INSTITUT COCHIN Endocrinologie métabolisme cancer

Rapport Hcéres

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

Section des Unités de recherche

Rapport d'évaluation

Unité de recherche :

Département Endocrinologie, Métabolisme, Cancer

de l'Institut Cochin

Université Paris 5

mars 2009

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

mars 2009

Rapport d'évaluation

L'Unité de recherche :

Nom de l'unité : Département Endocrinologie, Métabolisme, Cancer

Label demandé :

N° si renouvellement :

Nom du directeur : M. Pierre-Olivier COURAUD

Directrice du département : Mme Christine PERRET

Université ou école principale :

Université Paris 5

Autres établissements et organismes de rattachement :

INSERM

CNRS

Dates de la visite :

8-10 Décembre 2008

Membres du comité d'évaluation

Président :

M. Joël BOCKAERT, Université Montpellier 1

Experts :

Mme Loranne AGIUS, Université de Newcastle, UK

M. Frédéric LEMAIGRE, Université Catholique de Louvain, Belgique

M. Jean-François DUFOUR, Université de Bern, Suisse

M. Andreas BIKFALVI, Université Bordeaux 1

Expert(s) représentant des comités d'évaluation des personnels (CNU, CoNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) :

Mme Jennifer RIEUSSET, CSS INSERM representative

Mme Nathalie CHABBERT-BUFFET, CNU representative

M. Serge ROCHE, CoNRS representative

Observateurs

Délégué scientifique de l'AERES :

M. Pascal FERRE

Représentant de l'université ou école, établissement principal :

Mme Marie-Claude LABASTIDE, Université Paris 5

Représentant des organismes tutelles de l'unité :

M. Raymond BAZIN, INSERM

Rapport d'évaluation

1 • Présentation succincte du département

Le département compte dix équipes représentant 15 enseignants-chercheurs, 32 chercheurs, 27 ingénieurs et techniciens, 26 doctorants et 19 post-doctorants.

Les équipes qui composent le département sont les suivantes (Le numéro indiqué correspond au numéro figurant dans l'organigramme de l'Institut Cochin, EC: enseignant-chercheur; C: chercheurs; ITA: Ingénieurs, techniciens, administratifs; Doc: doctorants; Post-Doc: post-doctorants) :

10- Endocrine tumors and signaling (5 EC, 2 C, 2 ITA, 2 Doc, 2 Post-doc)

11- Mitochondrial transporters and Metabolism (3 EC, 2 C, 5 ITA, 2 Doc). *Cette équipe ayant été évaluée l'année dernière dans un autre cadre, elle n'a pas été ré-évaluée cette année).*

12- Insulin signaling, glucose sensing and glucotoxicity (1EC, 6 C, 3 ITA, 4 Doc, 3 Post-doc)

13- Regeneration, Ploidy and Senescence in liver pathophysiology (1EC, 3 C, 2 ITA, 1 Doc, 2 Post-doc)

14- Functional Pharmacology and pathophysiology of membrane receptors (2 C, 2 ITA, 2 Doc, 3 Post-doc)

15- Molecular and cellular pharmacology of receptors (2 C, 3 ITA, 1 Doc, 1 Post-doc)

16- Oncogenesis of digestive epithelia (3EC, 4 C, 4 ITA, 4 Doc, 2 Post-doc)

17- Lipids : metabolism and physiopathology (1EC, 2 C, 2 ITA, 2 Doc, 1 Post-doc)

18- CoupTFII and glucose metabolism (3C, 3 Doc, 1 Post-doc)

19- Genes, Nutrients and Iron (1EC, 4 C, 3 ITA, 3 Doc, 3 Post-doc)

41- Vascular niche and tumor micro-environment (2C, 1 ITA, 1 Doc, 1 Post-doc)

2 • Déroulement de l'évaluation

L'évaluation des dix équipes du département "Endocrinologie, Métabolisme, Cancer" s'est déroulée sur trois jours. La visite a été préparée par le directeur de l'Institut Cochin en concertation avec le président du comité de visite et le représentant de l'AERES. La documentation, très informative, a été envoyée au comité de visite suffisamment à l'avance pour permettre une analyse détaillée. Il faut souligner les gros efforts d'organisation réalisés par tous les membres de l'Institut Cochin pour que la visite se déroule de façon harmonieuse et efficace. Le Directeur de l'Institut Cochin a présenté l'historique, la structure et les grandes orientations de l'Institut puis la directrice du département a présenté les équipes et leur évolution au cours du dernier quadriennal ainsi que les perspectives de restructuration pour le nouveau quadriennal, les interactions entre les différentes équipes et la politique du département. Chaque équipe a ensuite présenté son bilan et ses perspectives et a été amenée au cours de longues discussions à répondre aux questions du Comité. Le comité a reçu les ITA/IATOS, puis les étudiants et post-doctorants du département. Une discussion finale du Comité lors de la dernière après-midi a permis de finaliser les appréciations concernant chqaue équipe. Les présents rapports ont été rédigés par le président de comité avec l'aide et l' accord des membres du comité de visite.

Le programme de la visite était commun la première demi-journée aux départements Endocrinologie métabolisme cancer et Génétique et Développement.

GENETIQUE & DEVELOPPEMENT et ENDOCRINOLOGIE, METABOLISME, CANCER 8-9-10 december 2008	
Monday 8 december	
09 :00	Welcome
09 :30	Meeting of the committee
10 :30	Presentation of the Institute
11 :30	Presentation of the department GD
11 :50	Presentation of the department EMC
12 :10	Lunch

ENDOCRINOLOGIE, METABOLISME, CANCER 8-9-10 december 2008		
Monday 8 december		
14 :15	15 :45	Team 15
16 :00	17 :30	Team 14
17 :45	18 :45	Team 41
19 :00		End of the auditions
Tuesday 9 december		
09 :00	10 :30	Team 10
10 :45	12 :15	Team 16
12 :30		Lunch
13 :45	15 :15	Team 12
15 :30	16 :30	Team 17
16 :45	17 :45	Team 18
18 :00		End of the auditions
Wednesday 10 december		
09 :00	10 :30	Team 19
10 :45	12 :15	Team 13
12 :30		Meeting with the research-assistants (technicians and engineers)
13 :15		Lunch
14 :15		Meeting with youg researchers (doc and post-doc)
15 :00		Final meeting of the committee
17 :30		End of the visit

3 • Analyse globale du Département

Le Comité a reconnu que la qualité globale des équipes du département "Endocrinologie, Métabolisme Cancer" était très bonne avec des projets ouvrant des perspectives qui devraient permettrent de véritables réussites scientifiques. Les équipes du département sont aidées par une utilisation excellente des plates-formes techniques avec de plus au sein des équipes un développement technologique de qualité (BRET, Tap-tagged pour GPCRs , modèles de souris..). Toutefois, il est apparu que l'interaction entre les équipes du département était faible et que la direction du département devait avoir un rôle moteur dans ces interactions. Il est d'autre part dommage que les interactions avec les cliniciens du site soient (à l'exception d'une équipe) très faibles. Lors des présentations des équipes, le Comité a été frappé par une surenchère de projets dont le nombre mériterait d'être réduit afin de concentrer une masse critique sur les projets les plus prometteurs. En outre, quelques équipes ne sont que la juxtaposition de deux, voire de trois sous équipes et il est difficile d'apprécier

la cohérence en particulier en termes de gouvernance. Enfin et eu égard à la qualité de la Science que le Comité a pu apprécier lors de ces journées, un effort doit être fait pour améliorer le niveau des publications qui est bon mais qui, au vu de l'environnement, devrait être encore meilleur avec des publications dans des revues généralistes de très haut niveau.

4 • Analyse équipe par équipe et par projet

Les rapports se sont attachés à analyser pour chaque équipe la qualité scientifique et la production, l'attractivité, la stratégie et le management, les projets et les ressources. Les différents items ont été notés "excellents ", "très bons" , "bons" ou "faibles".

Team 10 : Signalisation des tumeurs endocrine

La recherche de l'équipe « signalisation des tumeurs endocrine » est centrée sur la caractérisation moléculaire des différents types de tumeurs endocriniennes ainsi que l'identification les voies de signalisations associées. L'équipe présente une très bonne production scientifique dans son ensemble, régulière et soutenue. Elle est cependant hétérogène suivant les aspects abordés, de correcte pour les aspects moléculaires à très bonne voire excellente, sur les aspects cliniques et médicaux. L'équipe présente une très bonne attractivité scientifique, qui se traduit par un bon rayonnement, notamment grâce à sa participation très active à des réseaux internationaux dédiée aux tumeurs endocrines.

La stratégie présentée est bonne dans son ensemble. Cependant elle gagnerait en efficacité et en qualité par le développement d'approches complémentaires associées aux aspects moléculaires et à la validation fonctionnelle des résultats obtenus. En clair, les signatures des tumeurs décrites mériteraient d'être analysées de manière plus approfondie. Malgré ces faiblesses reliées à la stratégie, la qualité du projet de recherche a été jugée de très bonne qualité.

Les ressources de l'équipe semblent par ailleurs suffisantes sauf dans les aspects cellulaires (voir ci-dessous).

Points forts :

Les points forts de cette équipe sont une caractérisation moléculaire des tumeurs endocrines par des approches de génomique ayant un impact potentiel fort dans la caractérisation et la prise en charge de ces pathologies comme en témoigne l'excellence de la production scientifique en recherche clinique. On notera également une très bonne participation à des réseaux internationaux pour le développement de banques de tumeurs de patients.

Points faibles :

Cette équipe manque d'une expertise de biologie cellulaire et moléculaire convaincante.

Recommandations :

L'équipe devrait mettre l'accent sur la caractérisation moléculaire des voies de signalisations associées aux classes de tumeurs identifiées. Elle devrait également porter son effort sur la validation fonctionnelle des résultats obtenus (voies de signalisation, signature génomique). Cet effort pourrait se traduire par le recrutement d'un chercheur ayant une bonne expertise dans ce domaine.

Nom de l'équipe : Endocrine tumors and signaling

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

Team 12- Insulin signaling, glucose sensing and glucotoxicity

The originality and biomedical interest of the research in team 12 taken as a whole (Insulin signaling, glucose sensing and glucotoxicity) is very good. The team has an excellent scientific production with a high number of papers in very influential and high impact specialist journals (Diabetes, J. Clin. Invest. , Endocrinology…). Papers published by the team are very well cited. The review committee notes that the contribution of the two subgroups of the team is unequal: while the research performed on ChREB leads to high impact and well cited papers, the research output of the subgroup which focussed on Grb14 is modest and does not contribute significantly to the overall excellence of the group. A group which developed expertise in insulin signaling and O-glycosylation is proposed to join the team and constitute an additional subgroup. This additional group had a good scientific output, predominantly in specialist journals. Of note, this output comprised an interesting contribution to the development of BRET technology.

The attractivity of the team is excellent. The team members are invited speakers at international meetings, and are authors of commissioned reviews in high impact journals. They are experts in their field and their team has attracted a significant number of scientists which have permanent positions or post-doc or PhD fellowships.

Young researchers recently joined the group, including a promising young researcher who recently terminated a post-doctoral training in an excellent american laboratory.

The committee considered the team as very good in terms of strategy and management. The team leaders have attracted strong funding for their future research. The expected arrival of a permanent scientist who will develop projects on insulin signaling and O-glycosylation is expected to reinforce the group and to promote intra-team collaborations.

The overall level of the project is considered as very good. Some projects consist in a logical and coherent follow-up of the best recent findings, others contain innovative aspects and are expected to open new perspectives for the group and for the field of research. The focus of the subgroup on O-glycosylation projects represents an interesting opening, but still relies on a relatively low number of data. This would need attention in the coming two years. The team members have the required expertise to perform the work and plan efficient collaborations with other teams of the department. The evaluation committee encourages the team members and supports their future projects.

The unit has attracted funding that will allow to perform the proposed research. The team is dynamic as demonstrated by the inclusion of a new subgroup and by the recruitment of young researcher who recently ended a very productive post-doc.

Strong points :

Part of the team has an excellent scientific production.

The team has excellent national and international visibility and its members are considered leaders in their field.

There is a very good use of the technical platforms provided by the host institution.

The content of the research projects confer strong coherence to the group.

Weak points :

There is an unequal contribution of the team's subgroups to the overall quality of the team.

A plan for management of the respective responsibilities of the three future subgroup leaders is lacking.

The number of projects may be too high with respect to the number of team members.

There is an insufficient participation to international, in particular European, networks.

Recommendations :

The team must focus on most promising projects to avoid dispersal of expertise.

An effort must be made to improve the scientific output of the subgroup who contributed less to the excellence of the team, in order to avoid intra-team unequalities.

Team investigators must take initiatives to become integrated – and even lead- European consortia.

Nom de l'équipe : Insulin signaling, glucose sensing and glucotoxicity

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

Team 13 : Regeneration, Ploidy and Senescence in liver pathophysiology

The scientific quality and production of the team 13 could be better. There is a deficiency in the productivity of this team in the last years with a lack of publications in high ranked journals. This is also apparent in the number of citations which is stagnating. The potential for the next 4 years is there, but the team should be more dedicated to publish in high-ranked journal. The committee finds the scientific quality and production of the team 13 lower than expected.

With its variety of projects on original aspects of liver pathobiology (cell senescence, ploidy) the team is attractive and indeed recruited a CR2, has 4 post-docs, 9 master students and 4 BTS students. The team successfully interacts with clinicians, which increases its attractivity. The committee rates the attractivity of the team 13 as good.

In terms of strategy and management, this team focuses its efforts on 2 different areas, one with direct clinical implications (liver regeneration, fibrosis) and another one with less clinical relevance but with important cell physiological implications (the regulation of hepatocellular polyploidy). The 2 areas of interest of this team are run in parallel with little transversal interactions and without apparent attempt to bring both areas in a coherent project. The leader of the group studying ploidy outlined enthusiastically a well structured plan of a coherent set of experiments (physiological signals controlling polyploidy, polyploidy state and biological function, polyploidy and liver cell proliferation). The group working on regeneration and fibrosis does not have the same coherence and its expertise is fragmented in too diverse projects. The recent recruitment of a specialist of liver regeneration may help this group to focus. The management secured sufficient funding from French national agencies. The committee considered the team in the domain of strategy and management as uneven.

In terms of projects, there is a dichotomy in the team. One group is focused on ploidy which develops a set of questions for the next years: what is the impact of ploidy on cellular functions, what is the place of ploidy in cell proliferation and carcinogenesis, what are the signals maintaining ploidy? The projects in the second group deal with important questions (hepatocellular senescence, reversibility of fibrosis), but also projects on Growth Hormone and liver regeneration and on the role of FoxM1B. This lack of focus and identification to a single thematic is a concern for the committee. The committee considered the projects for the group working on ploidy as very good and those of the second group as too diverse and superficial.

The team has the ressources to develop the project on ploidy successfully. The committee is less convinced that contacts with the clinic will be enough to make significant contributions on the other axis of research. The role of hepatocellular senescence and liver fibrosis is a timely area of research; the team should establish collaboration to get the molecular tools and animal models to study this in depth.

Strong points :

This is one of the few units audited by the committee with fruitful links with the clinic.

The thematic of research is Interesting.

There is a coherent and logical plan on ploidy.

Weak points :

The team is uneven with one well structured portofolio of projects on ploidy and a less coherent plan on the second axis which is also less easy to define.

There is an insufficient participation to international, in particular European, networks.

The scientific productivity of the team could be better.

Recommendations :

The group working on senescence, fibrosis, regeneration, growth hormone and FoxM1B should develop a clearer, more focused strategy. The potential is there and the addition of a liver regeneration specialist might represent an opportunity to focus the research projects of the team.

The team should take initiatives to participate to European networks and get international attention and funding.

The investigators must pay a special attention to the publication of their work in high-rated journals

Nom de l'équipe : Regeneration, ploidy and senescence in liver pathophysiology

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

Team 14- Functional Pharmacology and pathophysiology of membrane receptors

The team have a well established position at the international level on the two central projects they are developping: the melatonin receptors (a GPCR) and the leptin receptors (a cytokine receptor). For both subjects they have made central contributions: - working on the orphan GPR50 GPCR (a homolog of melatonin receptors) they provided arguments for a general new concept of GPCR action: an orphan GPCR may have no specific ligand activation but may modulate, via hetero-dimerization the activity of another ligand activated GPCR; - they have developped the TAP-tagged method and associated proteomic for fishing GPCR interacting proteins; they have developped a BRET assay for cytokine receptor screening; - the discovery of a second transcript of leptin receptor acting as a negative regulator of leptin receptor. Taken as a whole, the productivity of team 14 is excellent with a high number of papers in very high impact journals (EMBO, EMBOreport; Mol Cell Proteomic, PNAS etc). Since 2003 the team leader has been cited 676 times). The leader is invited in international conferences.

Attractivity of the team is very good with 3 post-docs, 2 PhD students, 2 engineers but with only one permanent position (CR1 INSERM). The second permanent member who had also a role in the development of BRET technology is leaving to join team 12 in the department.

The committee considered the team as excellent in terms of strategy and management. The team is very well funded and recognized as a FRM (Fondation pour la recherche) team and has collaborative contracts with industry. The team leader is certainly the "boss".

The overall level of the project is considered as excellent. Several specific questions are asked for which the team has the capacity to give an answer especially with its industrial and academic collaborations :

- the functional roles of melatonin receptors heterodimers and the role of agomelatin as a new antidepressant.
- the possible role of GPR50 in mental disorders such as bipolar and seasonal depression and autism;
- the search for proteins which may modulate leptin receptors (using the proteomic approach developped).

A protein has already been identified and the study of its role in vivo is under way (gene disruption) gene knockdown (lentivirus coding micro RNa xpressed under a cell specific promoter etc…).

The unit has attracted funding that will allow to perform the proposed research.

Strong points :

The team has an impressive scientific production.

The visibility of the team is excellent and his leader is internationally recognized in his field.

The development of new techniques is remarkable.

The content of the research projects confers strong coherence to the group.

Weak points :

The critical mass is small.

Recommendations :

Initiatives must be taken to become integrated – and even lead- European consortia.

The ongoing programs would benefit from in vivo studies.

Attractivity should be increased to wellcome a permanent researcher.

Nom de l'équipe : Functional pharmacology and pathophysiology of membrane receptors

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

Team 15 : Molecular and cellular pharmacology of receptors

The international visibility of team 15 is excellent. This team succeeded to be one of the leader in a very competitive field of signal transduction and specifically on the role of beta-arrestins in cell physiology. The team leader is invited in congress on G-protein coupled receptors (GPCRs) and has a long standing collaboration,a laboratory in Montreal which is central in this research area. The team is now a "foreign" team of the GRUM(Groupe de Recherche Universitaire sur le médicament of the Montreal University). Taken as a whole, the originality and biomedical interest of the research in team 15 is excellent. The team has an excellent scientific production with a high number of papers in high impact journals (PNAS, , Mol Cell Biol, Nature Method). Since 2003 the team have been cited 800 times. .

The attractivity of the team is excellent. The leader has been invited to Gordon Conferences. The team has recruited one young scientist at CNRS who gave a favorable impression during the evaluation. The team succeeded in getting one ANR grant. Actually 5 PhD students and one post-doc are working in the team. Three technicians are in this team which is quite exceptional in France

The committee considered the team as very good in terms of strategy and management. The team leader has attracted funding and international collaboration for his future research.

The overall level of the project is considered as very good. Several aspects of beta-arrestin roles in cell biology which are original will be followed up in the context of GPCR role in chemotaxis :

- the regulation of chemokine receptor export to the membrane in particular the role of CD4 in CCR5 receptor export ;
- the physiological significance of the interaction of PTEN with beta-arrestin;
- the possible role of beta-arrestin in cancer cells. A screening of cancer tissues and leukemia libraries will be done for the evaluation of beta -arrestin 1 and 2 expression (collaboration with the GRUM);
- in silico screening for drugs capable of modulating interactions between beta-arrestin and partners; finaly, inductible and tissue specific knock-out mice for beta-arrestin 1 and 2 will be generated (in collaboration).

However, the coherence of the project could have been better. The implication of the different parts of the subject in "chemotaxis", the central aim of the project was not always obvious. The team is excellent in cell biology and techniques (BRET in particular) but should include more animal work. The evaluation committee encourages the team members and supports their future projects. The unit has attracted funding that will allow to perform the proposed research. The team is dynamic, as demonstrated by their international and national collaborations and by the recruitment of a young bright researcher.

Strong points :

The scientific production of the team is excellent.

The team has an excellent visibility and can be considered as a leader in their field.

There is a strong use and development of cellular biogy tools as BRET (associated in a Nature Method paper on the subject).

Weak points :

The project on the role of beta-arrestin in cancer is weak as exposed.

The number of projects may be too high and the focus on a « physiological » question should be stonger.

The team is not using the facilities of the Institute in terms of animal work.

Recommendations :

The team must focus on most promising projects to avoid dispersal of expertise.

If the work on cancer is kept, more efforts should be done to propose a more « argumented » project.

Nom de l'équipe : Molecular and cellular pharmacology of receptors

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

Team 16 : Oncogenesis of digestive epithelia

The team 16 has been working for many years on the role the beta-catenin in the hepatic and intestinal pathophysiology. This thematic is of a great interest to the scientific community and the team was able to make regularly significant contributions. This is reflected in its excellent scientific production with manuscripts published in high-ranked journals (Cancer Res, Dev Cell). The committee finds the scientific production of the team 16 excellent.

With currently 7 post-docs and PhD students, 3 of them having an MD, the team is attractive. Since 2004, 4 PhD thesis were successfully defended. The team 16 was reinforced in 2006 by a specialist in immunology of liver cancer. The review committee rates the attractivity of this team as very good.

This team outlined a clear strategy to develop its thematic and the leaders have presented original projects. The management has secured sufficient fundings from national agencies and an European contract allowing the team 16 to recruit. The committee considered the team as excellent in this respect.

The team 16 is focused on the role of beta-catenin on the oncogenesis of digestive epithelia. The thematic is articulated around four projects (role of the Wnt/beta-catenin signalling in intestinal tumorigenesis, role of the Wnt/beta-catenin signalling in development and liver physiology, mechanism of Wnt/beta-catenin-induced liver carcinogenesis) and a new one (role of the immune system in the Wnt/beta-catenin-controlled liver homeostasis and tumorigenesis). The first three projects are logical, and represent a coherent follow-up of the previous ones, while the fourth one opens new perspectives. They complement each others. The committee finds this portofolio of projects very good. The research unit is dynamic, has access to the resources necessary to achieve its goals and its leaders have attracted enough funding.

Strong points :

The scientific production of the team is excellent.

There is a well-balanced distribution of the projects in terms of science as well as resources.

There is an excellent use of the technical platforms provided by the host institution.

The content of the research projects confers a strong coherence to the group.

Weak points :

The number of projects and their scope seem very ambitious and the team should be careful to keep its focus

International visibility of the team is not very high.

Recommendations :

Multiplication of the projects must be avoided.

The team 16 should try to be more translational, to bring its projects closer to the clinic.

International visibility must be enhanced with more international collaborations.

The team could have more contact with the industry.

Nom de l'équipe : Oncogenesis of digestive epithelia

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

Team 17- Lipids : metabolism and physiopathology

Team 17 is a small team that is clearly focused on the study of the molecular biology, physiology and pathophysiology of carnitine palmitoyltransferase-1 (CPT1), a protein that is of fundamental importance for the understanding of the pathophysiology of fatty liver (Non-alcoholic fatty liver, NAFL), a common clinical condition in insulin resistance, type 2 diabetes and liver disease. The team is recognised internationally for its contribution to structure-functional analysis of the molecular biology of CPT1. The proposed project addresses timely issues on the role of CPT1 in fat accumulation in liver and muscle and on advancement of the structural studies with the goal of development of molecules to decrease the sensitivity of CPT to its physiologic regulator, malonyl-CoA. This is an ambitious objective from a team with an internationally recognised track record in the structure-function analysis of CPT.

The team has published 11 papers (inclusive of 5 collaborative papers and 2 reviews). The home-made papers are published in good but not outstanding journals. One full-time researcher is "non-publiant". The team is part of an EU grant. This is a low productivity in terms of number of publications. However, the generation of the transgenic mouse model expressing malonyl-CoA insensitive CPT1 should now facilitate progress for understanding the role of malonyl-CoA regulation of CPT1 in development of fatty liver.

Over the past 4 years the group has attracted 3 PhD students and 5 Masters students, and a recent Postdoctoral Fellow. This is a good achievement considering the size of the group.

This team is focused on the study of a single protein and has secured Grant Funding from Government (380kEu) and Scientific Societies (100kEu). It has selected various collaborating centres nationally and internationally to help progress the structure-functional studies towards the design of new strategies to alter the sensitivity of the enzyme with small molecules for therapy for fatty liver. The available funding, experimental tools and potential collaborations should enable productivity in the forthcoming years.
The proposed project encompases 3 areas of study: (i) Role of malonyl-CoA regulation of liver CPT1 in the pathophysiology of steatosis, insulin resistance and inflammation. The team now has all the experimental tools in place to determine the impact of uncoupling of CPT1 activity from malonyl-CoA inhibition on steatosis, insulin resistance and inflammation. This work should provide clear answers on the regulatory role of malonyl-CoA in development of fatty liver. (ii) Impact of fatty acid oxidation in muscle on lipotoxicity and insulin resistance. This work is based on an analagous approach as for the liver studies but requires in vivo electroporation for transfection of muscle. This will be done in collaboration with a group experienced with this technique. (iii) Structural studies with the long-term goal of development of pharmacological molecules to modulate malonyl-CoA sensitivity.This is a very challenging task. However, given that the structure-functional studies of CPT1 are the major strength of the PI, with appropriate collaboration, the PI is well placed to make a contribution to this important clinical application.
The proposed project to study liver and muscle CPT and develop new strategies for development of pharmacological molecules is ambitious. The availability of the necessary tools for the first two objectives

(liver and muscle physiology / pathophysiology) should enable steady progress on the first two objectives. Grant funding has been secured for the forthcoming 2 years.

Strong points :

The group has been studying the structural-functional aspects of CPT1 for a number of years and are well respected for the identification of the mitochondrial targeting motif of CPT.

The group has developed a murine model of liverCPT1 that is insensitive to malonyl-CoA. This model enables the study of the role of malonyl-CoA-inhibition of CPT1 to the pathophysiology of fatty liver.

The group has trained PhD (3) and Master (5) and Postdoctoral scientists.

Weak points :

The number of publications and their impact from the past 4 years has been low. This may be due to the lack of critical mass for the scope of the project.

Recommendations :

The team is recommended to publish the new work on the role of CPT1 in the pathophysiology of insulin resistance and fatty liver in high impact factor clinical journals.

Nom de l'équipe : Lipids : metabolism and physiopathology

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

Team 18 : CoupTFII and glucose metabolism

Team 18 is a recently constituted team, since two of the members (head of the team CR1 INSERM, CR1 CNRS) and joined in 2007 and the third one (DR2 CNRS) joined in September 2008.

Team 18 has contributed at a good level to the description of glucose and lipid homeostasis (role of COUP-TF II (Chicken Ovalbumin Upstream Promoter Transcription factor II), an orphan nuclear receptor activating gene transcription). The team has a good scientific production, irecently improved by three articles in very high or high impact specialist journals for 2008, its first year as a team. The review committee notes that the contribution of the most recent member of the team (DR2 CNRS) has not been included in the activity report.

Attractivity of the team is good. The team members have recruted one post doctoral trainee, three PhD and one MSc students. They are regular reviewers of scientific articles and actively participate in teaching, including responsibility of a MSc. They are involved in counseling for pharmaceutical industry (Servier and GSK), and the team leader is member of a clinical working group in ALFEDIAM (Association de Langue Française d'Etude du Diabete et Metabolisme).

The committee considered the team as good in terms of strategy. The team leaders have attracted regular funding for their research. However, the future role of DR2 CNRS deserves clarification, as well as the organisation of the team in the future.

The overall level of the project is considered as very good. It contains innovative aspects including a global understanding of glucose and lipid homeostasis at the central (hypothalamic) as well as peripheral (hepatic and pancreatic) level. The team has developped adequate mouse models for this project. They have also established collaborations with three National, one European and one Canadian team to reach their purpose. One of these collaborations includes genetic studies in a French cohort of patients and will potentially contribute to elucidate the role of comon genetic variants in glucose and lipid metabolism. The evaluation committee encourages the team members and supports their future projects.

The team has been funded as an emerging team (BQR) and has recieved some support from the Industry for 2008-2009.

Strong points :

The project aiming at a global understanding of glucose and lipid homestasis is original.

There is a favorable dynamics of publication in particular in 2008, first year as a team.

Weak points :

The strategy of the group is not clear especially concerning the role and importance of one of the team member in the projects.

Recommendations :

It is necessary to clarify the specific roles of the different team members, to ensure team cohesion for the future.

Nom de l'équipe : CoupTFII and glucose metabolism

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

Team 19 : Genes, Nutrients and Iron

Scientific quality and production: The team 19 is interested in the pathophysiological regulation of genes implicated in energy, oxygen and iron homeostasis and their possible implication in metabolic diseases and cancer. There are two major research axis, one on hepcidin and HIF in physiopathology and another on the role of AMPK in the regulation of energy metabolism. The originality and biomedical interest of the research in team 19 is excellent, and members are considered leaders in their field. The review committee notes that 1) the structure of the team clearly looks like to the juxtaposition of two teams without clear interactions and 2) the contribution of the two subgroups of the team is unequal, with a major contribution of the hepcidin subgroup to the overall excellence of the group. Taken as a whole, the productivity of the team is good, but there is a discordance between the quality of the work/project and the level of publications. In addition, the number of publications of one subgroups is artefactually high, linked to a lot of papers in collaboration.

Attractivity of the team is excellent with 3 post-docs, 3 PhD students, 2 engineers and 2 permanent positions (CR1 INSERM). The team members are experts in their field and they have attracted a significant number of scientists which have permanent positions or post-doc or PhD fellowships. One young permanent member of the team recently obtained "une ANR jeune chercheur".

The committee considered the team as very good in terms of strategy and management. The team leaders have attracted strong funding for their future research and have set up a lot of national and international collaborations. They have an excellent participation to international, in particular European, networks.

However, the number of projects may be too high and, in term of strategy, they have to focus on most promising projects to avoid dispersal of expertise.

The overall level of the project is considered as very good. They have a lot of sophisticated mice models to answer to original questions and part of the team propose potential therapeutic and diagnosis tools. However, the review committee notes that 1) there is too much projects in both subgroups of the team and 2) the scientific arguments linking hepcidin/HIF and cancer are poorly justified. The team has attracted funding that will allow to perform the proposed research. The team is dynamic, as demonstrated by their international and national collaborations and by the support to one young researcher.

Strong points :

The scientific production of the team is globally excellent.

Members of the team are considered leaders in their field.

There is an excellent participation to international, in particular European, networks.

There is an excellent transfer of technology for one group of the team.

Weak points :

There is unequal contribution of the team's subgroups to the overall quality of the team.

There is a discrepancy between the quality of work/project and the level of publications.

The number of projects may be too high with respect to the number of team members.

Recommendations :

The team must focus on most promising projects to avoid dispersal of expertise.

The subgroup who contributed less to the excellence of the team, must improve its scientific output in order to avoid intra-team unequalities by publishing more“home-made” publications in high-ranked journals.

Nom de l’équipe : Genes, Nutrients and Iron

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

Team 41 : Vascular Niche and the tumor microenvironment

The team is built around a young scientist (chargé de recherche 2) who has made substantial contributions to the angiogenesis field during her post-doc, which have been published in top-ranked journals (Developmental cell, Nature etc…). It is certainly unusual in the french system that a scientist at the beginning of his career is given the oportunity of a group leader position. The committee felt that because of the outstanding

contributions (which would certainly allowed her to be easily recruited as an assistant Professor in the US) the group leader position should be granted. The team leader has shown high maturity and leadership during the visit and has made a strong impression on the committee. The team will be enforced by the arrival of a research director (CNRS) who will bring his expertise on the angiotensin system.

In terms of attractivity, the team is at the beginning and the PI has just been hired. There is one post-doc already recruited and one PhD student. Another pos-doctoral fellow and a senior research assistant are being currently recruited. The group leader has also applied for a single investigator grant at the CNRS (ATIPE) which, will should give her more resources for structuring the group.

In terms of strategy, the committee considered the team as very good with the potential for the development of a strong group in angiogenesis research. The next 3 years will be crucial and the next evaluation term will allow to judge whether this group has successfully established itself.

The overall level of the project is considered as very good. It is centered on three aspects of angiogenesis research focussing on the molecular dynamics of VE Cadherine regulated by VEGF and angiotensin II, remodelling the cell-cell junctions during metastasis and the cellular interactions within the vascular niche. The aim is to determine the regulatory circuits involved in these processes. A number of strategies and methodologies will be used that look adequate to answer the questions raised within this project. However, the in vivo analysis should be somewhat enforced using genetically modified animals (Cre-lox etc.). There is up-to-now no translational perspective in this project and this should also be enforced in the fortcoming years. Finally, the unit has started to attract funding that will allow to perform the proposed research project.

Strong points :

The scientific production of the team leader during her post-doc is excellent.

There is strong potential for establishing an excellent group in angiogenesis research.

The project is in frame with the state-of the art angiogenesis research.

Weak points :

The critical mass of the group is presently small due to the fact that it is an emerging group.

The project is lacking some in vivo perspective as well as some translational aspects.

Recommendations :

Attractivity should be increased in order to reach a critical mass for the group.

In vivo analysis should be somewhat increased using genetically modified animals (Cre-lox etc.).

This project must include some translational perspective in the forthcoming years.

Nom de l'équipe : Vascular Niche and tumor micro-environment

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

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 7 avril 2009

DRED 09/n° 143

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'Institut Cochin « **Département Endocrinologie, Métabolisme, Cancer** » rattaché à mon établissement.

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

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

Le Président de l'Université

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Paris, le 20 avril 2009

Réponses au rapport du comité d'experts

Unité de recherche :

Département Endocrinologie, Métabolisme, Cancer de l'Institut Cochin

Université Paris 5

L'Unité de recherche :

Nom de l'unité : Département Endocrinologie, Métabolisme, Cancer

Label demandé :

N° si renouvellement :

Nom du directeur : M. Pierre-Olivier COURAUD

Directrice du département : Mme Christine PERRET

Université ou école principale :

Université Paris 5

Autres établissements et organismes de rattachement :

INSERM

CNRS

Dates de la visite :

8-10 décembre 2008

Team 12- Insulin signaling, glucose sensing and glucotoxicity

L'équipe a été formée en 2006 par l'association de deux groupes ayant une communauté d'intérêt pour l'étude au niveau fondamental de pathologies métaboliques, et ayant des approches expérimentales complémentaires, l'un suivant une approche intégrée basée sur des modèles animaux, l'autre suivant une approche plus moléculaire.

Le comité insiste dans son rapport sur la disparité dans la contribution de ces deux groupes à l'activité de publication de l'équipe. Nous pensons cependant que la publication régulière dans des journaux tels que Endocrinology, EMBO Reports, FASEB J. ou Mol. Endocr. (article accepté en avril 2009) n'est pas juste « modeste », même si, pour répondre aux critères actuels d'évaluation de la recherche, il est bien clair qu'il faut tendre à atteindre des revues « d'excellence ».

Ainsi que l'a souligné le comité, l'arrivée d'un 3ème groupe de recherche avec lequel des collaborations étaient soit déjà développées soit en développement via notamment des ANR obtenues en commun, va encore renforcer l'équipe. L'ensemble des projets a ainsi été reconnu comme conférant une forte cohérence à l'équipe dans son ensemble. Plutôt que sur un management pyramidal, l'équilibre et la cohérence de l'équipe reposent sur un intérêt commun porté aux études métaboliques, sur la complémentarité des approches expérimentales développées, et sur la confiance et la volonté d'interaction des responsables des différents groupes.

Team 13 : Regeneration, Ploidy and Senescence in liver pathophysiology

Publications :

The committee noticed the deficiency in the productivity of the team in the last years. It has to be underlined that the project concerning cell senescence, fibrogenesis and cirrhosis regression is a new project that just began in 2006. One publication that was submitted when the AERES came to visit us in December is now accepted for publication (Mitchell et al, Dual role of CCR2 in the constitution and the resolution of liver fibrosis in mice) and will be published in May 2009 in the American Journal of Pathology (IF 5.9). Another publication concerning the role of oxidative stress in the early steps of fibrogenesis has just been submitted for publication (Mitchell et al, Protection against hepatocyte mitochondrial dysfunction is not sufficient to block fibrosis progression in mice).

As for the recommendation to publish in highly rated journals, an additional paper about the liver ploidy topic has been submitted to Journal of Clinical Investigation (IF 16.9) in January. This paper has received positive reviews and the additional experiments asked by the referees have been performed. The paper has been resubmitted last week (Celton-Morizur et al, Insulin/Akt pathway controls a specific division program leading to the genesis of mammalian tetraploid liver cells).

Project :

The committee was very concerned by the lack of focus of one of the two subgroups, while also recognizing the originality and the interest of the raised question on hepatocellular senescence and reversibility of fibrosis. To answer the recommendations to focus on one area of research, we have decided to abandon the growth hormone and FoxM1B side projects, thus allowing the subgroup to focus only on the main part of the project concerning hepatocellular senescence and fibrogenesis. Indeed, the fibrogenesis project has already shown a fruitful link with the hepatology Department of the Cochin Hospital, as noted by the committee, producing two recent common publications (Mallet et al, Ann Int Med and Mitchell et al, Am J Pathol). In addition, our project entitled "Senescence in the evolution from fibrogenesis to cirrhosis and cancer" has very recently been selected for funding by INCa.

In contrast, the team did not understand the remark concerning the limited transversal interactions between the two subgroups. We orally presented to the committee a project that combined the two main topics of the team. Moreover, we applied in 2008 for a common funding application entitled: "Hepatocyte senescence in the sequence fibrosis-cirrhosis and hepatocellular carcinoma" (ARC-INCA-ANRS).

Team 17- Lipids : metabolism and physiopathology

Our team is a young team with an international recognition for our contribution to the structure-function analysis of carnitine palmitoyltransferase 1 (CPT1). We think that Science cannot exist without taking up challenges and risks. In 2005, we decided to explore the fundamental importance of the CPT1/malonyl-CoA partnership for the understanding of the pathophysiology of metabolic diseases related to obesity and type 2 diabetes. Validation of our strategy to modulate the CPT1/malonyl-CoA partnership has now been published in Biochem. J (Akkaoui et

al, 2009). Studying in vivo the impact of uncoupling of CPT1 activity from malonyl-CoA inhibition definitively requires the generation of transgenic mice. This was indeed a risk for a young scientist recruited four years ago but was successful. An oral communication at the « American Diabetes Association 69th Scientific Sessions » in June 2009 will present this new and unique transgenic model. We feel confident that this new work will allow publications in high impact factor journals.

Team 18 : CoupTFII and glucose metabolism

Answers to the points raised by the evaluation committee on team 18

In the committee report on team 18, two comments need to be answered, regarding the scientific activity and contribution of a senior team member who joined the team a few months ago.

Firstly, concerning his scientific activity during the last 4 years, it was included in the general activity of his former team (team 14) since he only joined team 18 last September. Briefly, it can be summarized as follows: 7 original papers, 5 review articles, 3 book chapters, 2 thesis defended, head chief of a Master of science at Paris Descartes University and a consulting activity in GSK pharmaceutical industry.

Secondly, concerning his contribution to the scientific activity of the team 18, this was clearly stated in the team project provided to the AERES committee. this senior scientist is developing a project on the regulation and contribution of the nuclear receptor COUP-TFII in the hepatic glucose and lipid metabolisms. This study has begun in September 2008 with a Master student and the preliminary results are very promising. Moreover, his background in nuclear receptors and energy metabolism fits very well with the team project.

Team 19 : Genes, Nutrients and Iron

We thank the committee of AERES for the evaluation of our team but we would like to discuss two points.

First, we feel that one of our project has not been adequately evaluated. It was mentioned: "the scientific arguments linking hepcidin/HIF and cancer are poorly justified."

Noteworthy, it is on the basis of this project that the young scientist who joined the group recently ranked 1st for a position at INSERM and 2nd at CNRS (during the CR1 selection process) in 2007 and was granted by an "ANR Jeune chercheur" in 2008.

We never intended to state that HIF was an oncogene by itself, as the committee might have understood. Our hypothesis relies on the recently demonstrated role of HIF in myeloid cell-mediated inflammation and the well established link between inflammation and cancer. These two elements prompted us to ask whether HIF could be a link between infection by Helicobacter Pylori (leading to inflammation) and cancer. We have all the genetic tools available (different conditional HIF KOs) to answer this question.

Moreover, concerning the role of hepcidin in tumor progression, an article published last month (Ojalvo et al., 2009), showed that hepcidin is expressed by the Tumor Associated Macrophages, strengthening our hypothesis.

Second, it is somehow surprising to us that the committee opposed the two subgroups constituting the team. We are convinced that the strength of the team resides in its global entity and that each group contributed to "the overall excellence" of the team through different and specific inputs. As mentioned by the committee, the team is largely involved in international European consortia. In particular, what the committee bitterly considered as an "artefactually high" list of publications actually results from a dense network of active collaborations within the EXGENESIS network, including 21 European partners.

Pierre-Olivier Couraud
Directeur de l'Institut Cochin

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Membre de l'IFR Alfred Jost

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COMPLEMENTS
Réponses au rapport du comité d'experts

Unité de recherche :

Département Endocrinologie, Métabolisme, Cancer de l'Institut Cochin

Université Paris 5

L'Unité de recherche :

Nom de l'unité : Département Endocrinologie, Métabolisme, Cancer

Label demandé :

N° si renouvellement :

Nom du directeur : M. Pierre-Olivier COURAUD

Directrice du département : Mme Christine PERRET

Madame,

En complément des réponses apportées par les équipes du Département EMC, voici un élément important concernant l'équipe 13: Regeneration, Ploidy and Senescence in liver pathophysiology qui vient de nous parvenir

Le projet "sénescence dans la séquence fibrose-cirrhose-CHC" dans le cadre du programme d'actions INCA Cancer du foie vient d'etre accepté.
Or, seuls 12 projets ont été financés dans le cadre de cet appel d'offres.

Je vous serais reconnaissant de bien vouloir en prendre note dans le cadre de la réunion d'harmonisation
Merci
Très cordialement,

Pierre-Olivier Couraud