SABNP - Structure et activité des biomolécules normales et pathologiques

Rapport Hcéres

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

Section des Unités de recherche

Rapport d'évaluation

Unité de recherche :

Structure et Activité des Biomolécules Normales et Pathologiques

de l'Université d'Evry

Mars 2009

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

Section des Unités de recherche

Rapport d'évaluation

Unité de recherche

Structure et Activité des Biomolécules Normales et Pathologiques

de l'Université d'Evry

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 : Structure et Activités des Biomolécules Normales et Pathologiques (SABNP)

Label demandé : UMR_S INSERM

N° si renouvellement : 829

Nom du directeur : M. Patrick CURMI

Université ou école principale :

Université d'Evry

Autres établissements et organismes de rattachement :

INSERM

Date de la visite :

10 Février 2009

Membres du comité d'experts

Président :

M. Didier JOB (Université de Grenoble)

Experts :

M. Michel STEINMETZ (Paul Scherrer Institute, Suisse)

M. Carsten JANKE (CRBM, Montpellier)

M. Simon SCHEURING (Institut Curie, Paris)

M. Franck PEREZ, (Institut Curie, Paris)

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

Mme Jane-Lise SAMUEL, CSS INSERM representative

Observateurs

Délégué scientifique de l'AERES :

M. Bernard DASTUGUE

Représentant de l'université ou école, établissement principal :

Mme Jeanine TORTAJADA, Université d'Evry

Mme Françoise RUSSO-MARIE, Genopole

Représentant(s) des organismes tutelles de l'unité :

Mme Catherine LABBE-JULLIE, INSERM

Mr Michel VOGEL,INSERM

Rapport d'évaluation

1 • Présentation succincte de l'unité

- Effectif : 21 personnes dont:
  - 7 enseignants-chercheurs
  - 2 chercheurs
  - 3 ingénieurs
  - 2 doctorants, tous financés
  - 1 technicien ou administratif
- Nombre de HDR: 3, tous encadrant des thèses
- Nombre de thèses soutenues depuis 4 ans : 2,
- Nombre de membres bénéficiant d'une PEDR : 1
- Nombre de publiants: 9 sur 9

2 • Déroulement de l'évaluation

Les membres du comité avaient reçu avant la visite tous les documents et les avaient lus. Une réunion préparatoire de 30min a permis aux différents experts du Comité de faire connaissance et de valider les consignes propres aux expertises AERES. Après un déjeuner spartiate avec le DU, au cours duquel des échanges constructifs ont été initiés, la visite a débuté après 13h, elle a été construite autour de 4 présentations par le DU (présentation générale et exposé thématique et 3 responsables de thèmes). Elle a permis d'évaluer aux plans scientifiques et structurels et de façon positive et constructive. Après les exposés et questions, une discussion a eu lieu entre le comité et les représentants des tutelles. En réunion à huis clos, une synthèse de l'évaluation, une ébauche de rapport a été réalisée en présence de l'ensemble du comité et du Conseiller scientifique. La fin de la visite et le départ du comité se situe à 17h30.

La visite sur site était bien organisée et s'est bien déroulée.

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

The laboratory was created two years ago, mainly as a structural technology platform. The core element of the platform was NMR but the platform has been rapidly extended by the adjunction of atomic force microscopy (AFM) technologies and of bio-informatic tools for structure-based drug design. The Unit Director has undertaken a major effort to organize the development and use of these facilities around a common theme: microtubule physiopathology. This effort is still in progress and will be pursued in the upcoming four years. Globally, the committee has expressed its appreciation for the vitality and energy developed by the team in its adaptative phase and has judged that the good progress achieved within a short amount of time by the group deserved full support from its institutional and funding partners for the next four years.

For Evry university and genopole leaders, this unit represents a very important basis for the development of technology and scientific education. Therefore the university and the genopole have invested very significant amounts of money and manpower to support the group, and they clearly intend to pursue their support.

The committee expresses its support and appreciation to the leader and his team. In four years, a future evaluation committee will, in the present committee's view, have to assess the progress achieved in the integration of the technological and biological programs and the group's ability to develop selected and cutting edge aspects of its many interesting researches into coherent and novel biological concepts. If this is successfully done, the group may reach its claimed goal to be at the forefront of microtubule research in the near future.

4 • Analyse équipe par équipe et par projet

Theme 1

The committee has appreciated the potential of the spastin work in progress. The study of spastin deficient neurons has led to a series of unexpected and intriguing observations which open exciting perspectives in terms of both cell biology and therapy. The use of the centrosomal protein CPAP as an inhibitor of tubulin assembly was also appreciated. A peptide derived from the centrosomal protein CPAP by the group has the unique property to inhibit the self aggregation of GTP tubulin. In principle, this could lead to the elucidation of the GTP tubulin structure which is a major goal in structural biology. Attempts to crystallize the tubulin/peptide complex have thus far been unsuccessful; The potential of the peptide for NMR studies, including, NMR studies of tubulin interaction with drug have been recognized. Intersting also is the discovery that a transcription factor YB1 has microtubule binding and stabilizing properties and can couple RNps to microtubules. This may be a starting point for an exciting research project. Obviously a lot of in vivo studies are needed before the real potential of this topic can be assessed but it is certainly worth trying. The group already plans structural researches on STOP proteins. If successful, these researches could also deliver novel and interesting information concerning microtubule structure and function.

Theme 2

Paramecium biology has been subject of sustained and very successful efforts in France along the years and many among us have expressed regret that a sad lack of human resources have precluded the full development of a field in which French research happened to be at the forefront. Paramecium research has recently been boosted by the emergence of siRNAs techniques which work extremely well in this organism and which made the use of functional genomics possible in a system displaying a remarkably complex microtubule cytoskeleton. In the past, the theme II leader has used Paramecium successfully to decipher the function of new members of the expanding tubulin family. Within the INSERM context, the use of Paramecium looks very attractive because of recent developments in human genetics showing a crucial role of primary cilia and of the corresponding protein transport systems in vital signaling pathways (Wnt, Heghog) and in a variety of human pathologies. Many of the proteins involved in human diseases have counterparts in Paramecium which are targeted by the team for functional studies.

Theme 3

The objectives of which are to model tubulin to better understand its interactions and design drug candidates. Microtubule drugs: the committee wishes to draw attention that tubulin is not precisely an original target in pharmaceutical research, Therefore, it is really important that the drug discovery activity of the group has in a way or another a cognitive interest. A second program developed in the theme III concerns polyamines as microtubule regulators. The group has developed a model in which polyamines promote facilitated diffusion of tubulin during polymer assembly. This model has actually been published but it seems to the committee that it remains to be demonstrated that diffusion is a limiting factor for microtubule nucleation and elongation, in the assembly conditions used by the group, and that polyamines are important microtubule regulators in vivo.

Nano diamonds

Apart from its main effort in the microtubule field, the team has developed methods to prepare fluorescent nanodiamonds. This work has been performed within the framework of a European consortium of which the team leader is the coordinator. These nano diamonds may have many attractive properties such as biocompatibility (absence of toxicity of carbon) and absence of photobleaching upon prolonged illumination.

Despite the interest of AFM data reported during the visit, the comitee noted that AFM in liquid environment would really useful in the context of the group's research. This will strengthen the activity of the entire unit and provide better visibility. One of the major advantages of the AFM is it's capability to image molecules under physiological conditions. Indeed, in liquid, interactions and influences of molecules and proteins at disposition from the group with microtubules could be studie.

5 • Analyse de la vie de l'unité

— En termes de management :

The laboratory was created two years ago, mainly as a structural technology platform. The core element of the platform was NMR but the platform has been rapidly extended by the adjunction of atomic force microscopy (AFM) technologies and of bio-informatic tools for structure-based drug design. The unit director has undertaken a major effort to organize the development and use of these facilities around a common theme: microtubule physiopathology. This effort is still in progress and will be pursued in the upcoming four years.

The Comitee notice the good quality of the management. Thus, the unit succeeded to gain many contracts and to raise money and fundings. The members of the unit look as motivated and happy to work together and appreciate their interactions . It was noted that the Evry University and the genopole have invested very significant amounts of money and manpower to support the group, and they clearly intend to pursue their support.

— En termes de ressources humaines :

The Unit Director was able to recruit new collaborators (2 MCU for example) in a recent past.

— En termes de communication :

The publications are of quality, the seniors are invited for lecture. It should be pointed out that the lab being 2 year-old, such an evaluation in rather premature.

6 • Conclusions

— Strengths :

Globally, the committee has expressed its appreciation for the vitality and energy developed by the team in its adaptative phase and has judged that the good progress achieved within a short amount of time by the group deserved full support from its institutional and funding partners for the next four years. In four years, a future evaluation committee will, in the present committee's view, have to assess the progress achieved in the integration of the technological and biological programs and the group's ability to develop selected and cutting edge aspects of its many interesting researches into coherent and novel biological concepts. If this is successfully done, the group may reach its claimed goal to be at the forefront of microtubule research in the near future.

Particularly, the committee has expressed enthusiastic appreciation concerning the potential of Paramecium research axis, for the clever discovery and use of the centrosomal protein CPAP as an inhibitor of tubulin assembly. In addition the committee has been impressed by the achievements of the group and the width of possible developments of the nano diamond project.

— Weaknesses :

The committee has been a bit concerned by the multiplicity of themes tackled by the group. It got the impression that instead of developing a full and coherent scientific program, the group tends to stop at relatively preliminary steps of its research to jump on possible biotechnological applications. The danger inherent to such a multiplicity of themes and interests is that it can happen that researches are developed in the absence of well selected and cutting edge questions, a realistic view of competition in the respective research fields, and of the scientific environment in general.

Regarding Theme III, the committee wishes to draw to Unit leader's attention that tubulin is not precisely an original target in pharmaceutical research, and that on this basis only, grants applications concerning their development will almost certainly be turned down.

But in fact the main concern of the committee, which extends to the whole activity of the group in its drug discovery efforts is that, obviously, the probability to really develop a new therapeutic drug is very low. Cognitive stakes in the current drug based projects of the group were not evident to the committee. Moreover, it was not clear to the committee how synthesis of a probably large variety of different chemical compounds will be secured and how the activity profiles of promising compounds will be assessed both in vitro and in vivo.

—Recommandations :

To continue the effort to better focus the activity of unit towards an unique research axis.

To maintain and develop the potential of Paramecium as a model for post genomic functional studies of the cytoskeleton.

To conduct AFM in liquid environment to be really useful in the context of the group's research. The committee is positive that the AFM team is able to implement this development.

It would be suggested to the Evry University to indicate precisely the scientific axis that they wish to actively develop in a near future.

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 D'EVRY
VAL D'ESSONNE

Université d'Evry-Val-d'Essonne
Cabinet de la Présidence

Affaire suivie par :
Emery Olivier
Téléphone :
01.69.47.80.46

Evry, le jeudi 16 avril 2009

Le Président de l'Université

à

Monsieur Jean-François DHAINAUT
Directeur de l'AERES

Objet : Rapport d'Evaluation de l'Unité U 829, S2100015338

Monsieur le Directeur,

Vous m'avez transmis le rapport d'évaluation de l'Unité « Structure et Activité des Biomolécules Normales et Pathologiques » (U829; INSERM UEVE) dirigée par le Dr. Patrick CURMI.

Vous trouverez ci-joints, en réponse au rapport qui lui a été adressé, ses remarques et ses commentaires.

Je me réjouis de la teneur très positive et encourageante de ce rapport et remercie le Comité pour la qualité de son travail d'évaluation. Je prend note des recommandations émises et témoigne que les travaux de cette unité s'inscrivent bien dans l'axe prioritaire du volet recherche du contrat quadriennal. L'Université soutient fortement cette unité, elle a en effet ouvert pour la campagne de recrutement 2009, deux postes de Professeur.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de mes salutations distinguées.

Le Président de l'université
d'Evry-Val-d'Essonne

Richard MESSINA

UNIVERSITÉ D'EVRY
PRÉSIDENCE
VAL D'ESSONNE

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

Laboratoire Structure et Activité des Biomolécules
Normales et Pathologiques
INSERM / UEVE U829
Docteur Patrick CURMI
Directeur

Evry, 8 avril 2008

Réponse du Directeur de l'UMR INSERM – UEVE U829 aux observations faites par l'AERES lors de la visite du 10 février 2009.

Les réponses sont indiquées en caractères bleus.

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

The laboratory was created two years ago, mainly as a structural technology platform. The core element of the platform was NMR but the platform has been rapidly extended by the adjunction of atomic force microscopy (AFM) technologies and of bio-informatics tools for structure-based drug design.

Comment from U829:

In addition, the lab has also acquired protein expression/purification tools, biochemistry instruments, cell biology and microscopy equipments. Furthermore, a cell culture laboratory was financed by INSERM and a dedicated lab has been created and funded by Genopole for the Paramecium team.

The Unit Director has undertaken a major effort to organize the development and use of these facilities around a common theme: microtubule physiopathology. This effort is still in progress and will be pursued in the upcoming four years. Globally, the committee has expressed its appreciation for the vitality and energy developed by the team in its adaptative phase and has judged that the good progress achieved within a short amount of time by the group deserved full support from its institutional and funding partners for the next four years. 5 For Evry University and Genopole leaders, this unit represents a very important basis for the development of technology and scientific education. Therefore the university and the Genopole have invested very significant amounts of money and manpower to support the group, and they clearly intend to pursue their support. The committee expresses its support and appreciation to the leader and his team. In four years, a future evaluation committee will, in the present committee's view, have to assess the progress achieved in the integration of the technological and biological programs and the group's ability to develop selected and cutting edge aspects of its many interesting researches into coherent and novel biological concepts. If this is successfully done, the group may reach its claimed goal to be at the forefront of microtubule research in the near future.

SABNP, INSERM U829 et Université d'Evry, bâtiment Maupertuis, rue du Père Jarlan, 91025 Evry, France
tel: 33 1 69 47 03 23 *fax:* 33 1 69 47 02 19 *e-mail:* pcurmi@univ-evry.fr

4 Analyse équipe par équipe et par projet

Theme 1 The committee has appreciated the potential of the spastin work in progress. The study of spastin deficient neurons has led to a series of unexpected and intriguing observations which open exciting perspectives in terms of both cell biology and therapy. The use of the centrosomal protein CPAP as an inhibitor of tubulin assembly was also appreciated. A peptide derived from the centrosomal protein CPAP by the group has the unique property to inhibit the self aggregation of GTP tubulin. In principle, this could lead to the elucidation of the GTP tubulin structure which is a major goal in structural biology. Attempts to crystallize the tubulin/peptide complex have thus far been unsuccessful; The potential of the peptide for NMR studies, including, NMR studies of tubulin interaction with drug have been recognized. Interesting also is the discovery that a transcription factor YB1 has microtubule binding and stabilizing properties and can couple RNPs to microtubules. This may be a starting point for an exciting research project. Obviously a lot of in vivo studies are needed before the real potential of this topic can be assessed but it is certainly worth trying. The group already plans structural researches on STOP proteins. If successful, these researches could also deliver novel and interesting information concerning microtubule structure and function.

Theme 2 Paramecium biology has been subject of sustained and very successful efforts in France along the years and many among us have expressed regret that a sad lack of human resources have precluded the full development of a field in which French research happened to be at the forefront. Paramecium research has recently been boosted by the emergence of siRNAs techniques which work extremely well in this organism and which made the use of functional genomics possible in a system displaying a remarkably complex microtubule cytoskeleton. In the past, the theme II leader has used Paramecium successfully to decipher the function of new members of the expanding tubulin family. Within the INSERM context, the use of Paramecium looks very attractive because of recent developments in human genetics showing a crucial role of primary cilia and of the corresponding protein transport systems in vital signaling pathways (Wnt, Heghog) and in a variety of human pathologies. Many of the proteins involved in human diseases have counterparts in Paramecium which are targeted by the team for functional studies.

Theme 3 The objectives of which are to model tubulin to better understand its interactions and design drug candidates. Microtubule drugs: the committee wishes to draw attention that tubulin is not precisely an original target in pharmaceutical research.

Comment from U829:

We do agree that tubulin is not an original target (i.e. a novel target) in pharmaceutical research. However tubulin/microtubules targeting drugs are among the most successful compounds for cancer chemotherapy whatever their direct/indirect impact on cell division. Moreover, understanding how these compounds act and efforts to develop novel ones represent an active and competitive research field and it is clear that all has not been discovered (see for example Hadfield et al., Progress in Cell Cycle Res. 2003 5:309-325, Buey et al., Nat Chem Biol 2007 3:117-125, Morgan et al., Chem Biol Drug Des 2008 72:513–524).

The effort of the "Molecular modeling & Drug design" team is to provide an accurate model of □- and □-tubulin to understand the molecular dynamics of tubulin and its interactions with different partners, either small molecules or protein fragments. Such an understanding will first enlighten the mechanism of vital biological processes. The results will also pave the way to design small molecules to interfere with these fundamental biological processes. In addition, it may occur that, among these small molecules, some of them could represent effective drug candidates because of their outstanding biochemical or cellular activities. This is only this subset of compounds that may be used in our drug design strategy. The drug design strategy

developed in the lab differs from industrial high throughput screening of molecules. It rather aims at discovering interacting pockets based on the knowledge of atomic structure and molecular dynamics and consists eventually at providing a 3D-pharmacophore. A 3D-pharmacophore represents the signature of pharmacological activity of selected or designed compounds. It describes a set of physicochemical centers in a geometric space. Any molecule fitting with the 3D pharmacophore is a drug candidate. The idea here is finally to patent the 3-pharmacophore and a small library of compounds to exemplify its uniqueness that could be used in a second time by pharmaceutical companies.

Therefore, it is really important that the drug discovery activity of the group has in a way or another a cognitive interest.

Comment from U829:

We do believe that by essence science is always cognitive and all information grasped along research programs is cognitive since it brings additional knowledge and novel views on specific mechanisms (biochemical reactions or ligand-receptor interactions in our case). With respect to this view, our researches have all, as first objectives, cognitive perspectives (work on tubulin structure, on its interaction with partners, its assembly, the modelization of its folding and dynamics, etc…). However, while science and cognition are academic concepts that motivate us in our daily research, one of our duties, as an INSERM unit, is also to produce information for medical applications. Valorization through industrial application, with the help of our institutions, represents a contribution from our community to reward the public for the money spent for financing public research programs.

Thanks to our experience and expertise we have brought the proof that our drug discovery methodology is able to lead to a real industrial valorization. We have filled a series of patents on diagnostic kits allowing quantitative measurements of a biomarker, which is specific of pathologies. Hence, we have a patent on an antiangiogenic drug acting of the cytoskeleton of vascular endothelial progenitor migration and proliferation. Based on the design of this compound, we are also currently bringing the proof of concept of the efficacy of a molecular probe that can be used for medical imaging (PET scan, MRI) for enlightening tumor vascularization with a strong collaboration of research teams of the Curie Institute and the ESPCI. This technology will be transferred to the medical imaging industry.

A second program developed in the theme III concerns polyamines as microtubule regulators. The group has developed a model in which polyamines promote facilitated diffusion of tubulin during polymer assembly. This model has actually been published but it seems to the committee that it remains to be demonstrated that diffusion is a limiting factor for microtubule nucleation and elongation, in the assembly conditions used by the group, and that polyamines are important microtubule regulators in vivo.

Comment from U829:

Microtubules are highly dynamical polymers for which diffusion plays a major role. The fact that diffusion can be a limiting factor is based on extensive literature on the power-law dependence of the nucleation duration with free tubulin concentration (Voter and Erickson J Biol Chem 1984 259:10430-10438) and on the linear relationship between free tubulin concentration and the elongation rate (Walker et al J Cell Biol 1988 107:1437-1448; Desai and Mitchison Annu Rev Cell Dev Biol 1997 13:83-117). Some of these latter measurements (Walker et al J Cell Biol 1988 107:1437-1448) were directly performed at the single microtubule level using videomicroscopy and seeded microtubules, thus avoiding the effect of nucleation and other potential artefacts. Our recently published results show that polyamines act positively on

microtubule assembly via facilitated diffusion. We however agree with the committee that this has now to be demonstrated in living cells. Ongoing researches will enlighten this point which could provide original and promising strategies to target microtubule dynamics indirectly.

6 Nano diamonds Apart from its main effort in the microtubule field, the team has developed methods to prepare fluorescent nanodiamonds. This work has been performed within the framework of a European consortium of which the team leader is the coordinator. These nano diamonds may have many attractive properties such as biocompatibility (absence of toxicity of carbon) and absence of photobleaching upon prolonged illumination. Despite the interest of AFM data reported during the visit, the committee noted that AFM in liquid environment would really useful in the context of the group's research. This will strengthen the activity of the entire unit and provide better visibility. One of the major advantages of the AFM is it's capability to image molecules under physiological conditions. Indeed, in liquid, interactions and influences of molecules and proteins at disposition from the group with microtubules could be studied.

Comment from U829:

Our group has acquired a good experience concerning AFM in liquid and two works were recently published dealing with the reversible binding of DNA to mica (Piétrement et al Langmuir 2003 19:2536-2539) and DNA/ligand interactions (Pastré et al Biopolymers 2005 77:53-62). However, performing high resolution imaging of cytoskeletal structures is very challenging and its feasibility remains to be demonstrated. The time lapse between two AFM images in liquid is longer than 30 s and thus not suitable to study microtubule elongation (~10 µm/min) or shrinkage processes. On the other hand, AFM images of fixed samples are very useful and our data show that they are indeed promising tools to observe intermediary structures like GDP-tubulin rings, microtubule bundling, microtubule/protein complexes and to measure microtubule length distribution.

5 Analyse de la vie de l'unité

— En termes de management : The laboratory was created two years ago, mainly as a structural technology platform. The core element of the platform was NMR but the platform has been rapidly extended by the adjunction of atomic force microscopy (AFM) technologies and of bio-informatics tools for structure-based drug design. The unit director has undertaken a major effort to organize the development and use of these facilities around a common theme: microtubule physiopathology. This effort is still in progress and will be pursued in the upcoming four years. The Comitee notice the good quality of the management. Thus, the unit succeeded to gain many contracts and to raise money and fundings. The members of the unit look as motivated and happy to work together and appreciate their interactions. It was noted that the Evry University and the Genopole have invested very significant amounts of money and manpower to support the group, and they clearly intend to pursue their support.

— En termes de ressources humaines : The Unit Director was able to recruit new collaborators (2 MCU for example) in a recent past.

Comment from U829:

The efforts to recruit new collaborators concern the creation of 2 Engineers positions (1 for the NMR platform by Evry University, the other in biology by INSERM). In addition, 1 Pr, 4 MCU, and an INSERM researcher joined our unit during the last three years together with a secretary provided by INSERM.

— En termes de communication : The publications are of quality, the seniors are invited for lecture. It should be pointed out that the lab being 2 year-old, such an evaluation in rather premature.

6 Conclusions

— Strengths : Globally, the committee has expressed its appreciation for the vitality and energy developed by the team in its adaptative phase and has judged that the good progress achieved within a short amount of time by the group deserved full support from its institutional and funding partners for the next four years. In four years, a future evaluation committee will, in the present committee's view, have to assess the progress achieved in the integration of the technological and biological programs and the group's ability to develop selected and cutting edge aspects of its many interesting researches into coherent and novel biological concepts. If this is successfully done, the group may reach its claimed goal to be at the forefront of microtubule research in the near future. Particularly, the committee has expressed enthusiastic appreciation concerning the potential of Paramecium research axis, for the clever discovery and use of the centrosomal protein CPAP as an inhibitor of tubulin assembly. In addition the committee has been impressed by the achievements of the group and the width of possible developments of the nano diamond project.

7 — Weaknesses: The committee has been a bit concerned by the multiplicity of themes tackled by the group. It got the impression that instead of developing a full and coherent scientific program, the group tends to stop at relatively preliminary steps of its research to jump on possible biotechnological applications. The danger inherent to such a multiplicity of themes and interests is that it can happen that researches are developed in the absence of well selected and cutting edge questions, a realistic view of competition in the respective research fields, and of the scientific environment in general.

Comment from U829:

As stated by the committee, the unit has been reorganized around a central theme: Microtubule physiopathology. For example, researches on dystrophin fragments and on Id2 have been discontinued. The unit director will take note of advices from the committee to further concentrate activity on its central interest.

Regarding Theme III, the committee wishes to draw to Unit leader's attention that tubulin is not precisely an original target in pharmaceutical research, and that on this basis only, grants applications concerning their development will almost certainly be turned down. But in fact the main concern of the committee, which extends to the whole activity of the group in its drug discovery efforts is that, obviously, the probability to really develop a new therapeutic drug is very low. Cognitive stakes in the current drug based projects of the group were not evident to the committee.

Comment from U829:

See above response.

Moreover, it was not clear to the committee how synthesis of a probably large variety of different chemical compounds will be secured and how the activity profiles of promising compounds will be assessed both in vitro and in vivo.

Comment from U829:

The synthesis of a large variety of compounds is out of the scope of our drug design strategy, (see above response).

— Recommandations: To continue the effort to better focus the activity of unit towards an unique research axis. To maintain and develop the potential of Paramecium as a model for post genomic functional studies of the cytoskeleton. To conduct AFM in liquid environment to be really useful in the context of the group's research. The committee is positive that the AFM team is able to implement this development.

Comment from U829:

See point-to-point responses above.

It would be suggested to the Evry University to indicate precisely the scientific axis that they wish to actively develop in a near future.

Comment from U829:

Our activities are in line with the main priority axis "Sciences génomiques et post-génomiques: application à la santé et l'environnement" of the Université Evry Val d'Essonnne. See the "Contrat quadriennal 2010-2013" of Evry university on http://www.univ-evry.fr/fr/l_universite/presentation_generale2/projet_d_etablissement.html .

Patrick CURMI