New drug treatments will be valuated for DM1 and FXTAS, for which little information has been provided. There may be a risk that the project will become over-extended, but at this point the team deserves the resources it needs to chase after its ideas.

Conclusion:

Strengths and opportunities:

The overall evaluation is highly positive. The team leader is bright, ambitious, and very knowledgeable. The team has made important findings and has excellent plans.

Weaknesses and risks:

At IGBMC the team is relatively isolated from others with expertise in the area of its research.

Recommendations:

The team is starting to form collaborations, but it would do well to become better connected to others working on muscle disease and RNA toxicity, at the Institute of Myology in Paris, for example, and in the international research community.

Team : TMN-2 Atherosclerosis and thrombosis

Team leader: Jean-Etienne FABRE

Workforce:

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

Assessment of scientific quality and production:

This team is dedicated to the mechanisms linking the plaque inflammation to atherothrombosis. They have developed in mice new models of atherothrombosis (test for on plaque thrombogenicity) and for measuring vasoconstriction in carotid arteries. Their results showed that:

- PGE2 produced by atherosclerotic plaques aggravates atherothrombosis. They have characterized a new drug blocking its EP3 receptor that is able to prevent atherothrombosis without inducing bleeding. They are studying which mechanisms control PGE2 production by plaques and have preliminary data suggesting that PPARg can be involved in this process;

- Atherosclerotic plaques produce Thromboxane A2 (TXA2) that mediates local vasoconstriction and plaque disruption, supporting the concept of “vulnerable plaque”;

- Neutrophils can enter the plaque and deliver their proteolytic enzymes, raising the possibility that neutrophils can be involved in plaque vulnerabilization.

Altogether, the on-going research may increase the knowledge of the plaque pathophysiology and open new routes for improving treatment of unstable angina.

The number of publication is low with only one original publication from the team, but with a high impact factor (J Exp Med 2007), 2 publications issued from external collaborations and 1 review. This low record track likely results from the size of the team (only one permanent scientist) and from time consuming work to set up new atherothrombosis models. Nevertheless, 3 manuscripts with a last position for the team's leader are under submission or preparation. The team delivered 3 communications to national (2) and international (1) meetings. 3 PhD defences occurred during the past 4 years.

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

The team obtained 4 grants over the last 5 years (for a total of around 200 K€). Recently, starting in 2011, it received one ANR grant for over 300 K€ (in association with another IGBMC team) that may allow for hiring of new personnel.

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

This theme is quite different from any other in the Institute making the PI and his team rather isolated. Some collaborations have developed, indicating that he is trying to integrate into the institute. But this theme has not achieved critical mass. The recent arrival of R. Ricci (team TMN-9) offers some limited overlap.

The team remains small and poorly visible, making it difficult to attract top-notch international or even national students. The applicant himself acknowledged that it has been difficult to attract high-level students. International visibility is poor. Nonetheless, the team's leader received the "Prix de l'Académie Nationale de Médecine" in 2007.

Assessment of the strategy and 5-year project:

The presented project is in continuity with the research performed in the group and is supported by interesting preliminary data. The project aims at deciphering by which pathways inflammation modulates atherothrombosis in order to identify new targets to prevent myocardiac infarction and stroke. Five key questions will be addressed: 1) the involvement of the LTB4 pathway, 2) the role of PPARg in the control of PGE2 production in plaques, 3) the role of the PGI2/PGD2 pathway, 4) the control by nuclear factors (PPAR, RXR, LXR) of the TXA2 pathway, and 5) the relative importance of these pathways in regard to disease context (hypertension, diabetes, infection…). The strategy was considered appropriate. However, given the previous limited productivity, the committee expressed concerns regarding the PI's ability to make a significant impact on the field.

Conclusion:

Strengths and opportunities:

The field of atherothrombosis is highly competitive. The scientific rational for this team to belong to the present Translational Medicine and Neurogenetics program is, in theory, good. However, the translational medicine aspect is not yet developed.

Weaknesses and risks:

The team's structure is very small and evidence for strong scientific interactions with others teams is lacking.

Recommendations:

The committee sees several alternatives: this team could be consolidated by recruiting stable researcher positions, merged with another existing team or integrated into another research unit outside IGBMC.

If the decision were to maintain the team and build around it, the recommendations of the committee would be to:

- Consolidate the team and publish as soon as possible the results obtained ;

- Establish more long-term collaborations within IGBMC and at national/international levels ;

- Establish clinical collaborations to valorise their expertise in atherothrombosis.

Team : TMN-3 Mechanisms of Monogenic Forms of Mental Retardation

Team leader: André HANAUER / Jean-Louis MANDEL

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	2	2	2
N2: EPST or EPIC researchers	1	1	1
N3: Other professors and researchers	1	1	1
N4: Engineers, technicians and administrative staff *****on a permanent position	1	1	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	2		
N6: Postdoctoral students having spent at least 12 months in the unit	0		
N7: Doctoral students	4		
N8: PhD defended	4		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	**11**	**5**	**4**

Assessment of scientific quality and production:

Mental retardation or intellectual disability (ID) is the most common reason for referral to genetic services, and is one of the largest socio-economic problems of health care. Most severe forms of ID have specific genetic causes, and there is reason to believe that the majority of these are due to defects of single genes. Yet, the vast majority of the underlying gene defects are still unknown, except for X-chromosomal forms, which have received much attention in the past.

This team has made seminal contributions to the elucidation of X-linked and autosomal forms of ID, with a focus on the most frequent X-linked form, the fragile X syndrome. Extending their previous finding that the fragile X mental retardation protein (FMRP) binds to its own mRNA via a G quartet structure, they now have shown that the G quartet structure is a potent splicing enhancer, and that binding of this structure by FMRP controls splicing of its own mRNA. Moreover, they have refuted an earlier, highly cited report that FMRP acts on miRNAs; showed that FMRP binds specifically to superoxide dismutase 1, SOD1, via a novel triple stem-loop structure in the RNA which leads to translational activation; and, most importantly, they identified G quartet structures in the 3' untranslated region of PSD-95, CAMKII and many dendritic neuronal mRNAs, showing that G quartet structures are signals for FMRP-mediated neurite targeting.

In parallel, the team has continued its successful studies into the pathogenesis of Coffin-Lowry syndrome and the function of protein kinase RSK2. In a series of publications, they refined the phenotype of RSK2 ko mice, reported that this defect leads to dysregulation of the cortical dopaminergic system and upregulation of the GluR2 subunit of the AMPA receptor, and showed that RSK2 has not only important roles in the regulation of axon growth and spine plasticity but also in glutamatergic neurotransmission.

In collaboration with others, they have also identified two major genes for Bardet-Biedl syndrome (BBS), which account for about 25% of the patients with BBS, a syndromic form of ID; and they contributed significantly to a high-profile publication associating 16p11.2 deletions with obesity.

Taken together, these studies are original and their results are highly relevant, because they deepen our insight into the etiology and pathogenesis of ID and related disorders and provide the basis for diagnosis, prevention and eventually, therapy.

The number of publications and their quality is high, and the same applies to other scientific collaborative communications, as indicated above.

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

Since 2007, the team has received numerous external grants totalling more than 1 million €, including annual support from the Collège de France for its PI, plus a recent grant from the ANR (until 2014). Together, this provides a solid financial basis for future scientific activities of the team.

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

The Team is very well integrated into the Institute. Numerous collaborations, joint publications and joint grant funding attest to this reality.

In 2009, the PI received the Prix de l'Académie Nationale de Médecine. Since 2010, he is a member of the EU-FP7 project GENCODYS, which unites a dozen strong European groups aiming to elucidate the molecular causes of cognitive disorders and to improve diagnosis and treatment. Since 2007, he has been scientific organizer and co-organizer, respectively, of several meetings, including two highly prestigious ones in 2010 and 2011. Moreover, he served as President and member, respectively, of several international and national review boards, and he, his co-PI and other members of his team were invited speakers at various international and national conferences and meetings.

Assessment of the strategy and 5-year project:

The research plan of this team entails four projects. The first extends an existing, successful research line aiming to understand in ever more detail the function of the FMR1 gene and the neuronal role of G quartets, which are not only found in the mRNA of FMR1, but also in many other genes that are expressed in neurons. Among other aspects, this ambitious, multi-facetted project encompasses the analysis of the ribonuclear complex surrounding the G quartet motif; the question whether this complex is a cation-dependent 'riboswitch'; identification of all mRNAs that can be co-immunoprecipitated with FMRP in mouse brain extracts; and the search for other proteins besides FMRP that have important roles in neuronal transport of mRNAs and might be targets for therapy.

The second project is a continuation of their long-standing, productive research into the pathogenesis of Rsk2 deficiency (Coffin-Lowry syndrome). Following up on their observation that in Rsk2-deficient mice, the Gria2 gene is up regulated, the team and collaborating groups will explore whether reducing GluR2 expression will normalize AMPA-mediated transmission. Modulation of the glutamatergic system, which has been successfully employed to ameliorate the symptoms in FMR1-deficient flies and mice, might also be an efficient strategy for treatment of Rsk2 deficiency.

Project no. 3, the high-throughput sequencing of a hundred known mental retardation (MR) genes in patients with ID and autism, is an extension of their studies focusing on the diagnosis and epidemiology of Bardet-Biedl syndrome. It will greatly improve the diagnosis of X-linked ID and related disorders in the 1000 FraX-negative males that are referred to the diagnostic laboratory, which is headed by the PI of this proposal. Furthermore, ruling out mutations in all known X-linked MR genes will identify families with novel defects that can be studied in more detail to find the underlying molecular changes. There was some debate within

the committee as to whether or not it might be better to adopt a broader approach, such as developing whole exome sequencing for diagnosis of such a heterogeneous disorder.

Project no. 4 is a novel one, which aims to elucidate the reasons for the male excess in MR, autism and other neuron-developmental disorders. First, the hypothesis that this excess is due to subtle mutations in X-chromosomal MR genes will be tested, using the methods developed for Project 3; thereafter, the team will focus on the effects of early androgen exposure on (gene expression patterns of) the developing human brain, using a variety of different approaches, including the use of iPS cells. There was limited enthusiasm within the committee for the experiments looking at the effects of early androgen exposure. The same experiment had been done by one of the committee members, but the results not published because of the difficulties involved in sorting out the thousands of signals that are obtained with this kind of experiment. No novel method for prioritizing the findings was presented. This project will be funded by a recent ANR grant (2011 – 2014).

Taken together, this proposal is a healthy blend of straight-forward/success-assured and ambitious, risk-taking research aspects, plus a project with a strong translational flavor linking research and molecular diagnosis.

Conclusion:

Overall opinion on the team:

The team has a very strong track record and standing in its field, and its PI is a scientific celebrity in France and beyond, as illustrated by his numerous awards and other indicators of esteem. As head of the diagnostic laboratory of the CHU, which is a reference centre for fragile X mental retardation, he is in an excellent position for doing research into the molecular causes of X-linked and other forms of ID, and for the translation of the results into diagnosis, prevention and therapy.

Weaknesses and risks:

State-of-the-art next generation sequencing equipment is a prerequisite for these studies. France has been remarkably slow in adopting this technology, and the planned upgrade of the existing sequencing infrastructure should not be delayed until 2013. Very soon, however, whole genome sequencing will become affordable enough to become the mainstay of genetic diagnostics, and in a few years from now, sequencing services will take over, rendering small institutional sequencing facilities obsolete. However, the demand for bioinformatic expertise will continue to increase.

Strengths and opportunities

The research proposal is a logical continuation of previous work into the pathogenesis of FraX and Coffin-Lowry syndrome, and the significant sex bias in patients with MR, autism and Hirschsprung disease is a scientifically interesting, hitherto unexplained problem. It is not clear which of the several explanations for this phenomenon are correct, but the work plan proposed will at least rule out some of the current hypotheses, even if it should not provide convincing proof for the ones that are favoured by the team.

Recommendations

- In view of the shared interest in translational research and similar needs, particularly in the field of next generation sequencing, it may be advantageous for this team to collaborate more closely with team TMN-6 ;

- High-throughput sequencing necessitates substantial bioinformatic support. In view of the limited available infrastructure, this may soon become a bottleneck.

Team : TMN-4 Physiopathology of Aneuploidy, Gene Dosage Effect and Down syndrome

Team leader: Yann HERAULT

Workforce:

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	3	3	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	0		
N7: Doctoral students	4		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**10**	**5**	**2**

Assessment of scientific quality and production:

The team's leader joined IGBMC in 2010, developed a research program focussed on the development of mouse models for chromosomal and genomic disorders and took the direction of the Institut Clinique de la Souris (ICS). Thanks to its high expertise in chromosomal engineering, the team developed several models of trisomy and monosomy and, in particular, aneuploid models covering the regions homologous to human chromosome 21. These models made it possible to decipher the genomic regions where dosage alterations contribute to the Down syndrome phenotype, revealed the genetic interaction of the different chromosome 21 regions, led to a new therapeutic approach based on the reduction of the GABAergic pathway, and constitutes, for the genetic and medical community, remarkable mouse models of Down syndrome. The work performed by the team at the IGBMC and in the previous lab in Orleans corresponds, since 2007, to 8 articles in peer-reviewed journals with a mean impact factor of 5 and notably 2 articles in Human Molecular Genetics. Two manuscripts are in revision (Plos One).

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

The valorisation activity of the team with 2 patents on Down syndrome treatment is very good. The funding capacity of the team's leader is excellent with several grants obtained as partner and especially 2 in the context of EU-Framework programs.

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

The team, thanks to its expertise in chromosomal engineering and development of mouse models, plays a central role at the IGBMC.

The number of invitations to international conferences and symposia (1-4 per year), the numerous scientific collaborations and the different scientific responsibilities of the team leader (Director of the ICS, director of the CELPHEDIA infrastructure for functional analysis in vertebrate models, coordinator of the national infrastructure Phenomin, "Investissements d'avenir 2011) unambiguously demonstrate his international visibility and clearly highlight that the team's leader is recognized as an international expert in animal models.

Assessment of the strategy and 5-year project:

The project, in the continuation of the previous work, will be focused on the characterization of the molecular bases of the Down syndrome phenotype, using the collection of mouse models and on the development of therapeutic strategies. One can be very confident of the ability of the team to generate important and useful results. The scientific project will also be extended to the development of mouse models for genomic disorders associated to mental retardation with the aim to determine which genes are sensitive to gene dosage alteration. This part of the project appears more as a series of technological contributions. Whereas mouse models should provide important information to dissect the molecular bases of genomic disorders and constitute important preclinical models, it is essential for the team leader not to restrict this scientific question to mouse models and to exploit the human CNV data bases which already indicate which genes are sensitive to dosage alteration.

Conclusion:

Strengths and opportunities:

This team has developed an internationally recognized technological expertise in chromosomal engineering and mouse model development. It has generated important tools and data in the field of Down syndrome and plays an important role in the supporting infrastructures at the IGBMC.

Weaknesses and risks:

It will be important in the future to preserve specific scientific projects, since like in all teams strongly involved in technological development, the risk could be to become a technological facility.

Recommendations:

Considering the scientific axis focused on gene dosage effect, it is also important for the team to reinforce interactions with medical geneticists not only to develop mouse models but also to decipher genes for which dosage alterations have a phenotypic expression in human.

Team : TMN-5 Opioid Systems and Brain Function

Team leader: Brigitte KIEFFER

Workforce:

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers
N1: Professors or assistant professors	2	2	2
N2: EPST or EPIC researchers	6	3	3
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff ***on a permanent position	2	2	
N5: Engineers, technicians and administrative staff * on a non-permanent position	2		
N6: Postdoctoral students having spent at least 12 months in the unit	4		
N7: Doctoral students	8		
N8: PhD defended	6		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	4	2	
TOTAL N1 to N7	**24**	**7**	**5**

Assessment of scientific quality and production:

As a focus, the team has investigated multiple aspects of the roles of the opioid system (in particular in the field of addiction, pain and cognition/emotion), using sophisticated mouse genetics and a broad spectrum of behavioral analyses, but also including imaging techniques (for receptor trafficking) in transgenic mice, gene expression analysis and pathway explorations, leading to the discovery of new target genes which are proposed to be explored in the following 5 year research period. The quality of research is excellent, and the work has had a very significant and long-lasting impact in their fields. This is reflected in 32 publications (first/last authors) and 34 joint publications within the last 5 years. The year 2011 was very productive, since 10 papers as first/last author were published, with one very high impact paper in Nature Neuroscience. In addition, several new transgenic mouse models have been developed recently. The new lines will give a rewarding output soon. In summary, this group uses state-of-the-art techniques to investigate fundamental biological questions in a successful manner.

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

The external funding is excellent (2 Mio EUR) and this mostly includes grants from very competitive agencies (NIH, EU, ANR). In particular, the EU and the NIH grants foster the international collaborations with internationally well-recognized groups.

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

The team's expertise in mouse genetics and the behavioural analyses fits very well into the institutes' theme of Translational Medicine and Neurogenetics. The group has long-standing recognition within the institute and is very central for the IGMBC as a whole. The aspect of translational medicine is, for example, nicely realized in the proposed investigations on a project aiming at de-orphanizing GPR88, a G protein coupled receptor, which was discovered by the team in a screen searching for genes involved in addiction. Furthermore, understanding the differential functions of the opioid receptors will lead to new strategies in using agonists in the treatment of pain, in particular for the treatment of chronic pain, where the emergence of tolerance still impedes efficient medication procedures.

The national and international visibility of this team is outstanding. The team leader and several members of the group are frequently invited speakers in well-known and established conferences. The team leader was elected as an EMBO Member in 2009. Furthermore, the team leader organized 5 symposia in international conferences, which again underlies the visibility and recognition of the team internationally. One patent was also issued. In general, the team is very well integrated into several networks and long-term collaborative projects.

Assessment of the strategy and 5-year project:

The future projects are very well based on the team's previous work. Thus, they can utilize a large repertoire of mouse mutants and also explore numerous target genes identified in the previous research period. Several new conditional knock-outs of opioid receptor genes will be generated. This is certainly a promising continuation of work. Furthermore, GPC88 is proposed to be de-orphanized and new emphasis is placed on the serotonergic system in regard to drug addiction, which is certainly a very interesting new field. In addition, and very importantly, new research fields will be touched, such as in vivo electrophysiology and advanced MRI techniques. The latter two projects are in close collaboration with groups in Basel and Freiburg, respectively. In the long-term, it is advisable to establish these methods at the IGMBC.

Conclusion:

Strengths and opportunities:

The group is excellently installed at the IGMBC and internationally very well recognized. The projects are very relevant for drug addiction, cognition and pain, and they are very promising. Several novel aspects will be investigated. The team is technically excellent, multi-disciplinary, and well connected.

Weaknesses and risks:

It is a very large group, but the team leader has undertaken the effort to structure the group by forming several subgroups investigating sub-projects. Currently, the group intends to expand the methodological repertoire to electrophysiology, but within the institute, no other group works in electrophysiology.

Recommendations:

It would be meaningful to strengthen neurophysiology/electrophysiology at the IGMBC.

Team : TMN-6 Recessive Ataxias

Team leader: Michel KOENIG

Workforce:

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

Assessment of scientific quality and production:

Mr. KOENIG and his team have made a series of very important discoveries in the identification of genes for autosomal recessive ataxias and other disorders. Indeed, he has positioned his group as the leader in the field of recessive ataxias. The team is committed to translational work and is currently developing a state of the art method for clinical diagnosis of this genetically and clinically heterogeneous disease. In recent years important discoveries have included ataxia with coenzyme Q deficiency and PHARC. The team has published in leading specialist journals such as Am J Hum Genet.

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

The team has been well funded with grants from ANR.

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

The team has very well established connections with the community of clinicians and researchers working on hereditary ataxias. Mr. KOENIG is indeed an international leader in this field. He has been frequently invited to speak at international meetings. He has done service on review committees for ANR,

Telethon, and AERES. He also has important teaching responsibilities. The research team is small, but it has many long-lasting collaborations with others in the field of hereditary ataxia.

Assessment of the strategy and 5-year project:

Mr. KOENIG and his team are highly accomplished, but their research plans could be more forward-looking with regard to new sequencing techniques. Next generation sequencing (NGS) allows disease gene identification to be done more efficiently and more broadly. This will lead to new comprehensive diagnostic tests and new therapeutic opportunities. Two of the disease genes discovered by Mr. KOENIG, for ataxia with vitamin E deficiency and ataxia with coenzyme Q10 deficiency, have direct therapeutic implications (i.e., appropriate treatment has real clinical benefit if the diagnosis is made early), and there will doubtless be more. Infrastructure support for NGS and human genetics research at IGBMC is currently limited compared to elsewhere, and this has limited the team's ability to take advantage of recent technological advances in the field.

Conclusion:

Recommendations:

IGBMC has an outstanding asset in Mr. KOENIG, a world leader in disease gene identification. However, the team's future plans are limited by resource limitations. The institute would do well to give him the support he needs to be fully successful.

Team : TMN-7 Pathophysiology of Neuromuscular Diseases

Team leader: Jocelyn LAPORTE

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	1	1	1
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	1	1	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	6		
N7: Doctoral students	3		
N8: PhD defended	4		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**13**	**3**	**2**

Assessment of scientific quality and production:

This team contributed important results to the genetic basis of neuromuscular diseases, with a specific focus on centronuclear myopathies (CNM). Over this last 4 years, they implicated for the first time the amphiphysin 2 gene in CNM and in myotonic dystrophy. This latter result was obtained in a fruitful collaboration with another IGBMC team. Interestingly, a functional link between amphiphysin 2 and two other genes that they previously implicated in CNM could be established, thus providing solid evidence for a novel cellular pathway regulating membrane tubulation in skeletal muscle cells. These results were immediately transferred to the genetic diagnosis laboratory of the Strasbourg hospital to implement these findings in diagnosis protocols for neuromuscular diseases. In parallel several animal models have been developed, characterized and used to investigate possible therapeutic approaches.

All these results are very original and of high quality. They were published in journals of excellent (Nature Genetics, Nature Medicine, JCI) or very good (PNAS, HMG,...) impact.

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

This team has been able to obtain excellent funding for its research. They obtained 4 grants from the ANR, got recurrent support from the Association Française contre les Myopathies, and were supported by the Fondation pour la Recherche Médicale as an FRM team. Most remarkably, they obtained significant funding from the American Muscle Dystrophy Association.

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

Mr. J LAPORTE and his team are now well recognized in the field of genetic centronuclear myopathies. He was invited to several national and international conferences, and was awarded 3 French research prizes and a Contrat Hospitalier de Recherche Translationnelle with the AP-HP. The team is now composed of 13 people, including 5 post-docs and 3 PhD students, mostly coming from abroad.

The team is implicated in numerous national and international collaborations. Specifically, Mr. J. LAPORTE is co-chairman of the international consortium on myotubular/centronuclear myopathies sponsored by ENMC since 2003 and is performing diagnosis on CNM for several clinicians worldwide. They are also collaborating with relevant teams to address specific biological points or develop a series of animal models in different species.

Altogether, the numerous grants obtained by this team reflect the quality and credibility of past and future research. Research costs for the next years are already well secured.

The team collaborates with many other IGBMC teams.

Assessment of the strategy and 5-year project:

The current project proposes to keep investigating the pathophysiology of genetic myopathies at several levels. First, the team will try to identify the genetic basis of CNM and other myopathies using Next Generation Sequencing. The committee very much appreciated this aspect of the project, which is at the core of the know-how of the team. It should provide useful data to get a sense of the genetic landscape of CNM and be of immediate use for diagnostic purposes.

A second part of the project is the characterization of a putatively novel pathway for the organization of skeletal muscle. This is an interesting and challenging cell biology project that might require experimental or conceptual tools beyond the resources of this group. Fortunately, most of these projects are conducted in collaboration with relevant teams, at the IGBMC or abroad. The use of the zebrafish as an experimental model to study skeletal muscle cell biology seems extremely relevant.

A significant part of the project should also be dedicated to the development and characterization of mammalian models, including mice and dogs, and be used for the preclinical validation of various pretherapeutic approaches. This part of the project might look a bit broad and ambitious, in comparison with the size of the team. However, it was acknowledged that most of this project will be conducted in close collaboration with other experienced groups.

Conclusion:

Strengths and opportunities:

This is an excellent team, extremely productive over the last four years, well recognized in its field at the international level, and able to get significant funding to conduct its research. The project is well focused on the analysis of centronuclear myopathies.

This team has excellent skills in human genetics and the proposed strategy to elucidate the basis of genetic myopathies was appreciated by the committee. This will probably provide strong contributions to the field and should definitively be encouraged. In addition, these results are of immediate interest for the clinicians.

The further identification of genes mutated in CNM will open many new interesting physiopathological questions.

Weaknesses and risks:

No obvious weaknesses identified.

Recommendations:

It will be important for this relatively small team to avoid spreading into too many directions and remain concentrated on a few well-identified questions.

Team : TMN-8 Biology and Physiology of Recessive Ataxia

Team leader: Hélène PUCCIO

Workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	1	2	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *****on a permanent position	1	1	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	5		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	1	2	
TOTAL N1 to N7	**10**	**3**	**2**

Assessment of scientific quality and production:

The research of this team and its scientific oeuvre is remarkably coherent, with a focus on the mode of action of the genes for Friedreich ataxia (FA) and other recessive forms of ataxia, and its scientific quality is excellent. In several articles published in journals like Human Mol Genet and PloS ONE, the team has shed light on the maturation of the Frataxin protein from its precursor polypeptide; shown that Frataxin is an essential component of a mitochondrial protein complex that is involved in the biosynthesis of iron-sulfur clusters; demonstrated that in mammals, Frataxin is also essential for the function of extramitochondrial Fe-S cluster proteins; that Frataxin deficiency leads to up-regulation of several mitochondrial proteases and to stress response that is different from that induced by oxidative stress. On the basis of these findings, they explored new therapeutic approaches for FA. Moreover, they have generated a wealth of interesting results that are as yet unpublished, ranging from tissue-specific inactivation of the FA gene in mice to the generation and investigation of mouse and human iPS-derived cellular models for different forms of ataxia. Together, this material should be good for at least half a dozen other publications in internationally visible journals.

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

The funding situation of this team is exceptionally favourable: apart from a large EU-ERC starting grant obtained in 2007, the PI has received numerous other grants, mostly from French funding agencies, but also from the EU through a European Friedreich's Ataxia Consortium. Since 2007, the team has received more than 3 million € from external sources.

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

The team is well embedded in the department, where research into ataxia has a long tradition and is also the main topic of a second group that focuses mainly on genetic and diagnostic aspects of this disorder. Nationally and internationally, the team has productive cooperations with numerous established groups working on FA and related subjects.

The PI of this team has been awarded the Jean Toy prize of the (French) Académie des Sciences in 2008, a Young Investigator award from the (US) National Ataxia Foundation as well as the afore-mentioned ERC Starting Grant Award. Recently, another member of the team has also received the Young Investigator Award of the National Ataxia Foundation, as well as a New Investigator Grant from the Friedreich's Ataxia Research Alliance.

The PI has been invited to speak at numerous national and international meetings and conferences, including a Gordon Research Conference on Iron-Sulfur Enzymes (New London, USA 2010) and two related meetings in Cambridge and London, respectively (2011), and one of her co-workers was also invited to two international meetings in 2010. Moreover, the PI has reviewed manuscripts for a variety of scientific journals including the Journal of Biological Chemistry, Brain, Human Molecular Genetics and FEBS Letters; she was nominated member of a Comité National du CNRS; participated in three visiting committees; and in 2011, she organized the 4th International Conference on Friedreich's Ataxia.

Assessment of the strategy and 5-year project:

In continuation of their successful research that linked Frataxin to the biosynthesis of iron-sulfur clusters (ISC), the team intends to study the mitochondrial ISC biosynthesis pathway in more detail, which consists of the ISC assembly on a scaffold protein and the subsequent transfer of the scaffold-bound ISC to the target apoprotein. Unravelling the different steps of ISC maturation, an essential biochemical pathway, and understanding the cellular response to ISC deficiency, will also be essential for understanding the pathogenesis of FA, other ataxias and several other known and unknown genetic diseases.

Previously generated cellular iPS models for FA will be instrumental in validating these pathways that have been identified in the mouse. Moreover, these iPS cells will be used for metabolome, proteome and transcriptome analyses, and for investigating the potential of different compounds to cure or alleviate FA.

In collaboration with a laboratory at Univ. Paris Descartes, the team will also employ its innovative AAVrh10 vector to deliver the frataxin gene into various parts of the brain, including the affected dorsal root ganglia, the heart and the pancreas of the mouse. If successful, they will perform toxicity studies in Macaca fascicularis, with clinical tests in FA patients as their long-term aim.

Another novel research project will focus on the hitherto unknown function of the ADCK3 and ADCK4 genes, which are involved in mitochondrial CoQ10 biosynthesis. A major asset for these studies will be a previously generated constitutive ADCK3 knockout mouse, a model for the human autosomal recessive cerebellar ataxia 2 (ARCA2).

Finally, in an attempt to find novel routes for treating trinucleotide instability diseases like Huntington's disease (HD) or FA, the team will investigate the role of transcription and DNA repair in trinucleotide instability and the potential of HDAC inhibitors as drugs for treating HD and FA. This project relies on the specific expertise of a newly recruited team member, who was attracted by the broad methodological spectrum of this team.

Taken together, this ambitious program with its healthy blend of fundamental and applied, established and innovative aspects deserves an excellent rating.

Conclusion:

Strengths and opportunities:

During the past 5 years, this team has established itself as one of the groups contributing significantly to the understanding of the biology and pathophysiology of recessive ataxias. Within the department and beyond, it is well connected; its financial situation is sound, and the research plan presented for the next 5 years is strong and promising. The establishment of methods for the generation of iPS cells should create further opportunities for fruitful scientific interactions.

Weaknesses and risks:

The only relative weakness is the publication record of this team, which does not quite match the otherwise excellent standards of the group.

Recommendations

Publish the backlog of data referred to in the Activity Report; aim for publication in impact factor >10 journals if possible. Make sure to preserve the coherence of the team despite its diversification (i.e., the novel research into trinucleotide instability).

Team : TMN-9 Signal Transduction in Metabolism and Inflammation

Team leader: Romeo RICCI

Workforce:

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

Assessment of scientific quality and production:

(This team has been at IGBMC since 2008 only)

The team leader came from the Institute of Cell Biology at ETH Zurich (Switzerland) and integrated the IGBMC late in 2010. The objective of this team is to decipher, from cellular biology to pathophysiology, new signal transduction pathways involved in metabolism and its related pathologies (metabolic syndrome, obesity, inflammation). The team leader has recently discovered a new signaling module, p38d/Protein Kinase D1 (PKD1), which is involved in 1) insulin secretion by ß pancreatic cell and protection against high-fat-induced insulin resistance and 2) neutrophil recruitment during lung inflammation. This discovery undoubtedly opens new original research projects with potent implications in metabolic diseases. This is reinforced by the recent finding of SNPs in the PKD1 gene in a cohort of type 2 diabetic patients. Furthermore, their search for putative PKD1 targets allowed them to find a promising candidate (Arfaptin 1) whose PKD1-mediated phosphorylation at specific, previously unknown, sites alters insulin secretion. Since his arrival at IGBMC, 2 new original projects started. First, by using a transcriptional screening approach, they identified the Hairless protein (a co-repressor of several nuclear receptors) as a potential key player during adipocyte and myoblast differentiation, which could modulate Wnt signaling. Second, by using transcriptomic and proteomic approaches, they identified in mouse fatty liver disease important modulations of the

ubiquitination pathway (known to be involved in cell cycle progression, cancer development and inflammation), suggesting that this pathway could be important for the regulation of hepatic metabolism.

In agreement with their late arrival in 2010, all the cited publications were obtained in the previous laboratory (ETH Zurich). The number was good (7) and the quality excellent with one Cell publication in 2009 as last author. Three manuscripts, in relation to the work conducted at IGBMC, are actually either in revision (1 at Immunity) or in preparation (2), all as last author. This is excellent taking into account the short time period in France.

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

The funding capacity is very good with 4 grants (for a total of 132 K€) during the last 4 years, and actually excellent with the awarding of an ERC starting grant in 2011.

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

Despite the PIs recent arrival he has already established links with many other groups at the IGBMC. The team already collaborates with 4 other IGBMC teams, indicating its successful and dynamic integration at the IGBMC. The team has already attracted 2 foreigner Post-Docs.

The team leader received 4 prizes/awards since 2008 ("Georg-Friedrich Goetz" research award-Switzerland 2008, Swiss Society for Endocrinology and Diabetology Young Investigator Award 2009, EMBO Young Investigator Award 2009, "Gutenberg" Chair-Alsace 2010) and is currently a recipient of an ERC starting grant since 2011. The number of invited seminars (6 in Finland, Spain, UK and Singapore) and invitations to international meetings (5 in Holland, Switzerland, Germany and Italy) shows the international visibility of the team leader. 3 PhD students are currently present in the team. The research projects are supported by strong international (Switzerland, USA, Spain, UK, Finland, Austria, Germany, Australia) and national collaborations.

Assessment of the strategy and 5-year project:

The research is highly original and at the interface of cell signaling/metabolism/pathophysiology with potent implications in metabolic diseases. The presented project is in continuity with the research performed in the team. It will: 1) continue the study of mechanisms downstream of p38d/PKD1 in the regulation of insulin secretion and neutrophil migration, 2) Investigate whether the p38d/PKD1 signaling module also exerts a role in other organs (brain, liver, adipose tissue…) in relation to metabolic diseases, and 3) Determine whether the ubiquitination pathway plays a role in the regulation of liver metabolism by using proteomic approaches. The strength of the overall project is the powerful combination of different "omics" approaches and transgenic models (specific-tissue knockout mice for several gene targets), which are possible due to the IGBMC platforms and the proximity of the ICS. Most of the tools and models are already obtained. The ubiquination project is a high-risk plan and largely unexplored. There is no doubt that this research axis will give new important insights into the regulation of metabolism. However, the team must acquire expertise in "real" metabolism in order to be able to fully exploit the future results obtained at the protein level. Collaborations with clinicians and networks of clinicians involved in metabolic disorders should also be developed. Additionally, it is not clear how the metabolic impact of the putative targets of ubiquitination modulation will be investigated. The risk is to stay at the biochemistry/cellular level if no metabolic investigations are planned.

Conclusion:

Overall opinion on the team:

This is a very promising team that should be encouraged to continue their work, which offers diversity of lines of research as well as novel and original general hypotheses.

Strengths and opportunities:

Its strength is its ability to integrate cell biology, high-throughput transcriptomic and proteomic screenings, transgenic mice models and pathophysiology to address innovative questions through cutting-edge projects. Since its arrival, the team has already taken advantage of the specific scientific environment of the IGBMC and should play a dynamic role in the « Translational Medicine and Neurogenetics » Program.

Weaknesses and risks:

No obvious weaknesses detected.

Recommendations

- Recruitment of scientist with expertise in the metabolism field ;

- Development of collaborations with clinicians in the framework of the IGBMC department of translational medicine ;

- Clarify the strategy for investigating the impact of ubiquitination modulation on metabolism ;

- Take care not to diversify too much the research projects since this could be detrimental to scientific production.

Team : TMN-10 Pathogenic Mechanisms of Polyglutamine Expansion Diseases

Team leader: Yvon TROTTIER

Workforce:

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

Assessment of scientific quality and production:

The work of this team is very relevant to the pathogenesis of Huntington's disease and the other neurodegenerative diseases that are caused by polyglutamine expansion. It is interested in understanding why polyQs are only toxic above a certain size, leading it to focus on aggregates as the toxic entity and mechanisms of polyQ aggregation. The team studies of mutant protein aggregation have been well done. They offer insight into the disease mechanism and point toward possibilities for therapeutic intervention. They have also explored mechanisms of retinal regeneration in SCA7 mice, considering it to be a potential therapeutic approach. The team leader is a senior author on a number of publications in moderate to high impact journals such as Neurobiol Dis, PLoS Genetics and Hum Molec Genet.

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

The team has obtained grant support from outside organizations in the last 4-5 years, most recently from the AFM. With one exception the team has not secured significant new research funds.

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

Mr. TROTTIER and his team have been involved in national and international collaborations, such as EUROSCA. He has participated in review panels and international meetings in his field.

No prizes or awards are listed, although Mr. TROTTIER has been invited to participate in international meetings and there have been fellowship awards for trainees in the lab. The team is relatively small and has not recruited from abroad.

Assessment of the strategy and 5-year project:

The team plans further investigations of the toxicity of mutant polyglutamine in a range of model systems, from in vitro cell-free to cell culture and retina. There are plans for a high throughput screen with a cell-free polyglutamine aggregation assay, but the assay is not yet well developed (e.g., with an established signal to noise ratio). In-house support for high throughput screening at IGBMC is currently limited, and the plans for outside screening are not well defined. Screening for inhibitors of polyglutamine aggregation has been done elsewhere previously. The current approach may be more sensitive, but its feasibility has not yet been demonstrated and its novelty is not clear. Similarly, the planned retinal studies may have limited relevance, in that the importance of neurogenesis in the disease mechanism is not yet substantiated.

Conclusion:

Strengths and opportunities:

Overall, the strengths of this research team are its history of contributions to polyglutamine disease research, its collaborative interactions with other research groups, and the outside funding it has received. The team has also published well, and there are opportunities for further contributions to the understanding of the mechanisms of polyglutamine diseases and to the development of treatment for these disorders.

Weaknesses and risks:

The weaknesses are that the novelty of the research plan is limited, and its feasibility and relevance remain to be established.

Recommendations:

The review committee recommends that the team focus on validating the assay to be used for compound library screening and on demonstrating its superior sensitivity relative to others that have been used previously. The disease relevance of the retinal studies of neurogenesis could be better addressed. In general, the team (and the research field in which it operates) could use more novel approaches to the critical steps in the molecular and cellular pathogenesis of polyglutamine disease and to the points for effective therapeutic intervention.

PLATFORMS

High-throughputScreening

Leader: Laurent BRINO

The high-throughput platform for RNAi and small molecules screening was set up at the IGBMC in 2006. Since that time, instrumentation for high-throughput screening has been purchased, expertise in developing cell-based assays was acquired, and a few screens have been performed. Essential instrumentation currently exists and acquisition of additional equipments is projected (e.g., Operetta).

The platform is in good shape but much work remains to be done to make it state-of-the art. Progress should be made in a number of areas: 1. Screening should go beyond subset libraries and become genome-wide; 2. The imaging platform should become more versatile and go beyond the tools provided by the instrument manufacturer as these are optimized for specific applications. Specifically, the use of Cell Profiler should be considered; and 3. Bioinformatics should be further developed to facilitate screen analysis and data storage.

Overall, Mr. BRINO should be congratulated for his efforts at getting the facility off the ground. Exciting science should emerge from this platform, which is an essential component of the IGBMC.

Imaging

Leaders: Jean Luc VONESCH and Yannick SCHWAB

The imaging centre of the IGBMC is composed of two teams, a team taking care of light microscopy (headed by Mr. Jean-Luc VONESCH) and a team taking care of electron microscopy (headed by Mr. Yannick SCHWAB), composed of six and four engineers/technicians, respectively. The Imaging centre can look back at a 20 year long successful history, and care has to be taken now to let the facility develop in the future in a manner similar to the past; the facility not only provided service but has also developed new tools and has a rather successful past in this regard. While Mr. Jean-Luc VONESCH has been instrumental in developing microscopy techniques and commercialize them with Leica, the new developments of the platform as a whole include the implementation of correlated light and electron microscopy. New instruments are either being installed (PALM) or planned (STED), so that the facility will be in a rather competitive state.

For the future, it will be very important that the imaging platform is guided by a Scientific Steering Committee, which helps the platform leaders to take important decisions and prioritise experiments to be performed in the facility. This will be even more important as the facility will move to the new building, the CBI. It can be anticipated that the project requests to be treated by the imaging platform will increase significantly in the next few years, and the steering committee will be invaluable in helping the facility to purchase new instruments and keep the older once running. Team DSC-14 leader, Mr. Julien VERMOT has been doing a great job as the head of the user committee, and he could head the steering committee (which could replace the user committee, but should be more involved in “steering” the facility). A good balance between letting the heads of the facility do what they can do best, and yet provide a broad spectrum of services at an affordable price, will have to be found. It is hoped that the relocation of the platform to the new building does not socially uncouple the people working in the facility from the scientists working in the IGBMC building.

Microarray and Deep Sequencing

Leader: Christelle THIBAULT-CARPENTIER

This group of 12 engineers/technicians provides the infrastructure and service to run microarrays or deep sequencing analyses. They run an Affimetrix and an Agilent micro-array platform and an Illumina sequencing platform, plus additional equipment for sample preparation and quality control. A scientific committee, who defines the strategy and resources, directs the facility. The group is subdivided in three services, microarrays, deep sequencing and informatics. They support the community by participating in the design of the experiments and analysis of the data and have run approx 10000 hybridisations and 800 sequences since 2007. The microarray facility shows a fairly steady usage over the years, while the sequencing activity is rapidly increasing since it started in 2008. The user groups are from the Institute, the larger French community, non-French institutes and a number of companies. The facility participates in several national and international consortia and has been accredited with the ISO 9001 certification.

The group contributed to > 60 publications including some senior author publications.

The facility plays a crucial role in the research programmes of many of the groups at the IGBMC and the wider community. It has been very productive as demonstrated by the number of papers with authorships for members of the facility. It is crucial that the facility is maintained at the highest level with the latest state of the art technology. Many of the high-level science projects and clinical studies are dependent on this. The Institute has been slow in adopting deep sequencing technology and is presently a little slow in updating its Illumina equipment (planned early next year).

Overall this is an important facility that serves the community well. It is run by experienced staff and benefits from being housed in the Institute with close contact with research groups. There is, however, an almost complete absence of pricing and cost/benefit numbers in comparison to other centres or outside services. It is recommended that attention be paid to cost/pricing. In particular outsourcing needs to be monitored, as this is expected to become the future, particularly in the clinical arena with exome and whole genome sequencing at a cost comparable to running micro-arrays. A further recommendation concerns data storage that has not been addressed properly, and needs attention before problems develop.

Proteomics

Leader: Adeline PAGE

The Proteomic platform is relatively small (3 personnel units) and it was established recently as reorganization of the Mass Spectrometry platform.

It is open for services to Institute internal users, as well as to external users of different origins, from academics to industrial ones.

The Platform responsible has set up an intranet system for users to submit applications to the services, as well as a complete service costs scheme. When possible, the Platform also establishes contract agreements with industrials user to provide services.

The facility host four standard instruments, a MALDI-TOF, an ESI-TOF and two nanoESI-linear Ion Trap mass spectrometers. Funding was recently obtained with the aim to acquire a much higher resolution ORBITRAP mass spectrometer.

Their expertise and the performed measurements are essentially devoted to classical proteomic analysis (if necessary combined with proteolytic digestion and protein separation by SDS-PAGE and HPLC). Recently they set up the Multidimensional Protein Identification Technology (MudPIT) analysis.

Strengthening of structural mass spectrometry, which would have major potentialities and exploitation in this institute, should be thoughtfully considered.

Structural Biology and Genomics

Leader: Catherine BIRCK

The Structural Biology and Genomics platform has been reorganized in 2009 and currently provides service in two modules (1) protein production and biophysical characterization (AUC, ITC, SLS) and (2) 3D structure determination by crystallography. The group provides service, training and methods development and is involved in IGBMC internal (majority) and external collaborations and projects. Users are either collaborators (with co-authorships of the platform scientist) or provide a contribution to consumables. This mode of operation appears to run smoothly. The platform performs very well and strongly benefits from being part of the Integrated Structural Biology Department, thereby taking advantage from the available state-of-the-art expertise in structural biology. An expansion of the service to include support with NMR and EM structural biology is planned, although no additional staff is requested as the NMR and EM groups are supposed to contribute. It is not completely clear how efficient this will be and whether resources (personnel and instrumentation) are available.

The platform helps ISB researchers to tackle challenging projects, for example, by implementing and developing expression techniques for large eukaryotic protein complexes. The platform is well integrated nationally in the FRISBI project and internationally in the INSTRUCT node of IGBMC. The platform performs very well. It provides an important and well-used service to IGBMC. It should remain integrated with ISB and also move to the new CBI building.

INFRASTRUCTURES

Center for Integrative Biology (CBI)

Leader: To be named

As the leading center in structural biology in France, the new Center for Integrative Biology (CBI) at IGBMC will offer a unique opportunity to bridge the gap from the atomic and sub-cellular molecular structures up to the animal with the implementation of cutting-edge facilities linked to methodological developments in integrative structural biology. This long-awaited European-wide center will represent a first foray to integrate multi-scale technologies in life sciences combining state-of-the-art research and educational activities through the INSTRUCT and FRISBI programs in structural biology. While the final stages of this infrastructure project are approaching, the reorganization of the research groups and associated platforms should be carefully planned with all the concerned staff members.

Mouse Clinical Institute (ICS)

Leader : Yann HERAULT

This is a major facility, which provides an integrated platform for generating mutant mice and for comprehensive phenotypic analysis, as well as providing a mouse facility for the Institute. It serves the IGBMC, the French scientific community and the wider European community. In addition to their expertise in handling ES cells and generating mutant or transgenic mice, the phenotyping possibilities offered by the Institute are very impressive. These include general and specialised pipelines ranging from metabolics and biochemistry to cardiovascular-respiratory or behavioural studies. The Institute provides a precious resource, which has been extensively used. When it was established by Pierre CHAMBON in 2002, it had very significant industrial support. This has virtually disappeared with the contract work for industry now representing less than 10% of the total activity. With a staff of over 100, many of whom are employed on short-term contracts, the financial situation is a source of anxiety. However the Institute has been very proactive in establishing nationally and internationally funded consortia, notably in the context of EU projects on the mouse model. For example, it is currently part of Eumodic, and of the Avenir funded Phenomin consortium of French national phenotyping facilities. Importantly also, under Y. HERAULT's leadership, the ICS is part of the IMPC (International Mouse Phenotyping Consortia) which includes key centers in Europe, the United States and Japan. Scientifically these activities are important and they are also financially helpful. In addition, the role of the ICS as a major partner in international consortia contributes to the visibility of French science in this area.

5 • Grading

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

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

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

❖ Overall assessment of the unit :

Institut de génétique et biologie moléculaire et cellulaire

Unité dont la production, le rayonnement et le projet sont excellents. L'animation est excellente mais l'organisation doit être sensiblement améliorée.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-CAVARELLI**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-CHAN-KASTNER**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-CHARLET-BERGUERAND**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-CHARVIN**

Équipe non notée pour la production et le rayonnement dont le projet est excellent.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-DAVIDSON**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-DEJAEGERE**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-DOLLE**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-EGLY-COIN**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team: **POURQUIE-FABRE**

Équipe dont la production, le rayonnement et le projet sont bons, mais pourraient être améliorés.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-GEORGES-LABOUESSE**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-GIANGRANDE**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE- GRADWOHL**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE- GRONEMEYER**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-HAMICHE**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-HANAUER-MANDEL**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-HEITZLER**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-HERAULT**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-JARRIAULT**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-KIEFFER Brigitte**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE- KIEFFER Bruno**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-KLAHOLZ**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-KOENIG**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE- LABOUESSE**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-LAPORTE**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE- MARK-GHYSELINCK**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-METZGER-CHAMBON**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-MORAS**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-POCH**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-PODJARNY**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-POURQUIE**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-PUCCIO**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE- REINA-SAN-MARTIN**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-RICCI**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-RIO-TOMASETTO**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-RIVELINE**

Équipe non notée pour la production et le rayonnement dont le projet est très bon.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-ROCHETTE-EGLY**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-SCHNEIDER**

Équipe non notée pour la production et le rayonnement dont le projet est excellent.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-SCHULTZ**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-SERAPHIN**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-SOUTOGLOU**

Équipe non notée pour la production et le rayonnement dont le projet est excellent.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-SUMARA**

Équipe non notée pour la production et le rayonnement dont le projet est excellent.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-TORA**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-TORRES-PADILLA**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-TROTTIER**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-VERMOT**

Excellente équipe à tous points de vue.

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-VIVILLE**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-WASYLYK**

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

Grading table:

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

❖ Overall assessment of the team : **POURQUIE-YUSUPOV**

Excellente équipe à tous points de vue.

Grading table:

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

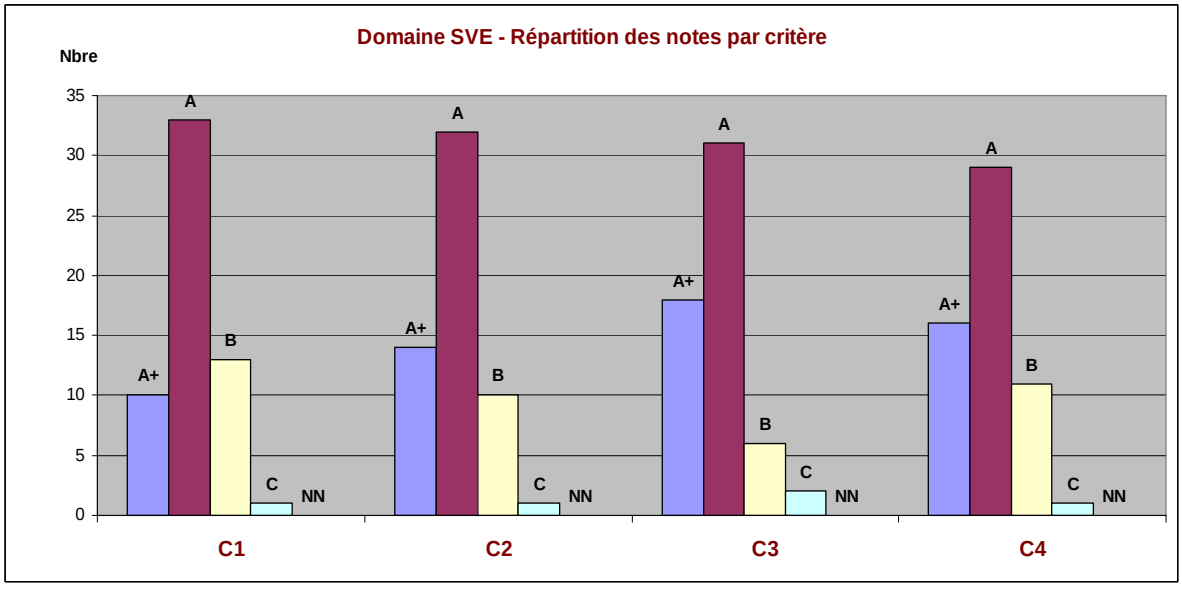
6 ● Statistics per field : **SVE au 10/05/2012**

Notes

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

Pourcentages

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



7 • Supervising bodies' general comments

UNIVERSITÉ DE STRASBOURG

Monsieur Pierre GLORIEUX
Directeur de la Section des Unités de recherche
Agence d'évaluation de la recherche et de
l'enseignement supérieur (AERES)
20 rue Vivienne
75002 PARIS

Alain BERETZ
Président

Strasbourg, le 5 mars 2012

Objet : Rapport d'évaluation de l'UMR 7104, UMR_S 964, UM 41 Institut de génétique et de biologie moléculaire et cellulaire (réf. S2PUR130004533-RT)
Réf. : AB/EW/N° 2012-043

Cher collègue,

Affaire suivie par
Eric WESTHOF
Vice-président Recherche
et formation doctorale
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Direction de la recherche

Je vous remercie pour l'évaluation de l'unité de recherche « Institut de génétique et de biologie moléculaire et cellulaire » (IGBMC – UMR 7104, UMR_S 964, UM 41) dirigée par Monsieur Olivier Pourquié.

Le rapport d'évaluation souligne à juste titre l'excellence de la recherche menée à l'IGBMC et sa place incontestée à la pointe de la recherche internationale. L'analyse produite par le comité d'experts constitue également un outil précieux pour la gouvernance de l'unité de recherche. Les problèmes de gouvernance, déjà identifiés par les tutelles, mais cernés avec justesse et rigueur par les experts du comité de visite, représentent un risque pour l'avenir de l'IGBMC.

Tout en reconnaissant le travail scientifique considérable effectué par Olivier Pourquié, les Président des trois tutelles de l'IGBMC, Alain Fuchs pour le CNRS, André Syrota pour l'INSERM et moi-même se sont vus dans l'obligation de mettre un terme à son mandat de directeur à compter du 1er juin 2012. Une direction provisoire sera mise en place ; elle s'appuiera sur quatre départements scientifiques et sur la structure de gouvernance recommandée par le comité de visite de l'AERES.

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

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

Alain BERETZ

P.J. :

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

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Illkirch, le 28 février 2012

Madame,

En réponse à votre mail du 14 février, veuillez trouver en retour le rapport d'évaluation de l'AERES concernant notre unité avec nos commentaires ainsi que les 2 annexes suivantes :

1 – correction des **erreurs factuelles**

2 - **observations de portée générale**

Nous restons à votre disposition pour tout complément d'information.

Veuillez agréer, Madame, mes salutations respectueuses.

Professeur Olivier POURQUIE

Directeur de l'IGBMC

Professeur Olivier POURQUIE
Directeur de l'IGBMC

Olivier Pourquié
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Rapport de l'AERES sur l'unité : Institut de génétique et de biologie moléculaire et cellulaire – IGBMC – UMR 7104 – UMR_S 964 – UM 41

Observations générales sur le rapport d'évaluation

DEVELOPMENT AND STEM CELLS (DSC) PROGRAMME

Team DSC-1: Single cell Biophysics

Team leader: Gilles CHARVIN

I would like to thank the AERES committee for providing constructing feedback about my research group. Please find below a short reply to some issues that were raised in the evaluation report.

Funding

I make all possible efforts to maintain funding at an acceptable level. In 2011, I applied for a starting grant from Ligue Contre le Cancer (unsuccessful), an ANR grant (coordinator, decision pending), and an ATIP/Avenir grant (decision pending). In addition, I got a starting package as I joined the IGBMC in nov 2010, and one of my postdoc was awarded an ARC fellowship starting February 2012 (3 years).

I will certainly continue to apply for any young investigator grant program in the upcoming years.

Meetings

Please note that I was an invited speaker at a satellite meeting (called "Future approaches in life microscopy") of the EMBL Imaging conference (Seeing is believing, Imaging the processes of life, March 2011).

Team DSC-5: Cellular and molecular mechanisms of nervous system differentiation

Team leader: Angela GIANGRANDE

1.Internal collaborations

I am much in favor of collaborations, which raise from complementary interests and expertise. Collaborations I have/had with people at IGBMC and contributions to the life of the IGBMC:

I Fragile x mental retardation pathway with JL Mandel. Several joint grants (NIH, HFSP), a student from his group stayed in my laboratory for almost two years and I hired a postdoc (EMBO fellowship). Several papers including a very well cited work linking the disease to actin cytoskeleton remodeling. The student, A Schenck, was still included in a 2011 paper.

II I collaborated with the other drosophilist, P Heitzler, which led has to a joint article.

III I share with P Heitzler the fly facility and my group has trained a technician on state of the art transgenic approaches that are now available to the IGBMC and A Hamiche is using this fly service.

IV As I have started working on mice, I sought the collaboration of S Chan. A manuscript will be submitted shortly, which will open the possibility to apply for commun funding.

IV INCA grant with L Tora and A Hamiche on epigenetics. I have also had several grants with other members of the institute over the years.

V I organized the first IGBMC meeting on Development in 2009, together with two other scientists. This fostered interactions with internationally renowed scientists, the integrations of junior scientists in the institute and the establishment of novel collaborations.

VI Last november, I organized a bilateral Franco-Taiwanese symposium on neurobiology as Taiwan seaks to establish a strong partnership. Half of the speakers were from the IGBMC.

VII I have been the promoter of the IGBMC imaging facility since 1992, under the auspices of P Chambon. I have been responsible for the facility until 2009 and applied for many institutional grants together with other IGBMC scientists. This facility is beneficial to all IGBMC members.

2. Hiring a staff scientist

I agree with the comments, I am planning to 'present' a postdoc, upon submission of a first author article, as also recommended by our bureau.

Team DSC-7: Genetic and molecular analysis of early neurogenesis in Drosophila Melanogaster

Team leader: Pascal HEITZLER

I have carefully read the report of the AERES evaluation committee concerning my team. The committee recommends me to actively search for a group to help other scientists in their projects. This conclusion is strongly unfair and is the complete revers of the expected evolution for a scientist that spends nearly 40 years of his life with creative genetics.
I am a geneticist at core, and my culture is to explore development and patterning of the nervous system. It is not anecdotal. My significant contribution were mainly due to original screens and scientific approaches. My work was not limited to fly genetics, since I developped molecular tools as well (Chip, dLMO…). During my carreer, I was willing once, for the boon of IGBMC, to share all these tools with colleagues that has complementary competence in biochemistry.
As often happens with geneticists, as my initial role of 'passeur d'idées' becomes obsolete, collaborators turn into competitors. As I always try to minimize any noise, the remaining reduced Drosophila community imposes me spartan working conditions, including scientific isolation and recurrent sanitary plagues. Unfortunately, as I moved forward with my own team, several accidents happen that considerably delay our progression. For example, we had to rebuild many in house available plasmids, a situation that is fully against the University spirit. I started historically with two assistant technicians that had competence within the fly pushing facility but lack any formation in biology, maybe a fault of mine to have accept such an handicap. We nethertheless did so great job in accurately mutating entire families of microRNAs.
My team is nevertheless not isolated within the institute. I feel well integrated in my department. Even if other department are less prone to use Drosophila as a model, I have contact with colleagues

potentially interested on conserved mechanisms during human haematopoiesis but further hindrances need to be broken for effective collaborations.
Both the enhancer-promoter and the 'neuromirs' projects deserve a new repertoire of competences and I am constantly searching for good postdocs. The present situation (small size) remains transient and several pists are now open.
The statement that I will not diversify my repertoire of methods comes also from lowering rumors. With the dLMO/mirna projects, we will explore more functional aspects of the developping nervous system, including axonal guidance and NMJs, as I have already now a talented PhD student on that topic. More problematic will be the impact of the AERES report, if maintained in its extant version, on my current funding applications.
I was and I am still faithful to IGBMC during all these years. As all core geneticists, I like truth and dignity. The AERES report questions my independence at IGBMC. I will be open for discussion with my direct hierarchy. It will be just a crash, stopping my progression at IGBMC together with my own valuable and original projects as this will just require revisiting extant forces, and obvious regulation for viability and normal atmosphere.

Team DSC-15: Primordial germ cells (PGC) ontogeny and pluripotency

Team leader: Stéphane VIVILLE

It is said that the two proteins Tex19 and SCS2 studied in the laboratory, are of unknown function. This is true for Tex19, but not for SCS2, which, as mentioned during the oral presentation, belong to the large family of deubiquitinase enzymes, the particularity of SCS2 being its specific expression in ES cells and in the testis.
It is said that "the publication output of the laboratory is rather limited" and only 3 papers are mentioned. In fact, 8, including the 3 mentioned above, have been published as peer-reviewed articles in international journals as corresponding author in the considered period out of a total of 23.

It is stated that productivity is "rather limited" considering size of the team, but it should be noted that 3 of the teachers/researchers contribute only part time to research and have significant teaching and clinical responsibilities.
It is acknowledged that "work on human infertility is clearly of social importance" and on another side working on infertile mouse models is considered as "unlikely to have important impact".
I would like to mention my surprise on the fact that the committee considers the research on the human genetics of infertility "as moderately satisfactory". Indeed, so far only mutations in 4 genes have been clearly identified as having consequences in human male infertility and 2 of them have been described by Stéphane Viville's team. Work on additional novel genes involved in infertility was also presented, but was not mentioned in the report.

As mentioned by the committee the PI "has successfully raised funds both nationally and internationally". It is hard to believe that the referees of these financed projects were not convinced by their potential impact. Also there is a contradiction between the comments made at the beginning of the report and those at the end. At the beginning the panel states that 'Stéphane Viville and colleagues have a double Tex19-1/2 mutant, which has a fully penetrant phenotype. Preliminary results point to potentially interesting effects on reprogramming and transposon regulation in primordial germ cells, as well as placental defects'. In contrast at the end, these potentially interesting effects are reduced to 'unlikely to have important impact'. It is difficult to understand why the potentially interesting effects on reprograming and transposon regulation that are suggested by the mouse knockouts are suddenly dismissed as unlikely to have an 'important impact'. The last statement seems to pre-empt results of the analysis that have still to be made. Only once this has been done will it be clear whether or not the results will have an important impact.

FUNCTIONAL GENOMICS AND CANCER (FGC) PROGRAMME

Team FGC-2: Transcriptional regulatory networks and signaling in cancer

Team leader: Irwin DAVIDSON

There seems also to be a misunderstanding in the conclusion section, where the panel has some concerns about the work on the '*melanoma project' focussed around the TRIM proteins and targets and in particular the non-coding RNAs*. In fact, aspects concerning non-coding RNAs do not apply to the melanoma project at all, but concern the hepatocarcinoma projet. There seems to have been some confusion about this that was also evident during the exchange that I had with the panel. To be clear, the major project concerning the TRIM proteins focusses around their role in hepatocellular carcinoma. We also have some preliminary evidence that one of the TRIM proteins may be an interactor of the MITF transcription factor in melanoma.

I take heed of the recommendations of the panel concerning the need to maintain focus and prioritize carefully the projects in order to remain competitive.

Team : FGC-10 Protein Networks and Complexes Regulating Eukaryotic mRNA Decay

Team leader: Bertrand SERAPHIN

- Due to some misunderstanding of the report (partly due to the particular functioning of the French system), some comments do not reflect on the factual group situation.

- The fact that sufficient funding was obtained over the last 10 years to support the activity of an even larger group in the same area appears to have been overlooked.

Others: There is no mention of general activities (ANR, local advising...) nor of funding obtained to support general activities in Gif/Yvette or Illkirch.

Integrated Structural Biology (ISB) Programme

Team : ISB-5 Expression of genetic information

Team leader: Dino MORAS

The proposal that the two senior associates in the existing team should continue their work and co-direct the group in the future (after validation by ad-hoc procedures) is in my opinion independent of the recruitment of a high profile structural biologist in the Department. A high profile internationally recognized scientist, whose appointment is a priority for the department, will likely bring her/his own thematic and will have no reason to take over a research project that has been positively evaluated.

Team : ISB-9 Ribosomes

Team leader: Marat YUSUPOV

"Although the group has good external funding, it remains relatively modest in size. Given the large number of exciting projects, it would appear that some expansion may be beneficial, especially to support the most challenging and therefore long-term projects."

Currently, we have very limited space of the lab.

Team : ISB-7 Action and inhibition studies of pharmaceutical targets

Team leader: Alberto PODJARNY

In general, the AERES report is a good analysis of the past work and current situation for the proposed joint team Podjarny-Ruff.

I would like to clarify the potential for success for Hsp90 project, as according to the AERES report it was not clear enough in the team report and presentations. This is mentioned in the following paragraph:

"The project that benefits mostly from the complementary expertise ofthe two groups (Hsp70/Hsp90) is very challenging, highly risky and competitive. The potential for success of this project was not clear from the report and presentations"

Indeed, the project, which concerns the complexes of Hsp90, mainly with TPR2A, is challenging, risky and competitive.

However, we have several reasons to believe we can do it, as follows:

1) We have a strong collaboration with the group of Lynne Regan, Yale University, USA, who is one of the world leading experts in the subject.

2) Following the work of Lynne Regan, my group has solved the structure of a complex of TPR2A with an Hsp90 peptide.

3) Ruff's group has worked with Hsp90 and also has a strong background in structure determination of protein complexes.

4) We have a strong collaboration with the mass spectrometry lab in Cronenbourg, notably with Sarah Sanglier, who have developed new techniques to detect conformational changes in macromolecules that can be applied to the analysis of the Hsp90 complexes. In fact, the MS lab has already worked in other complexes including Hsp90 (http://www.jbc.org/content/285/41/31304.abstract).

Translational Medicine and Neurogenetics (TMN) programme

Team : TMN-2 Atherosclerosis and thrombosis

Team leader: Jean-Etienne FABRE

I thank very much the committee for its dedicated work. However, there are some points that I wish to clarify.

a) **About integration of our group in the IGBMC**. We in fact do not feel isolated in IGBMC, and in contrary, we have the feeling our integration is improving. First, R.Ricci's recent arrival offered us the opportunity to discuss several collaboration lines. Romeo is interested in p38δ as a key factor in neutrophile migration; we will test this effect in neutrophil invasion of atherosclerotic plaques. In addition, Romeo is studying the impact of PKD1 on obesity-related insulin resistance, a condition which is strongly associated with atherosclerosis. More recently, we and Ricci's teams developed mass-spectrometry based screening of the eicosanoid class of lipids (to which PGE2 belongs to). This approach will allow for a state-of-the art and systematic screen of pro-inflammatory lipids in the context of atherosclerosis. Thus, our research clearly offers possibilities for very successful future interactions, in particular with the team of R. Ricci. Second, our studies both stimulated and benefited from the state-of-art imaging, for example in setting the macroscope device in collaboration with JL Vonesch and D Hentsch. Third, we take part to the IGBMC rich intellectual environment, as for example shown by the ANR obtained through collaboration with Daniel Metzger.

b) **About our poor international visibility and the concern regarding our ability to make a significant impact on the field**: While our total number of publications is not overwhelming (in fact directly due to the size of the team), its impact on the field has been significant. This can be judged in several ways. Our JExMed paper got 50 citations, and triggered some scientific debate between English, German, Japanese and American teams. In addition, the interest raised by this paper led several established teams/companies to seek a collaborative relationship (T Coffman, North Carolina; Lina Obeid, South Carolina; Von Der Muehlen and Von Elverfeldt in Freiburg, K. Peters in Australia and Decode genetics in Iceland). Furthermore, this is really the time when we are reaping the fruits of our early work: we have currently four papers almost finished, written or submitted. One of them has been reviewed by Nature Medicine and we currently revise it. Finally, the recent increase in our funding will allow us to recruit more people, included a post-doc, and to increase our team size. For all these reasons, we firmly think we can impact the field of atherothrombosis, and we will.

c) **About the recommendation to establish clinical collaborations to valorise their expertise in atherothrombosis**": in fact, we currently have a clinical collaboration running at "hôpital civil" in Strasbourg set up to evaluate the impact of PGE2 in human pathology. Therefore, we already took this direction and we will strengthen it.

In conclusion, our team is becoming a force in the IGBMC. This results from its unique position in the IGBMC where it benefits from the exceptional environment, and where it develops pathophysiological studies that bridge basic knowledge to the patient and impact the field of atherothrombosis.

Team : TMN-10 Pathogenic Mechanisms of Polyglutamine Expansion Diseases

Team leader: Yvon TROTTIER

We would like to thank the AERES committee for recognizing the quality and originality of the work accomplished by the team during the past 4 years and for acknowledging the international impact of our findings.

The novelty and feasibility of our screening project have been already acknowledged by our industrial partner. The team is proud to develop one of IGBMC translational medicine projects. We believe that several misunderstandings are at the basis of the criticism regarding novelty and feasibility in the AERES report.

1) The comity has overlooked that we developed the first screen to look at selected combinations of compounds that could act synergistically to prevent the formation of toxic aggregates. Beneficial effects generated through compounds synergy would directly translate in a diminution of drug dosage in patients. Although intuitive, combinatorial approach to block aggregation has never been developed for amyloid diseases.
2) It is wrong to state that our in vitro "assay is not well developed". Our pilot assay has been presented to the AERES comity and acknowledged by collaboration with an industrial partner. The assay is fully set-up and has reached statistical scores Z'>0.9 before automation, meaning robust reproducibility.
3) It is inexact to say that "support for high-throuput screening is limited". Our assay is at the automation phase at the screening platform PCBIS (http://www.pcbis.fr/).

Concerning the retinal studies, we hardly understand the argument that they "may have limited relevance, in that the importance of neurogenesis in the disease mechanism is not yet substantiated". The rationale to study adult retinal neurogenesis in our disease model is double; on a fundamental point of view, neurogenesis in mammalian retina is largely unknown, and our SCA7 retina model provides a unique opportunity to characterize the phenomenon; on a disease point of view it is important to understand the role of neurogenesis in the progression of the disease, as it may represent a potential therapeutic target for diseases which have to date no treatment.

It is also surprising to read the false statement that the team "has not recruited from abroad" since one Russian post-doct and three PhD students from Libanon and Greece have provided major contributions to our studies.

In conclusion, we already fulfilled AERES recommendation to validate the assay of our screening strategy. The validation has been presented to the comity and we are currently testing compounds developed by our industrial partner. We believe, and so does our industrial partner, in this approach using the strength of compound synergy to develop solutions to amyloid-like aggregates in neurodegenerative diseases.

Microarray and Deep Sequencing

Leader: Christelle THIBAULT-CARPENTIER

We would like to qualify several statements of the report:
1. There is, however, an almost complete absence of pricing and cost/benefit numbers in comparison to other centers or outside services: Cost efficiency has been a priority for the platform since its creation, and has notably been a constant improvement goal closely monitored within the ISO2001 procedures. Prices are publicly available on the platform's website and attractiveness of the platform is attested by its success in winning several open calls for tender for large projects, as recently as 2011. Prices for sequencing will be significantly lower in the future as in December 2012, we acquired our new generation HiSeq2000 machine. In addition, the integration of our platform into the French national 'France Génomique' network means that our pricing will be competitive with the other national platforms. Microarray prices are strongly competitive as compared to other national platforms.
2. The platform is slow in updating the present Illumina equipment: This is true, but the slowness reflects the administrative delay in receiving the funds for new equipment. We applied for national infrastructure funding in october of 2010 and at the time of writing (February 2012) funds have still not arrived. Nevertheless, other sources of funding have allowed us to advance and acquire a HiSeq 2000 in December 2012.
3. Data storage has not been addressed properly: The platform equipped itself in 2011 with a new server with 96 cores, a RAID storage capacity of 65TB and a backup disk capacity of 96TB. Thus, data storage should not be an issue in the foreseeable future. Moreover, this is a flexible system that allows addition of further storage discs.