Identité cellulaire et réponse au stress dans la physiologie et la pathologie du système digestif

Rapport Hcéres

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

Section des Unités de recherche

AERES report on unit:

Cell Identity and Stress Response in Physiology and Pathology of the Digestive System

Under the supervision of :

University of Strasbourg

INSERM

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et de l'enseignement supérieur

Section des Unités de recherche

Le Président de l'AERES

Didier Houssin

Section des Unités de recherche

Le Directeur

Pierre Glaudes

Unit

Name of unit:	Cell Identity and Stress Response in Physiology and Pathology of the Digestive System
Acronym of unit:	D.CISiPh
Label requested:	UMR_S
Present no.:	UMR_S682
Name of Director (2009-2012):	Ms Michèle KEDINGER
Name of project leader (2013-2017):	Mr Jean-Noël FREUND

Members of the committee of experts

Chair:	Mr Claude SARDET, Montpellier
Experts:	Mr Juan IOVANNA, Marseille
	Mr Maarten VAN LOHUIZEN, Amsterdam, The Netherlands
	Mr David TOSH, Bath, United Kingdom
	Mr Klas WIMAN, Stockholm, Sweden
	Mr Pierre VIERLING, Nice
	Ms Nadine CERF-BENSUSSAN, Paris (representative of INSERM)
	Mr Albert TRAN, Nice (representative of CNU)

Representatives present during the visit

Scientific Delegate representing AERES:

Mr Jean ROSENBAUM

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

Mr Eric WESTHOF, University of Strasbourg

Ms Marie-Josèphe LEROY-ZAMIA, INSERM

Report

1 • Introduction

Date and conduct of visit:

The review took place on January 10th 2012 at the present site of implantation of the unit (Inserm Building, Hautepierre hospital, Strasbourg). Oral presentations describing past and future research programs of the unit were made by the proposed director (Mr Jean-Noël Freund) and by the 2 team leaders participating in the new project. The visiting committee also met separately (in the absence of the direction/team leaders), with the technical staff, researchers with permanent positions, non-permanent lab members (Students, Post-docs) and the representatives of institutional authorities (Strasbourg University, Medical Faculty and Inserm). All members of the committee were present from the beginning to the end of this visit and have participated to the final discussion on the report that took place at the end of the visit. They have also returned independently their argued comments to the chairman.

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

The project proposed by Mr Freund is named "Cell Identity and Stress Response in Physiology and Pathology of the Digestive System". It comprises a team of the present U682 and a new incoming team that was constituted only a few months ago (September 2011).

Team 1- "Intestinal identity, from stem cells to pathology" (resp. Mr Freund). This team was part of Inserm Unit 682 (Strasbourg) during the 2007-2011 period and was entitled "Homeotic transcription factors of the Cdx family in the development and pathology of the digestive and hematopoietic systems". It currently involves 14 people (7 permanent staff-1 DR1, 3 CR1, 1 PUPH, 2 ITA).

Team 2 "Molecular mechanism of the stress response and pathology of the digestive system" (resp. Mr Christian Gaiddon). This team results from the fusion of the group "Mechanisms of cell death with a focus on the p53 family" hosted by Inserm Unit 692 (Strasbourg) during the 2007-2011 period, with a former member of the team "Control of endocrine cell differentiation in the pancreas and intestine" from Inserm U 596 (IGBMC, Strasbourg). In addition, they have been joined very recently by an engineer who was previously working on a local proteomics platform. This new team has moved to Team 1 location (U682, Inserm building, Strasbourg) in September 2011. It currently involves 7 people (3 permanent staff – 1DR2, 1 CR1, 1 ITA).

The proposed Inserm unit will be located in the Inserm building currently occupied by Inserm U682 on the site of the University Hospital (CHU) of Strasbourg-Hautepierre. The proposed allocated space is 1211 m2. .

Of note, additional projects have been proposed to Inserm by other teams of the current U682. In agreement with Mr Freund's project, these other projects propose to be hosted in the same building and to continue to share the current facilities of U682 (administration, animal house…).

Management team:

The proposed director of this unit (JN Freund) is currently the PI of one of the U682 teams. He is a man of energy and drive, and a productive and imaginative scientist. He has a strong expertise in team management and has been involved in the very time-consuming National Committees of Inserm and in several local scientific councils (University, Ligue Contre le Cancer…). He has the support of team members. Overall, the staff involved in this project shows enthusiasm and cohesion at all levels (researchers, ITA and students). Moreover, it should be stressed that members of Team 1 and 2 have already collaborated (co-signature of scientific publications) for several years. Thus, there should be no major management problem.

Unit workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1 (0.1 FTE)	1 (0.1 FTE)	1 (0.1 FTE)
N2: EPST or EPIC researchers	4+1+1	6	6
N3: Other professors and researchers	-	-	-
N4: Engineers, technicians and administrative staff ***on a permanent position****	6 (4.6 FTE)	6 (4.9 FTE)	
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	5+2		
N8: PhD defended	6+2+1		
N9: Number of Habilitations to Direct Research (HDR) defended	3		
N10: People habilitated to direct research or similar	5+1+1	7	
TOTAL N1 to N7	**24 (21.7 FTE)**	**13 (11 FTE)**	**7 (6.1 FTE)**

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

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

*** This table includes the technical staff (1 IE Inserm), who joined Team 2 and was not mentioned in the unit's application 2.5 form submitted to AERES. Three people are not directly affected to a Team since they are working on common facilities shared with another unit, explaining why the total numbers of technical staff in Team 1 + Team 2 does not equal 6.

2 • Assessment of the unit

Overall opinion on the unit:

The overall aim of the proposed Unit is to explore the role of transcription factors and pathways (focusing on Cdx and p53 families, Ngn3, Wnt..) regulating cell identity and cell stress in the development, homeostasis and diseases (cancer, inflammatory diseases) of the digestive system.

The research performed by team 1 on the physiological roles of CDX factors in the normal gut and in digestive diseases is of very good quality. They have developped a very valuable know-how on these issues, notably through the generation of original and pertinent animal models. Their work has been published over the past years in international journals ranging from good to very good (Gastroenterology, Gut, Dev. Cell etc…) and all projects have been financed by grants.

Team 2 is a new team having only formed a few months prior to the review. The academic work performed by its members on the transcription factors Ngn3 and p53 is of good quality and has been published over the past years in international journals ranging from good (Development, Cell Death & diff., JBC, etc..) to very good (JCI). All projects have been financed by grants.

The scientific projects that are proposed on these factors (see evaluation team by team for details) are coherent with and in the continuity of the previous work published by these two teams with, in the case of team 2, a clear refocusing on the general theme of the unit, i.e. intestinal development and carcinogenesis. Team 1's projects also show a global move to clinically relevant questions. Competences and techniques required for the new projects are already largely mastered in the lab, or through ongoing and pertinent local and international collaborations. Notably, all projects of Team 1 and a large fraction of Team 2's projects are based on a very valuable know-how on the development of animal models to study the mammalian digestive system. Therefore, with a single exception (see below), there is a strong coherence in the overall scientific project and decision to merge.

Indeed, Team 2 is also developing a sub-project on chemotherapeutic drugs that is, at this stage, distinct from this overall aim and unity. It aims at developing an original collection of ruthenium-based compounds with anti-tumor activity (publications and patents on this subject). This ongoing program involves close collaborations with local and foreign chemistry labs and with a small biotech (Almetis) recently launched by Team 2 leader. This translational project opens multiple opportunities and is seen as an asset for the new unit, provided that it meets at some point the overall theme and models of the unit, i.e. cancers and homeostasis of the digestive system.

Although the overall scientific content of the project appears very good, it also appears as a program in transition that needs to be more focused. Some of the sub-projects were judged as excellent and highly feasible, although a few others (Team 2) clearly require rapid adjustment, as detailed below in the team by team evaluation. Some thought should be given to the limited personnel resources available and to the effort which will be required to advance each of the numerous individual projects in a competitive manner (notably in fields that are outrageously competitive, such as on p53 family or chemotherapeutics). The visiting committee encourages team leaders to define collectively clear priorities for the unit and to focus strength and funds, at least at the beginning, on a more limited number of projects.

Strengths and opportunities:

1. The proposed director of this unit (Mr Freund) is a man of energy and drive. The two team leaders are productive and imaginative scientists. Enthusiasm and cohesion of the team members at all levels (researchers, ITA and students). Although collaborative projects between Team 1 and Team 2 still need maturation, there is clearly a will to work together with excellent perspective of cross-fertilizing interactions on projects dealing with intestinal development and diseases.

2. Both Team 1 and 2 have developed very valuable expertise in their field. Team 1 has a long-standing track record on the role of intestinal CDXs factors and very valuable know-how and international collaborations on these issues, notably through the generation of original and pertinent animal models. Team 2 has a good track record on p53-dependent stress and Ngn3-dependent developmental pathways and more recently on organometallic compounds with anti-cancer properties.

3. The scientific production is very good. Team members have delivered constant high quality results in their field. Their work was published over the past years in international journals ranging from good to very good (participation to 51 publications in peer-reviewed journals since 2007, including 23 as senior/corresponding authors in JBC, CDD, NAR, Cancer Res. JCI, Gastroenterology, Gut, Development, Oncogene etc...).

4. Team 2 has a valuable activity of valorisation (patents & creation of a biotech company) and good connections with chemistry labs. This is a potential asset for the unit.

5. All projects have been well funded by national and international grants or by industrial contracts. This shows good ability to raise funds through competitive grant applications.

6. Good track record in training PhD students. 9 PhD students have obtained their PhD degree under the supervision of a Team 1 or 2 members since 2007. 7 others are currently trained. They were/are all fully supported by fellowships.

7. The new project of Team 1 is in the continuity of the previous work, based on solid preliminary data, interesting and original animal models, and fruitful ongoing collaborations. It has clear cognitive and possible therapeutic impacts in the fields of gut development, homeostasis and pathologies as well as concerning the identification of potential therapeutic targets. It shows a global move to clinically relevant questions. Although the scientific content of Team 2 project appears also very good, it is a new program in transition that needs to be more focused (see below and evaluation team by team).

8. Competences, techniques and facilities required for the new projects are already largely mastered in the lab, or through ongoing and pertinent local and international collaborations. Good connections with several high-profile technical facilities available in Strasbourg.

9.There is a long-term project to create a large cancer research center on the same campus. This should open multiple opportunities for collaborations and improved the international visibility of the teams involved in this project.

Weaknesses and risks and recommendations:

1. Some thought should be given to the limited personnel resources available and to the effort which will be required to advance each of the numerous individual projects in a competitive manner (notably in fields that are outrageously competitive, such as on p53 family, stem cells or chemotherapeutics). Regarding Team 2, this period of change and fusion should be taken as an opportunity to focus on the strengths of the group and matching these to unmet needs in the field. The committee encourages team leaders to define collectively clear priorities for the unit and to focus strength and funds, at least at the beginning, on a more limited number of projects. Detailed recommendations are given in the team by team evaluation part.

2. Projects on ruthenium-based anticancer compounds are original and have obvious potential for industrial development but face challenges to clarifying what has to be done by the spin-out company, by academic collaborators, and by the team itself with its limited workforce.

3. Although their science is very good, unit members, as a whole, lack publications in very high impact multidisciplinary journals and the invitations to international conferences and participations to international networks do not match the excellent quality of their work. This is clearly detrimental to the visibility and attractiveness of the unit and could easily be improved by appropriate and collectively organized communication. This should also provide the opportunity to attract self-funded post-doctoral fellows.

4. Although all projects have been financed by grants in the past, the new proposal promises to be very expensive (numerous animal models, stem cells culture etc…) and will require additional funding that have not yet been obtained through new grants. This could become, at least transiently, a potential area of weakness. This point needs to be addressed.

5. The large number of mouse strains with complex genotypes that will be required to achieve the projects might be difficult to handle in parallel without identifying priorities and without a greater support in terms of animal husbandry.

6. The external teaching commitment of unit members is modest. Given the close proximity of the University of Strasbourg, the good contacts with its representatives, the excellent track record of the teams in the training of their PhDs, and the global move to clinically relevant questions, there is room for greater interaction with undergraduate students (medical and scientific students) and with teaching communities (notably to attract MCU and PUPH) in the future.

7. The close link with clinicians is still loose (1PUPH in the unit for 10% of its time). The global move to clinically relevant questions will require reinforcing the clinical partnership and expertise through the recruitment of additional PU/MCU-PH. Ongoing efforts in this direction already exist and should be encouraged by the Medical Faculty.

3 • Detailed assessments

Assessment of scientific quality and production:

Both Team 1 and 2 have developed very valuable expertise in their field.

Team 1 has a long-standing track record on the role of intestinal CDXs factors and very valuable know-how, international collaborations and recognition on these issues, notably through the generation of original and pertinent animal models. Their work has been published over the past years in international journals ranging from good to very good (Gastroenterology, Gut, Dev. Cell etc…).

Team 2 is a new team having only formed a few months prior to the review. The academic work performed by its members on p53-dependent stress and Ngn3-dependent developmental pathways the is of good quality and has been published over the past years in international journals ranging from good (Development, Cell Death & diff., JBC, etc..) to very good (JCI). This team 2 has also a good and more recent track record on organometallic compounds with anti-cancer properties. This resulted in valuable activity of valorisation (patents & creation of a biotech company) and good connections with chemistry labs. This is a potential asset for the unit.

Altogether their scientific production is very good and resulted in 51 publications in peer-reviewed journals since 2007, including 23 as senior/corresponding authors in JBC, CDD, NAR, Cancer Res. JCI, Gastroenterology, Gut, Development, Oncogene etc....

All previous projects of Team 1 and 2 have been well financed by national and international grants or by industrial contracts. This shows good ability to raise funds through competitive grant applications.

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

There are invitations to international conferences and participation to numerous collaborations at the national and international levels. However there are also few invitations to high-profile conferences and participation to funded international networks. This record does not match the excellent quality of the work and is clearly detrimental to the visibility and attractiveness of the unit. This could easily be improved by appropriate and collectively organized communication.

Assessment of the unit's governance and life:

The proposed director of this unit (Mr Freund) has the support of team members. Overall, the staffs involved in this project show enthusiasm and cohesion at all levels (researchers, ITA and students). Moreover, it should be stressed that members of Team 1 and 2 have already collaborated (co-signature of scientific publications) for several years. Moreover, the new projects proposed by Team 1 and Team 2 clearly indicate a will to work together with excellent perspective of cross-fertilizing interactions on projects dealing with intestinal development and diseases.

Thus, there should be no major management problem.

The day-to-day organisation of the new unit seems to be good and appropriate. Indeed, the research unit will organise weekly lab meetings including all the staff, journal clubs, and annual meetings to follow the progress of the PhD student's research. These meetings are mainly intended to foster in-house communication, to take decisions concerning the organisation and life of the lab, and to build interactions between the teams.

Assessment of the strategy and 5-year project:

Overall the strategy and 5-year project plan appear largely built on their previous and successful track record. A proportion of their projects represents the natural progression and translation of this previous work whilst some are new. Although the overall scientific content of the project appears very good, it also appears as a program in transition that needs to be more focused. Some of the sub-projects were judged as excellent and highly feasible, although a few others clearly require rapid adjustment, as detailed below in the team by team evaluation. Some thought should be given to the limited personnel resources available and to the effort, which will be required to advance each of the numerous individual projects in a competitive manner (notably in fields that are outrageously competitive, such as on p53 family or chemotherapeutics). The visiting

committee encourages team leaders to define collectively clear priorities for the unit and to focus strength and funds, at least at the beginning, on a more limited number of projects.

Assessment of the unit's involvement in training:

Apart the PUPH, whose duty is statutorily devoted to teaching, 4 of the 6 full time researchers contribute to teaching at Universities at the Licence and Master (M) levels. 7 M, 2 DUT and 7 BTS students have been hosted in the teams during the 2007-11 period.

Good track record in training PhD students. 9 PhD students have obtained their PhD degree under the supervision of a Team 1 or 2 members since 2007. 7 others are currently trained. They were/are all fully supported by fellowships. Of the 9 PhD fellows who graduated, 5 are persuing post-doctoral studies in France and abroad, 3 are assistant-professors abroad and 1 is professor in Bordeaux.

4 • Team-by-team analysis

Team 1: Intestinal Identity, from Stem Cell to Pathology

Team leader: Mr Jean-Noël FREUND

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1 (0.1 FTE)	1 (0.1 FTE)	1 (0.1 FTE)
N2: EPST or EPIC researchers	4	4	4
N3: Other professors and researchers	1 (0.2 FTE)	0	0
N4: Engineers, technicians and administrative staff * on a permanent position	3 (2.7 FTE)	2 (2 FTE)	
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	6		
N8: PhD defended	6		
N9: Number of Habilitations to Direct Research (HDR) defended	3		
N10: People habilitated to direct research or similar	5	5	
TOTAL N1 to N7	**16 (14 FTE)**	**7 (6.1 FTE)**	**5 (4.1 FTE)**

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

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:
http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

This team has a long standing track record on the role of intestinal Hox genes CDX1 and CDX2 in intestinal physiology, intestinal development, stem cells and pathologies of the digestive system (cancer, inflammatory diseases). They have developed a very valuable know-how on these issues, notably through the generation of original and pertinent animal models.

They made several original contributions in this field that were among the first to really dissect the role of CDX2 in intestinal development and to prove its key role in intestinal identity. Notably, their recent publications point at: 1/ the role of CDX factors in the maintenance and functional identity of the adult intestinal stem cells; 2/ the existence of multiple regulations (transcriptional, splicing, post-translational) of CDX2 activities in normal gut that could be altered in digestive diseases; 3/ they also reveal that CDX2 activity is multifaceted and relies not only on its transcriptional activity, but also on an unexpected network of protein-protein interactions that link this factor to the beta catenin oncogenic pathway and to DNA repair; 4/ surprisingly, they also discovered that CDX2 hinders cell migration and impacts on dissemination of colorectal cancer (CRC) cells, again suggesting an important role for CDX factors in tumorigenesis. Overall, all these studies have been conducted in a logical and coherent way, bringing new lights on the in vivo functions of the CDX pathways in normal and pathophysiological situations.

This recognized expertise and the original reagents developed on CDXs also led to strong international collaborations (Italy, UK, the Netherlands, Portugal etc…) that resulted in participation to a number of high-ranking papers (Development Cell, Gut, Gastroenterology, Development). These fruitful collaborations, as well as the quotation of their work in recent reviews, confirm that the team has a recognized leadership on CDX2 in gut biology. Altogether, the publication record is very good (quality and quantity) with regard to the number of workers in this team. All scientists of this unit are producers. The committee was pleased to observe that junior members (CR) of this team are corresponding /last authors on two of the recent publications of the lab, showing that the team leader encourages his permanent staff to develop their own sub-projects on CDX and rewards these efforts.

Altogether, the members of this team have published 39 articles (among which 1 review) and 2 book chapters over the last five years (01/2007-2011), of which 19 include a team member as a first and/or senior author. Most of those have been published in the top ranked specialized journals dealing with cancer and gastroenterology studies (including, 3 in Gastroenterology (IF=11.7), 4 in Gut (IF=10), 1 Am J Gastroenterol (IF= 6.9), 1 Am J Pathol (IF=5.5), 1 J. Pathol (IF=5.4), 2 in Clin Gastroenterol Hepatol (IF=6.2), 1 Cancer Res (IF=7.5), 2 in Oncogene (IF=6.4), 1 Biomaterial (IF=7.9)), as well as in scientific journals with a large audience (including, Development Cell (IF=12.7), 3 in Nucleic Acids Res (IF=7.0), 2 in Development (IF=6.9), 2 in J Biol Chem (IF=5.6), 2 in Cell Death Diff (IF=8.9)). Of note, The PU-PH that participates to Team1's project has also contributed (co-author) to one article in The Lancet (IF=30.8). 6 PhD students have graduated on this work.

Although this record of publications should be considered as excellent, the committee has identified two points that could be improved. First, the high impact factors (>10) articles published as first/last authors are in specialized journals (Gastroenterology, Gut). Considering the very good quality of their results, the team as a whole is encouraged to try to publish in more general higher impact journals. Second, there are limited numbers of reviews (regarded as an indicator of international expertise). This could be easily improved regarding the recognized know-how of the team on CDXs and the wide audience of reviews addressing the roles of developmental factors in human diseases.

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

Team1 has been very successful in raising French grants (14) from governmental (2 INCa, 3 University of Strasbourg, 2 Canceropole) as well as from non-governmental cancer agencies (3 Ligue Contre le Cancer, 4 ARC). The group has also raised funds from foreign agencies for a total amount of 200 k€ (AICR (UK), Fundaçao para a Cienca (Portugal), and AFR (Luxembourg)). Although the group must be commended for their efforts in obtaining all these small grants that provide very valuable additional funding to the unit (this effort should be pursued), the committee encourages the team to apply for larger French and international grants (on a collaborative basis) to obtain greater return for their effort. This is a very timely issue since the financial support is guaranteed for 2012 but not yet for the following years.

Although it is clear that at this stage the fundamental subjects developed by the team does not justify an active strategy of valorisation (no patent), they have developed good relations with a private company (Normoxys) and obtained a research contract (144 k€). Nonetheless, Team 1 investment in detecting cdx2 levels and activities in human diseases (CRC, Barrett syndrome…) might result in the future in medical valorisation (diagnostic, prognostic). However, this still requires additional studies that should be considered as one of the objectives of the next five years project.

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

The team has been very attractive for students. The number of masters (numerous) and PhD students that are currently trained (6) or that have already defended their PhD over the last four years (6) is very good regarding French standards and the size of the team. Although the recruitment of students appears to be mostly local, some are/were non-French and self-funded. This effort to attract foreign students should be pursued and amplified. Regarding PhD & master students present in the unit during the visit, it is worth commenting on their quality and commitment. The team as a whole is to be congratulated in developing an enthusiastic group of students who are clearly strongly committed to research and who value the training experience immensely. They spoke universally about the high quality and enthusiasm of the supervisors in the unit. The committee suggests that team members should increase their participation to undergraduate teaching duties and to the organization of the doctoral school.

Compared to students, the number of post-doctoral fellows (1 during the 2007-2011 period, none at present) is far too low fur such productive team. The team should improve its external communication and greater emphasis should be placed on individuals obtaining independent post-doctoral fellowships (ARC, Ligue contre le Cancer, FRM, Marie Curie, ERC, others). Of note, one full-time CR1 INSERM researcher, who had a post-doc position in the team, has been recruited in 2007.

Although the team leader and the PU-PH associated with the group have been invited to several meetings, it was not to high profile international conferences. With appropriate communication, the review committee believes that the cutting-edge questions that are currently addressed in the project should provide the opportunity to improve the participation at such high profile meetings, and therefore, improve the international communication of the team. The team leader has been awarded in 2008 by AICR.

Nonetheless, this unique and recognized expertise in CDXs in gut has resulted in several fruitful academic collaborations (collaborative papers in Development Cell, Gut, Gastroenterology, Development), both at a national and international level (Italy, UK, the Netherlands, Portugal etc…). However, the committee encourages the team to participate to organized european/international networks to obtain more return for these collaborative efforts (access to EEC fundings).

Assessment of the strategy and 5-year project:

The team to be created involves all the permanent staff that is currently associated with Mr Freund's team within the present Inserm unit 682. Most of the scientific projects that are proposed are coherent with and in the continuity of the previous and ongoing research works (see supra).

The group foresees three main lines of research:

1. they propose to pursue the exploration of novel CDX2 interactors, regulators and target genes that they have identified, focusing on their roles in CDX2-dependent biological functions, animal models and associated pathologies (see below).

2. they propose a very ambitious phenotypic and pathophysiological characterization of several original and very pertinent animal models that address the impact/role of CDX2 in digestive diseases (CRC, inflammatory diseases, oesophageal metaplasia / Barrett's), leukemia, organ development/renewal (intestine and stomach) and stem cells behaviour.

3. The team leader has initiated two other new projects that are not directly linked to CDX factors as they aim at exploring, in vivo, the notion of stem cells asymmetrical division in mouse gut and its potential alteration(s) in tumor-prone animals.

Regarding CDX2 projects, most of the animal models have already been developed in the lab so the group can hit the ground running. Competences and techniques are largely mastered and the team already benefits from the large panel of technical platforms available in Strasbourg. Moreover, pertinent local and international collaborations have already been initiated on these projects, including with a PU-PH from Caen (France) with strong clinical expertise on inflammatory bowel diseases. Of note, this PU-PH is willing to join the unit during the next mandate. The committee encourages this global move to clinically relevant questions that opens new opportunities to develop intellectual property, fruitful medical/clinical collaborations, and importantly, additional opportunities of funding. Altogether, these assets suggest a good feasibility for these CDX-related projects.

However, the review committee recommends that priorities be identified and that the number of sub-projects be transiently reduced to make timely headway on subjects that have the best chance to be considered as milestones and to be published in high-profile journals. Along the same line, the large number of mouse strains with complex genotypes that will be required to achieve each of these ambitious sub-projects might be difficult to handle in parallel without identifying priorities and without a greater support in terms of animal husbandry. Finally, the field of intestinal stem cells/progenitors is extremely competitive and therefore projects should be more carefully considered in terms of planning, workforce and questions to be addressed. The visiting committee recommends to focus on CDX2 in stem cell differentiation, which provides a 'niche' for this team in this competition.

Conclusion:

- *Overall opinion on the team:*

The research performed by this team on the physiological roles of CDX factors in the normal gut and in digestive diseases is of very good quality. It has been published over the past years in international journals ranging from good to very good and all projects have been financed by grants. Many original animal models have been developped in this lab so the group can now hit the ground running. Competences and techniques required for the new projects are already largely mastered in the laboratory, or through ongoing and pertinent local and international collaborations. Overall, they are coherent, logical, and should provide new insights into the mode of action and biological functions of CDX factors and address their role in gut cancers and inflammatory diseases. These projects indicate a global move to clinically relevant questions that fit with the missions of Inserm. However, choices may have to be done to focus on a more limited number of sub-projects to make timely headway on the most promising subjects.

- *Strengths and opportunities:*

1. A dynamic team headed by a solid and imaginative group leader with long standing track record on the role of intestinal Hox genes CDXs in intestinal physiology, intestinal development, stem cells and pathologies of the digestive system (cancer, inflammatory diseases). Very valuable know-how and international collaborations on these issues, notably through the generation of original and pertinent animal and cellular models.

2. They have delivered constant high quality results in their field. This work was published over the past years in international journals ranging from good to very good (best of their speciality) and all projects have been financed by grants.

3. The new project is in the continuity of the previous work, based on solid preliminary data, interesting and original animal models, and fruitful ongoing collaborations. It has clear cognitive and possible therapeutic impacts in the fields of gut development, homeostasis and pathologies as well as concerning the identification of potential therapeutic targets. It shows a global move to clinically relevant questions that fit with the missions of Inserm.

4. Dynamism of the leader and enthusiasm and cohesion of the team members at all levels (researchers, ITA and students).

- *Weaknesses, risks & recommendations:*

1.Although the record of publications is very good and the team should be considered as very productive, the high impact factors (>10) articles published as first/last authors are in specialized journals (Gastroenterology, Gut). The visiting committee recommends to also targeting more general high impact journals. Of note, ongoing efforts in this direction already exist and should be continued. Such publications in top-journals will certainly require focusing future efforts on a more limited number of projects.

2.Although the research achievements of the team are well known by academic scientists, the presence of team members on the international scene (meetings, conferences, reviews) does not fit this excellent know-how and therefore, could be easily improved. The visiting committee encourages team members to develop a more ambitious approach for their international communication (meeting co-organization, writing of reviews, participation to international networks, invitations of high profile scientists to give talks in the unit, etc..).

3.The number of post-doctoral fellows is far too low for such productive team. Greater emphasis should be placed on individuals obtaining independent post-doctoral fellowships. Again, this will require improving external communication.

4.The global move to clinically relevant questions will require to re-inforce the clinical partnership and expertise, either thru the recruitment of additional PU/MCU-PH (ongoing) or thru supervision of medical students in the lab (M2, PhD). Again, ongoing efforts in this direction already exist and should be continued with the help of the medical faculty and of hospital. Notably, this could fit the need to strenghten the capacities in the field of immunology in relation with chronic inflammation and cancer

5.The large number of mouse strains with complex genotypes that will be required to achieve the projects might be difficult to handle in parallele without identifying priorities and without a greater support in terms of animal husbandry.

6.Finaly, part of the future project aims at exploring stem cells behaviours in vivo and their role(s) in development and diseases. This theme of stem cells is highly competitive and requires a critical mass of investigators per subject that might be difficult to obtain on all the aspects of the proposed projects. The visiting committee recommends to focus on CDX2 in stem cells differentiation which provides an interesting ‘niche’ for this team in this competition.

Team 2: Molecular mechanisms of the stress response and pathology of the digestive system

Team leader: Mr Christian GAIDDON

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	1 [1 FTE]	
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	2	2	
TOTAL N1 to N7	**7**	**3**	**2**

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

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

*** This table includes the technical staff who joined team 2 and was not mentioned in the unit's application 2.5 form submitted to AERES

• Detailed assessments

Assessment of scientific quality and production:

This is a new team having only formed a few months (September 2011) prior to the review. This proposed Team 2 is a fusion of a senior CR1 Inserm coming from IGBMC (Strasbourg) with a former sub-group of Inserm U692 (Strasbourg) headed by a DR2 CNRS and composed of 4 graduate students. They have been very recently joined by an engineer who was previously working on a local proteomics platform. All are producers.

In his previous lab (U692), the group of the team leader has developed two main projects:

1/ the role of the p53 protein family and of its regulators in neurodegenerative processes. They made original contributions on the role of p53 family in the response of neurons to neurotoxic stresses (including to anticancer drugs) and in the cell death occuring during Alzheimer disease.

2/ This interest for anticancer drugs and their stress response led him to develop a second project in collaboration with chemists (from CNRS Strasbourg, Mexico and Trieste) aiming at exploring the potential of an original collection of organometallic ruthenium-based complexes as new anticancer drugs. Using cellular and animal models, they have established these drugs are active on cisplatin-resistant cancer cells, through mechanisms that are still not fully understood but that could involved stress response signaling pathways linked to alteration of cellular energy metabolism. Ongoing studies also suggest these compounds could be less toxic for healthy organs than organometallic platinum compounds. Based on these promising observations, they recently launched a spin-out company (Almetis, 1 employee) for developing these derivatives at a pre-industrial level. This new company has recently won the National Award OSEO but is still at the very early stage of its development and is not yet ready to support expensive developments and preclinical studies.

Between 2007 and 2011, their academic work on these subjects led to 11 original articles in good journals of biology or chemistry, including 4 as senior/corresponding author [2 in Cell death & diff (IF=8.5), Cancer research (IF=7.5) and J Biol Chem (IF=5.3)]. Of note, the scientist who has recently joined the team is associated with the work published in this J Biol Chem article in 2011. This work also led to two patents on novel neuroprotective agents and on the use of the ruthenium-based compounds to target cancer. Finally, it led to 3 PhD defences. Altogether the record of production (publications + patents + spin-out) should be considered as good with regard to the small size of the group and time that was devoted to create a private company. However, this production also shows a lack of focus and suggests that priorities have not been clearly identified during the past four years. The move to this new Inserm unit is an unique opportunity to identify such priorities and to synergize efforts with Team 1 on “digestive” themes.

3/ The second senior scientist has worked on a third project, unrelated with those described op.cit. In his former lab (IGBMC), he has been instrumental in the development of animal models (KO & KI Mouse and zebrafish) to explore the role of the transcription factor neurogenin (Ngn3) in the normal development of enteroendocrine and pancreatic endocrine cells, as well as in enteroendocrine cell dygenesis. This very elegant work also led to the identification of a novel transcription cascade, involving Ngn3 and Rfx6, required for pancreatic islet cell development. Altogether, between 2008 and 2011, this scientist has published 6 original articles, 1 review and 1 book chapter, including two as first and/or co-corresponding author in JCI (IF=14.2) and Development (IF= 6.9). He was also co-author of 2 excellent articles derived from international collaborations on pancreas progenitor cells and Tuft cells, published in Cell (IF 29.9) and J Cell Biol (IF 9.9), respectively. Altogether, these projects have been conducted in a coherent way, bringing interesting and new lights on the molecular determinants of endocrine cell differentiation in the digestive system. The research themes and excellent expertises developed by this scientist fit very well with those of Team1 and should bridge the gap between the two teams.

Altogether, 3 PhD students have graduated on these three subjects.

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

The team leader has an intense activity of valorisation. He obtained two European patents (of which one is under negotiation for commercial licensing). He was also actively involved in the transfer of his academic work and patent on anti-cancer drugs incorporating ruthenium towards a small company (Almetis) that he participated to create. This start-up was recently awarded 2 prizes in a national competition (OSEO). This expertise in obtaining international patents and in developing a spin-out company is an asset for the unit as a whole.

The team leader has also been very successful in raising national funds for his lab (as principal investigator) from industry (Almetis, Axoglia) and from governmental (ANR, OSEO, EGIDE, INCA, AFR) as well as from non-governmental agencies (ARC, AFM, INCA, Ligue Contre le Cancer). This represents a very good productivity for a small group. However, the committee encourages the new team to also apply for international grants (on a collaborative basis and through participation to EU networks) that would not only provide additional funding for salaries (postdoc), but also increase their visibility.

The scientist that joined the team has been co-principal investigator (PI) of one major grant (ANR Genopath) from his former lab (IGBMC). He has currently no financial support as PI but several applications are in progress with governmental and non-governmental agencies. If these applications were not successful, this could become a potential area of weakness for the rapid development of the excellent (and expensive, because of animal models) project proposed by this senior scientist. The recruitment and financial support of students, ITA or post-docs on his project should be seen as a priority for the team and for the unit.

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

This is a new team having only formed a few months (September 2011) prior to the review, making difficult to evaluate the reputation and attractiveness of the team as a whole. It must be emphasized that this Team 2 project brought together productive scientists/ITA coming from three distinct campuses, arguing for a good attractiveness, at least locally. 2 post-docs for a 2- and 3-year period and 5 PhD students (2 have defended their PhD) have worked in the group over the past period. Among these 5 PhD students, 4 have been trained in the University of Strasbourg and one abroad. Similar emphasis should be placed on attracting new post-doctoral fellows.

The international visibility of the senior members of the team is in the average. They have been invited to several conferences, but few of them were high impact international conferences.

Nonetheless, Team 2 members have several ongoing national and international collaborations (Japan, USA, UK, Italy…) with academic labs. Of note, the local collaboration of the team leader with a chemistry lab from the University of Strasbourg has been very successful and resulted in the development of the original collections of organometallic ruthenium-based compounds used by Team 2 to identify new anti-cancer agents. This collaboration has resulted in the publication of 5 articles and the creation of a biotech. The committee encourages the team to now move a step ahead by participating to organized european/international networks to obtain more return for these collaborative efforts (access to EU fundings).

Assessment of the strategy and 5-year project:

The team to be created involves two natural and senior leaders that have the will, at least in part, to manage their own subject and sub-group, making unclear the new team organization and future management. However, it should be stressed that this is a jointly-agreed merge between two senior scientists who have already collaborated and have a strong will to help each other, suggesting there should be no major management problems.

The scientific projects that are proposed are coherent with and in the continuity of the previous work published by these two scientists (see supra), with a refocusing on the general theme of the unit, i.e. intestinal development and carcinogenesis.

They foresee three main lines of research:

1. In the continuity of team leader's interest for the p53 family (p53,p63,p73) the two senior scientists jointly propose to pursue the investigation of the expression, function and regulation of these 3 factors in digestive development, intestinal responses to stress (including response to chemotherapeutic treatments) and digestive tumorigenesis (CRC). This overly ambitious project includes an evaluation of the functional interactions of the p53 family with major developmental pathways (Wnt, Notch, CdX, Ngn3) and the development of complex animal models that are based on the expertises of the CR1 and that will require close collaborations with Team 1.

2. The second project builds on the previous work of the incoming scientist on the transcription factor Ngn3 in the pancreas and on the Ngn3 KO animal models that he developed in IGBMC. It aims at specifying Ngn3 functions in intestinal endocrine cells, gut homeostasis and intestinal tumorigenesis.

3. A third set of projects is proposed by the team leader and is directly connected with the objectives of his start-up (Almetis). They aim at exploring the molecular mechanisms involved: i/ in the anti-tumor effects of ruthenium-based compounds and, ii/ in the cytoprotective effects of flavonoid-derived molecules towards cis-platinum toxicity. This vast program also plans to pursue the development of additional organometallic compounds (osmium, gold) to try to improve their bio-disponibility and toxicity. These projects involves several ongoing collaborations with local and foreign (Italy, South Africa, Mexico) chemistry labs.

The projects on the p53 family are overambitious, and lack focus and direction in an extremely competitive field. Regarding the animal models that are proposed, the lack of expertise of the team in the very complex in vivo functions of p53 family members might preclude contribution on these factors at the forefront. The visiting committee strongly recommends that priorities be identified as soon as possible considering there is here a real danger for the team as a whole to invest its limited workforce in such a very competitive and expensive project. A focus either on p63 or p73 could limit the risks. For example, p73 transcriptional and post-transcriptional regulations during intestinal development and tumorigenesis may constitute an interesting and relatively unexplored « niche » for this group. Alternatively, greater complementarities between the members of Team 1 and 2 could be achieved by focusing on the role of Cdx2 and p63 in Barrett's oesophagus. In any case, the review group recommends a closer integration of this project with Team1 expertise, models and pathophysiological questions.

The project on Ngn3 raises fascinating questions on how enteroendocrine cells could impact on intestinal crypt and stem cell homeostasis. This project also raises pertinent questions about a possible but still hypothetical role of Ngn3 in carcinogenesis. This project is original and should benefit from cross-fertilizing interactions with Team1. It will undoubtedly help to bridge the research between Team1 and Team2. As already mentioned for Team1, the large number of mouse strains with complex genotypes that will be required to achieve this project might be difficult to handle without a greater support in terms of animal husbandry. The recruitment of additional lab staff working directly on this project is also urgently needed. Since this new and ambitious project is not yet supported by grants (results of applications are pending), an active and immediate help might be required to promote a more rapid launch of this promising project.

The project on ruthenium-based anticancer compounds is original and potentially very interesting in terms of translational research. Although it is too premature to judge, it is possible that these ruthenium-based compounds might be tailored to become effective therapeutic agents that could replace the existing platinum-based drugs used in clinics. However, since the international competition on anticancer chemotherapeutics is cutthroat it is recommended to avoid dispersion of the research directions and to clarify what has to be done by the spin-out company and academic collaborators, and what has to be developed within the team (molecular mechanism of action, in vivo toxicity profile, ADME assessments, pharmocokinetic studies). As a matter of priority, the group should focus its entire limited workforce on obtaining more solid information about the molecular mechanism of action of these compounds. Regarding their anticancer properties, it is also recommended to focus on tumors, animal/cellular models and questions that could create a synergistic effort with Team 1, i.e. focus on tumors of the digestive tract and explore the impact of these compounds on the different cell types of the gut, including normal and cancer stem cells/progenitors, when available.

Conclusion:

This is a new team having only formed a few months prior to the review. It associates two productive biologists with complementary expertise and interest on the p53 family-dependent stress response and on developmental pathways, respectively. Their academic work of good quality has been published over the past years in international journals ranging from good to very good and all projects have been financed by grants. Their efforts are also aimed at the evaluation of a new class of anti-cancer chemotherapeutic drugs developed by the group leader in collaboration with chemists. On this subject, the team leader has an intense activity of valorisation that resulted in patents and creation of a biotech. The scientific projects that are proposed for the new team are coherent with and in the continuity of their previous work with a clear refocusing on the general theme of the unit, i.e. intestinal development and tumorigenesis. However, at this stage there are too many interesting sub-projects for a limited workforce, and some of these projects are overambitious in extremely competitive fields (p53 family, chemotherapeutic drugs). Priorities have to be identified and should aim at reinforcing integration with Team1 expertise, models and pathophysiological questions.

- *Strengths and opportunities:*

1.Complementary expertises of the two senior scientists. The highly motivated group leader has a good track record on p53-dependent stress responses and more recently on organometallic compounds with anti-cancer properties. He has a valuable activity of valorisation (patents & creation of a biotech company) and good connections with chemistry labs. This is a potential asset for the unit. The second senior scientist has a very valuable know-how on animal models. He has an excellent track record on the genesis and role of enteroendocrine and pancreatic endocrine systems. Its expertise and new project fit very well with those of Team1 and should bridge the gap between the two teams of the proposed Inserm unit.

2.The two senior scientists of the team have delivered constant good quality results in their field. This work was published over the past years in international journals ranging from good to very good and all projects have been financed by grants.

3.Although priorities remain to be identified and some directions to be reconsidered (see below), the new scientific project as a whole is ambitious and addresses interesting questions with a potential of cross-fertilization with Team1. Hence, it shows a pertinent refocusing on the general theme of the host unit, i.e. intestinal development and tumorigenesis.

4.Dynamism and enthusiasm of the team members at all levels (researchers, ITA and students). The integration of this team in the unit is seen as a very positive move by all members of the unit and signs of promising synergies with team1 are already detectable.

- *Weaknesses, risks & recommendations:*

1.Some thought should be given to the limited personnel resources available and to the effort which will be required to advance each of the numerous individual projects in a competitive manner. This will certainly require to focus strength and funds, at least at the beginning, on a more limited number of projects.

2.Projects on the p53 family lack focus and direction in an extremely competitive field. We recommend that priorities be identified as soon as possible. A focus either on p63 or p73, and/or on specific digestive pathologies (for example, Barrett's oesophagus) could limit the risks.

3.Projects and biological questions on Ngn3 are very original, based on solid preliminary data and pertinent animal models, and represent a source of cross-fertilizing interactions with Team 1. However, current workforce to develop this promising project is grossly insufficient and it is not yet supported by grants (results of applications are pending). This is a weakness that might preclude the expected "quick start" of this ambitious project. Immediate support (funding & staff) to this project should be considered as a priority.

4.Projects on ruthenium-based anticancer compounds are original and have obvious potential for industrial development but face challenges to clarifying what has to be done by the spin-out company, by academic collaborators, and by the team itself. We recommend to focus in the laboratory on obtaining more solid informations about the molecular mechanisms of action of these compounds and on investigating this question in tumors, animal/cellular models of the digestive tract handled by Team 1. The current biological questions on these compounds might rapidly move to clinically relevant questions (in vivo toxicity profiles, ADME assessments, pharmocokinetic studies) that will require to establish a better local partnership with oncologists and pharmacists. There are multiple opportunities that have to be explored (fundings, students etc…).

5.A strategy has to be designed to attract self-funded post-doctoral fellows and additional investigators with permanent positions. This will require developing external communication of the new team on the most promising projects.

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 :

Cell Identity and Stress Response in Physiology and Pathology of the Digestive System

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

Grading table:

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

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

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 : **FREUND-GAIDDON**

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

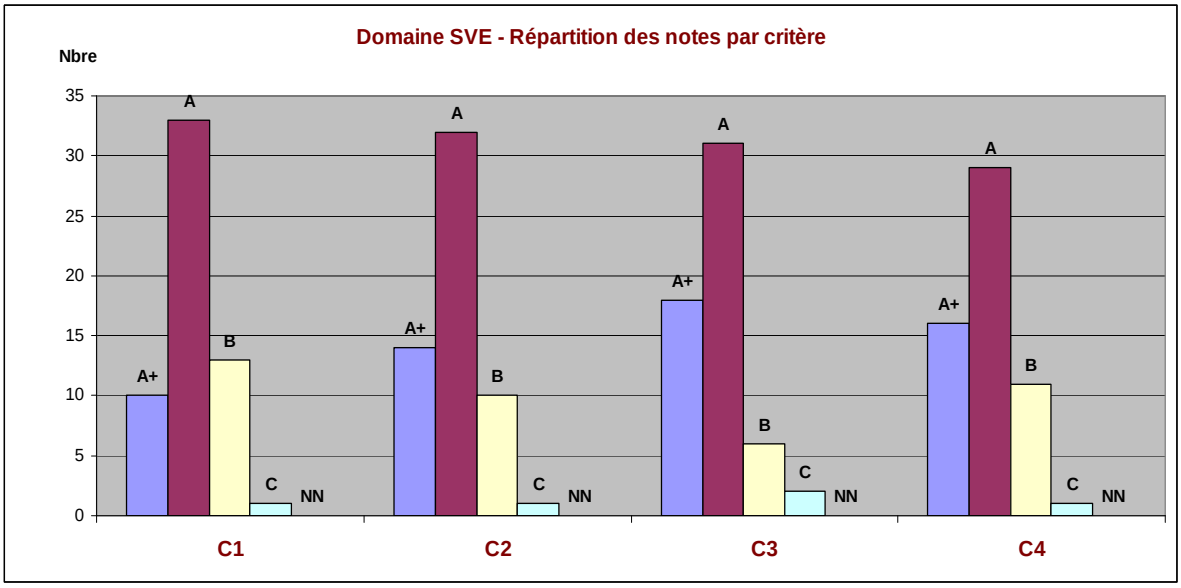
6 ● Statistics per field : **SVE au 10/05/2012**

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 8 mars 2012

Objet : Rapport d'évaluation du projet d'UMR_S Identité cellulaire et réponse au stress dans la physiologie et la pathologie du système digestif (réf. S2PUR130004561-RT)
Réf. : AB/EW/N° 2012-105

Affaire suivie par
Eric WESTHOF
Vice-président Recherche
et formation doctorale
Tél : +33 (0)3 68 85 15 80
eric.westhof@unistra.fr

Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation du projet d'unité mixte de recherche (Université de Strasbourg et INSERM) « Identité cellulaire et réponse au stress dans la physiologie et la pathologie du système digestif » porté par Monsieur Jean-Noël Freund.

Vous trouverez ci-joint les réponses du porteur du projet concernant les erreurs factuelles et les remarques et appréciations du comité d'experts.

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

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

Alain BERETZ

4 rue Blaise Pascal
CS 90032
F-67081 STRASBOURG cedex
Tél. : +33 (0)3 68 85 15 80
Fax : +33 (0)3 68 85 12 62
www.unistra.fr

P.J. :

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

Instituts thématiques
Inserm
Institut national de la santé et de la recherche médicale

UNIVERSITÉ DE STRASBOURG

Unité 682
3, avenue Molière
F-67200 Strasbourg

Jean-Noël Freund
Strasbourg, March 6th 2012

Sir,

We thank the members of the Review Committee and the Committee Chairman for their careful examination and constructive criticisms of this new project of Inserm Unit entitled "Cell Identity and Stress Response in Physiology and Pathology of the Digestive System".

We are grateful for the positive appreciation and comments of the Committee on the overall quality of the scientific project, the global strategy of creating one Unit with 2 complementary teams, and the management of the Unit. Concerning the weaknesses and threats that were highlighted, we would like to clarify and take into account the following points:

- We agree with the Committee that an important issue relates to the financial support of the project, a point insufficiently addressed during the presentation. A number of national and international grants end in 2012 concomitantly with the work done in the current Inserm Unit. For the next project, half of the external financial support is already guaranteed for the first year (Ligue contre le Cancer) and several national applications are pending (6 ANR, 2 ARC, 1 ITMO/Inserm Multidisciplinary Project). In addition, as recommended by the Committee, we are already intensifying our efforts to obtain international grants. In this regard, the Team 2 has just applied to a European ETB grant in partnership with companies and academic labs. Team 2 is also a member of a new European COST program on the biological activity of organometallic compounds, and it is using its contacts in this program to motivate collaborators abroad for the constitution of an FP7 consortium. We will continue and amplify our efforts in this direction.

- We share the Committee's opinion that the work proposed by Team 2 needs more focussing. We stand by our choice to present all of the exciting possibilities related to this project but regret not having clearly pointed out the priorities for the next 5 years. We take this opportunity to clarify our strategy.

  THEME 1: Function and regulation of the p53 family in development and diseases of the digestive system:

  Within the p53 family, we will focus on p73 in intestinal development and tumourigenesis. Indeed TAp73 isoforms have been shown to be important for the response against DNA damage or anticancer drug treatments in colon and gastric cancer cells, and high expression of ΔNp73 correlates with a poor prognostic in these cancers. In addition, preliminary data of Team 2 indicate that the activity of p73 is in part regulated by post-translational modifications. In general it is largely unknown which role p73 isoforms play in physiological processes (differentiation, proliferation, response to cellular stresses) in normal untransformed cells and how they precisely contribute to tumour formation and progression. Therefore, we will focus on:

  1) the expression profile of p73 during intestinal development and cancer;
  2) the regulation of p73 proteins activities at the post-translational level;
  3) the production of transgenic mice allowing tissue-specific and inducible expression of ΔNp73 and TAp73 in the digestive system.

  In addition, in the course of the next 5-year period, the Team 1 will develop novel models for studying the *Cdx2* gene in Barrett's esophagus and subsequent cancerization, a process that might involve p63. In this context, and to further strengthen the collaboration between the two teams, we wish Team 1 to benefit from the skill and tools of Team 2 on p53 family members to develop original studies on p63 in these Cdx2 mouse models.

  THEME 2: Mechanisms of stress response specific to stem cells and differentiated cells in the intestine.

  We thank the Committee for sharing our enthusiasm on addressing the function of enteroendocrine cells in intestinal crypt and stem cell homeostasis and how their deregulation contributes to tumour progression in the digestive system.

Tel (direct): **+33 (0)3 88 27 53 65** - Email: jean-noel.freund@inserm.fr

We are aware that without the recruitment of further lab staff this project would be difficult to advance in a competitive manner. In this respect we have already posted several grant applications where we have asked for a Post Doc or PhD salary and will continue doing so. In addition, we have also submitted a project at the Ecole Doctorale for a PhD position.

THEME 3: Development of new therapeutic approaches for digestive system diseases.

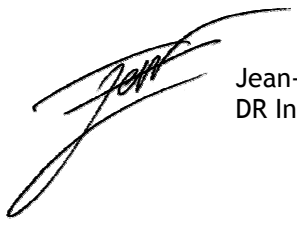
We will specifically focus our work on organometallic compounds and strengthen our multidisciplinary network of national and international collaborations with groups in Strasbourg, Mexico, US and South-Africa. The repartition of the workload is very precise and meets a systematic organization of three principal collaborators having well-defined roles for the concerted development of the projects:

1) Chemist laboratories: synthesis, physico-chemical characterization and primary in vitro biological tests of organometallic compounds;
2) Team 2: proof of concept and mode of action studies of most promising, highly selected compounds, on cancer cell lines of the digestive system;
3) Start-up Almetis or other industrial partners: proof of concept regarding other types of cancers and necessary toxicity, pharmacokinetics and ADME studies.

- Although the Committee considered our scientific production as very good, it also pointed out that publications in multidisciplinary very high impact factor journals were lacking. We strongly believe that the coming in the new Unit of two senior scientists with novel research interests and skills, as well as the willingness of the two Team leaders and of the staff members to develop transversal and complementary projects, will lead to the production of high quality data of interest to a wider audience.

- The Committee has underlined the evolution of Team 1, together with the input provided by the new Team 2, to clinically relevant questions and further encourages increasing partnerships with clinicians. We share this opinion and, in agreement with the Hospital and University authorities, we have already put a lot of effort to recruit a PU-PH expert in chronic inflammation and cancer to the Hospital and the Unit for the 4th trimester of 2013, with a 50% FTE participation to active laboratory studies. Future mutual benefits of this partnership can already bee foreseen with the recent joint application to two grants (ANR, ARC). We are also welcoming motivated medical students to develop their interest for research through careful training and clinically pertinent projects in the hope of future partnerships. For instance, we are currently training 1 internal physician in Master-2 ("Année Recherche") who wishes to stay in the lab for a PhD and 1 medical student for the two-year period of Master-1/2 in the context of the highly-competitive "Ecole de l'Inserm – Liliane Bettencourt" fellowship. Last but not least, we will benefit of the creation of the "Institut Regional du Cancer" in close vicinity to our lab, and we are committed in this context to take an active part in the development of strong reciprocal partnerships and expertise with clinicians.

- The Committee highlighted the excellent quality of the work performed and considered the scientific production as very good but noticed that visibility and attractiveness could be improved. Although we would like to stress that more than half of our body of PhD students was international (10/17), we are aware that these points are critical for international grants, high-quality collaborations and recruitment of post-docs. Thus, we will in the future i) enhance our efforts to present the Unit and its work to high profile international meetings, ii) submit reviews article to selected journals and iii) spend more time teaching in national Master or PhD programs. This will also help us to pursue our strategy to increase the research potential (1 Posdoc recruited on a permanent Inserm position in 2007, creation of the Team 2 with 2 senior scientists in 2011) by engaging new researchers, both locally and also young scientists currently in Postdoc. As recommended by the Committee, we will also negotiate with the Inserm and University to reinforce the technical staff, in particular to increase the working potential at the level of the animal facility.



Jean-Noël Freund
DR Inserm