Signalisation, neurobiologie et 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 :

Signalisation, neurobiologie et cancer

de l'Institut Curie

Février 2009

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Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	Pierre Glorieux

Février 2009

Rapport d'évaluation

L'Unité de recherche :

Nom de l'unité : Signalisation, Neurobiologie et Cancer

Label demandé : UMR_S INSERM, UMR CNRS

N° si renouvellement :

Nom du directeur : M. Frédéric SAUDOU

Université ou école principale :

Institut Curie

Autres établissements et organismes de rattachement :

INSERM

CNRS

Université Paris 11

Date de la visite :

29 Janvier 2009

Membres du comité d'évaluation

Président :

M. Marc PIECHACZYK, CNRS, Institut de génétique moléculaire de Montpellier

Experts :

Ms. Annie ANDRIEUX, CEA, Institut de recherche en technologie et science du vivant, Grenoble

M. Jose ARAMBURU, Universitat pompeu fabra, Barcelona, Spain

M. Giampietro SCHIAVO, Cancer research, Molecular and neuropathobiology laboratory, London, UK

M. Axel BEHRENS, Cancer research, Group leader of Mammalian Genetics laboratory, London, UK

M. Charles THEILLET, Institut de recherche en cancérologie de Montpellier

M. Philippe MONTCOURRIER, Université Montpellier 2

M. Bernard DUCOMMUN, Toulouse, not present at the date of the visit because of a strike

Ms. Isabelle MANSUY, Zürich, Switzerland, not present at the date of the visit because of a strike

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

M. Thierry GALLI, CSS INSERM

M. Michel RAYMONDJEAN, CoNRS

M. Thierry DARRIBERE, CNU

Observateurs

Délégué scientifique de l'AERES :

M. Charles DUMONTET

Représentant de l'université ou école, établissement principal :

M. Daniel LOUVARD, Institut Curie

Représentants des organismes tutelles de l'unité :

Ms. Annick SALINI, INSERM

Ms Isabelle HENRY, INSERM

Ms Daniele MURCIANO, INSERM

Ms Urzula HIBNER, CNRS

M. Jacques BITTOUN, University

M. Martin KREISS, University

Rapport d'évaluation

1 • Présentation succincte de l'unité

- Total number of members: 28,5 including
  - 1 resarcher with teaching duties (MCF)
  - 5 resarchers including 2 DR and 3 CR
  - 10 postdoctoral fellows
  - 6 PhD students, all funded: 3 MENR, 2 Institut Curie, 1 Région Ile de France
  - 6.5 engineers , technicians and administrative assistants including 1 AI CNRS, 3,5 Curie (CDI), 2 CDD
- HDR: 5 HDR, dont 4 encadrent des thèses
- Number of students who have obtained their PhD since 4 years: 7
- Average length: 3,5 to 4 years, with 1 to 3 first author paper / student (including papers in Cell, Nat Medicine, EMBO J., Blood...)
- Nomber of publishing lab members: 7 out of 4 (neurobiology team); 3 (oncogenesis team)

This research unit originates from the UMR146 Curie Institute-Orsay, and is made up of two teams led by outstanding scientists.

The applicant unit currently includes 28.5 members. The recruitment of two additional (junior) groups is planned with the aim of expanding the Unit's expertise and savoir-faire. Additional space will be necessary to accommodate these new teams. Should the unit be created, there is a strong commitment of the Curie Institute's Scientific Director to find the required space in the vicinity of the two existing groups. Importantly, the new teams should also benefit of a "start-up package" from the Curie Institute. An official search has already been launched and candidates are currently interviewed. In parallel, contacts have been established with several promising young researchers.

The general theme of the research unit is signaling in neuropathology and cancer. So far, the neurobiology group has essentially been involved in the study of Huntington's disease (HD), whereas the oncogenesis group has essentially studied hematological and lymphoid malignancies. The two groups recently observed that they had been working on common signaling pathways and molecules in their respective systems. The association of the two team leaders, both experienced scientists with complementary expertise and common questions in signaling, is the leading force of this application. New promising common research lines have already been initiated. This corresponds to an important partial evolution of the neurobiology group towards cancer.

The projects presented by the two group leaders largely rely on extensive use of mouse models and, to a lesser extent, Drosophila. They are aimed at both basic and translational research and one is common to the two teams.

All equipments required for the success of the project (including animal facilities and imaging platforms) are available locally. The unit also benefits from common facilities available at the Paris campus of Curie Institute (transcriptomic, proteomic, microfluidic platforms, etc...).

2 • Déroulement de l'évaluation

The members of the committee received a clear and informative written document two months prior to the visit.

The visit took place on January 29, 2009. The committee first met in a closed-door meeting with the scientific delegate of the Aeres who explained the Aeres policy and gave indications on the criteria of evaluation. The oral communications started with a general presentation of the Curie Orsay and Curie Paris campuses by the Scientific Director of the Curie Institute. Then, the candidate director, presented both the history and the project of the applicant research unit. This was followed by scientific presentations by the leaders of the two founding teams. The committee then met and discussed sequentially with (i) the ITA/ITOS, (ii) the students and post-docs and (iii) the staff scientists and assistant professors. These discussions were followed by a meeting with the Institut Curie director and INSERM, CNRS, and University Paris 11 representatives. After a closed-door meeting of approximately one hour, the committee met with the candidate director of the applicant unit for further discussion.

3 • Analyse globale de l'unité, de son évolution et de son positionnement local, régional et européen

The already mentioned search is intended to recruit two junior groups, preferably with expertise in neurobiology and, possibly Drosophila genetics. This would complement the mouse genetic approach already used by the two existing groups. Contacts with several candidates have also been taken in parallel. Sufficient space is in principle guaranteed on the same floor as that of the two existing groups by the Scientific Director of the Curie Institute for this operation. Moreover, a start-up package by the Curie Institute should help the new team leaders to set up their laboratory. The committee is convinced that this operation will be highly beneficial for the future applicant unit to foster projects with even higher added value. The committee also feels confident with the criteria of excellence and scientific coherence that will be used for the selection of these new groups.

The committee was impressed by the quality and originality of the research carried out by the two constituting teams on the basis of several elements: (i) outstanding past achievements of the two groups, (ii) their high standard publication records, (iii) the quality and the ambition of the overall project of the future research unit, (iv) the international visibility of both group leaders who have made seminal observations in their fields and are attractive to international young scientists, (v) their robust network of national and international collaborations, and (vi) the efforts for translational research. Regarding the last point, the participation of the neurobiology group to a planned clinical trial based on its findings as well as common efforts by the two groups (in collaboration with the Transfer Department and the cancer hospital of the Curie Institute) to find new calcineurin inhibitors are particularly noteworthy. The group leaders have been involved in many expertise activities (i.e. paper reviewing, grant applications, scientific advisory boards, editorial work) and have been invited to present numerous seminars and lectures at scientific meetings, further proving their international status.

The two founding groups were until now operating in largely unrelated fields. Instead of proposing an opportunistic side-by-side association, they proposed a strong research interface on common scientific grounds in Neurobiology and Cancer. The recent evolution of part of the neurobiology lab towards topics related to cancer and the promising results recently obtained in common by the two groups convinced the committee that real collaborations have already started. Moreover, the committee is utterly convinced that the new unit will allow cross-fertilization, the neurobiology group bringing its cell biology expertise and the oncogenesis group contributing its cancer and mouse model know-how. The committee encourages the two groups to hold on this collaborative line and to find yet more synergism.

As for the candidate director, the committee is convinced that he is an outstanding and charismatic scientist. He has made major scientific achievements and has true management capabilities (i.e. to attract funds, create links with other laboratories at the local, national and international level, and contacts with various organizations, participation to expert panels). These past achievements represent important assets to secure the success of his research unit. All categories of personnel were very supportive of the candidate director and expressed their satisfaction/enthusiasm concerning the prospective of creating this new unit as well as their own future contribution.

Importantly, the involvement of the applicant research unit in the training of students and young scientists is exemplified by the high number of students and post-docs in the two applicant groups. Interestingly, many of them are foreigners, which testifies for the international attractiveness of the two teams. Next to this, there are two assistant professors among the staff scientists and one group leader is responsible of one teaching unit of the European master of Genetics at Paris 7. Finally, it is important to note that the Paris 11 University representative expressed the strong will of this university to strengthen the links with the research units located on the Curie-Orsay campus. How the Paris 11 University might practically support the applicant unit could however not be discussed.

4 • Analyse équipe par équipe et par projet

Team 1: "Cell Signaling and Oncogenesis"

This team has a long-standing and well-established international reputation in the field of oncogenesis. In recent years, many interesting observations have been made. Non-exhaustively, they relate to: (i) the role of the FLI-1 and PU.1 Ets family of transcription factors in mouse erythroleukemia models, (ii) the role of the TEL-JAK2 fusion oncoprotein resulting from chromosomal translocations found in human ALL and CML in leukemogenesis using genetically engineered mice and (iii) the role of the calcineurin phosphatase in aggressive forms of human and mouse B- and T-cell malignancies via its activation by signals emanating from the tumor environment. The last observation may have important implications as it shows that both calcineurin may have pro-oncogenic actions in vivo and might possibly represent a target for pharmacological intervention in lymphoid cancers. The work led to numerous publications in high standard journals (i.e. Nat Med, JCI, Blood, MCB, Canc Res, Oncogene, JBC), a patent application and numerous seminars and communications at meetings.

Based on its former work and expertise, the group now proposes an ambitious and convincing project largely based on the use of engineered mutant mice. Among the proposed specific objectives are: (i) the elucidation of the molecular basis of the pro-oncogenic activity of persistent STAT5 activation in T-cell leukemogenesis, (ii) the dissection of the intrinsic role of calcineurin in leukemogenesis, in particular via its action on the NFAT family of transcription factors and (iii) the study of the importance of calcineurin and/or the NFAT transcription factors in breast cancer cell migration, invasion and metastasis.

Strong points:

The project is ambitious and addresses important issues. Long-standing expertise, high status in the field and a robust network of national and international collaborations are valuable assets. The production of the group (12 persons) is all the more remarkable that all of its projects were supervised by only two senior researchers. The group leader is currently the director of UMR146 (made up of 8 teams, which all showed satisfying to excellent productivity). He was frequently solicited for his expertise. His objectives are in keeping with the expertise/know-how/adaptability of the group.

Weak points:

Increasing the number of staff scientists would help.

Nom de l'équipe : Cell Signaling and Oncogenesis

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 2: "Cell Signaling and Neurobiology"

The group has long been studying the molecular mechanisms and signaling pathways controlling neuronal cell death in HD. Many important observations were made during the past years. They include, among others: (i) the role of huntingtin (Htt) in axonal transport of BDNF, (ii) the identification of cysteamine as a drug of

potential interest in the treatment of HD, (iii) the possible use of HDAC6 inhibitors to compensate the axonal transport deficit observed in HD by increasing microtubule acetylation via recruitment of molecular motors, (iv) the identification of several kinases and phosphatases (Akt, SGK, cdk5, calcineurin) impacting on

phosphorylation of Htt and, thereby, its toxicity, (v) the identification of Htt as a component of the DNA damage response pathway in neurons.

This has led to numerous publications in high standard journals (Cell, JCI, EMBO J, J. Neurosci., Development, etc…) and numerous seminars and communications at meetings.

The proposed project is very ambitious and convincing. Some aspects are particularly imaginative. Most of the questions asked are the logical continuation of the former lines of research. However, new issues will be addressed by combining not only cell biology and mouse genetics, but also Drosophila genetics and analyses of new human pathological diseases.

Among the "non-classical" functions of Htt that will be addressed, are: (i) the implication of Htt in the control of mitosis and the response to DNA damage, (ii) the involvement of Htt in breast cancer and (iii) the role of Htt in ciliogenesis in health and disease.

There is also a strong investment of the group in translational research in particular through (i) its role in a clinical trial using cysteamine, (ii) the search of new inhibitors of calcineurin supported by the PIC program (Cooperative and Incentive Program) of the Curie Institute and (iii) participation to complete ENT (ear-nose-throat) evaluation of HD patients.

Strong points:

The project is ambitious and addresses important issues. Some specific objectives and approaches are particularly imaginative. Long-standing expertise, demonstrated efficacy in the field, ability to develop and adapt new technologies to answer new biological questions, and a robust network of national and international collaborations are very valuable assets. The objectives are in keeping with the size (17 persons)/expertise/know-how/adaptability of the group.

Weak points: None.

Nom de l'équipe : Cell Signaling and Neurobiology

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+

5 • Analyse de la vie de l'unité

The working conditions (space, equipment of the laboratory, common facilities, budget, support of the Curie Institute, scientific animation, access to technological platforms, excellent relationships between people and groups, etc…) are there to guarantee the success of the proposed objectives. As this is an applicant unit, it is difficult to forecast the future social relationships within the unit. However, in the context of the founding groups originating from the former UMR146 and having a long-standing common life side-by-side, the committee is confident in their ability to make the best use of human resources and to develop a stimulating intellectual environment. Moreover, as already mentioned, all personnel involved in the application are enthusiastic about the project. They all expressed their overall satisfaction concerning their current situation/supervision/condition of work in the UMR146. Additionally, no non-solvable problem could be detected during the visit. Current personal and technological interactions between the groups seem excellent. Collaborations have already started and should increase in the future.

6 • Conclusions

Strong points:

The two groups have already made several outstanding achievements and are leaders in their field. The team leaders are internationally renowned scientists. The proposed objectives are strategically in line with past projects. They are ambitious yet realistic. Moreover, collaborations between the two groups of the applicant unit have already started and should lead to interesting results. The switch of part of the neurobiology team to cancer should strengthen the links with the oncogenesis team. The recruitment of two new teams will conceptually and technologically increase the critical mass of the unit. The planned scientific activities

(internal seminars, external seminars, retreat, participation to meetings, etc…) are aimed at reaching the highest achievements. Furthermore, there are true translational research efforts, some benefiting from the internal PIC program of the Curie Institute and others in connection with the Hospital (including in the Curie Institute). The project and the director are supported by all personnel.

Weak points:

Although the desire to strengthen the links between the two groups is likely to be genuine, there is a potential risk of "side-by-side coexistence". Careful attention must therefore be paid to maintaining and developing collaborations. A careful choice of the new groups and new collaborators (staff scientists and/or technicians) may further help. Technical staff is limited and should be increased. Adequate measures should be taken to recruit upon the arrival of the new groups. The help of the Paris 11 University at this level (via the creation of technician, MC and/or professor positions) would be a convincing demonstration of its will to support the applicant unit.

Overall conclusion:

Taking into account the individual qualities of the two founding groups of the applicant unit and the high quality of the proposed project the Committee has no doubt that outstanding work with major scientific impact will be generated from this new Unit.

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

UNIVERSITÉ
PARIS-SUD 11

Le Président de l'Université Paris-Sud 11

à

Monsieur Pierre GLORIEUX
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 10 avril 2009.

N/Réf. : 127/09/GCo/LM/LS

Objet : Rapport d'évaluation d'unité de recherche
N° S2100012423

Monsieur le Directeur,

Vous m'avez transmis le trois avril dernier, le rapport d'évaluation de l'unité de recherche « Signalisation, neurobiologie et cancer », et je vous en remercie.

L'université prend bonne note de l'appréciation et des suggestions faites par le Comité.

Veuillez trouver ci-joint un message du directeur d'unité.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma sincère considération.

Guy COURRAZE
Président

Pour le Président empêché
La Vice-Présidente

UNIVERSITE PARIS-SUD 11 - Présidence - 91405 ORSAY CEDEX

Sylvie VOISIN

P.J. : Commentaires de Mr SAUDOU

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CENTRE DE RECHERCHE

institutCurie
Ensemble, prenons le cancer de vitesse.

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Ref : Volet 1 : Observations générales

Orsay, April 3rd, 2009

To whom it may concern,

Please find below our comments to the AERES report :

General comments for the Unit « Signaling, Neurobiology and Cancer »

We thank the committee for its comments. Overall most of the comments are extremely positive on the scientific quality of the teams and their individual projects and, on the overall unifying project of the Unit and the synergies that will emerge from this project. However, the future Director of the Unit is fully aware of the potential risk of « side-by-side-coxistence » and will pay a lot of attention to this risk by encouraging the collaborations between the two founding groups. The continuation and further expansion of existing collaborations between the two groups are therefore extremely important and are given a high priority.

In addition, besides high scientific standards, the recruitment of new group leaders will be conditioned by the existence of clear and objective interfaces between their scientific interests and those of existing teams. Willingness to effectively strengthen interactions along these lines will be a major requirement in our selection process.

Finally, we hope that, as suggested by the committee, a strong support in term of technicians, Ingénieurs d'Etude and/or de Recherche and/or MCF will be effective from our different « tutelles » to make sure that we are in a good position to achieve our objectives.

Specific comments for team 1 « Cell Signaling and Oncogenesis », J. Ghysdael.

The Team 1 group leader is fully aware that additional staff scientists would help to further structure the laboratory. We hope and expect that our novel "tutelle", the Paris 11 University will help by providing our team with a dynamic MC, eager to pursue a scientific career.

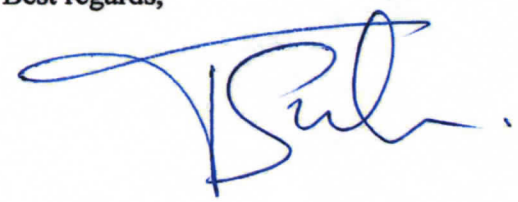
Specific comments for team 1 « Cell Signaling and Neurobiology », F. Saudou.

There are only positive comments from the committee. We also expect, as for team 1, a support from our tutelles. In our case we have a tremendous need for technician/Ingenieur de Recherche and a strong support from our « tutelles » would be recognized as an encouragement to our project that was favorably evaluated by the AERES.

Thank you very much for your support,

Sincerely Yours,

Best regards,



Frédéric Saudou, PhD
DR1, Inserm