Maladie d'Alzheimer : facteurs de risque, soins et accompagnement

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit

Maladie d'Alzheimer : facteurs de risque, traitement et prise en charge

University Paris 5

March 2009

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

Section des Unités de recherche

Evaluation report

Research unit

Maladie d'Alzheimer : facteurs de risque, traitement et prise en charge

University Paris 5

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2009

Evaluation report

The research unit :

Name of the research unit : Maladie d'Alzheimer : facteurs de risque, traitement et prise en charge

Requested label : EA

N° in case of renewal :

Head of the research unit : Ms Anne-Sophie RIGAUD

University or school :

University Paris 5

Other institutions and research organization:

Date of the visit :

11th March 2009

Members of the visiting committee

Chairman of the commitee :

M. Philip SCHELTENS, VU University Medical Center, Amsterdam, Netherlands

Other committee members :

Ms Helene AMIEVA, Université Victor Segalen, Bordeaux, France

CNU, CoNRS, CSS INSERM, INRA, INRIA, IRD representatives :

No CNU member was available on the date determined for the visiting committee.

Observers

AERES scientific representative:

M. Erwan BEZARD

University or school representative:

M. Brunot VARET, University Paris 5

Evaluation report

1 • Short presentation of the research unit

- Number of researchers with teaching duties : 14
- Number of full time researcher : 1
- Number of post doctoral fellows : 1
- Number of PhD students : 5
- Number of technicians and administrative assistants : 4, including 2 full time and 2 for 10%
- Number of HDR : 2, both are students advisors
- Number of students who have obtained their PhD during the past 4 years : 2
- Average duration of PhD during the past 4 years : 3.5 years
- Number of lab members who have been granted a PEDR : 0
- Number of "publishing" lab members : 12 out of 15

2 • Preparation and execution of the visit

The visit went smoothly with all aspects of the evaluation covered satisfactorily.

Time : from 13 :00 to 13 :20
Time length : 20 minutes
Door-closed meeting : committee members and AERES representative

Time : from 13 :20 to 13 :50
Time length: 30 minutes including questions
Presentation by the director of the unit : past activity and projects

Time : from 14 :00 to 14 :45
Time length: 45 minutes including questions
Presentation by the leader of team #1 : past activity and projects

Time : from 14 :45 to 15 :30
Time length: 45 minutes including questions
Presentation by the leader of team #2 : past activity and projects

Time : from 15 :30 to 16 :00
Time length : 30 minutes
- Meeting with PhD students and postdoctoral fellows
- Meeting with engineers, technicians and administrative assistants

Time : from 16 :00 to 16 :20
Time length : 30 minutes
Door-closed meeting : committee members, AERES representative and University representative

Time : from 16 :20 to 17 :20
Time length : 60 minutes
Door-closed meeting : committee members, AERES representative

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The unit is mainly a clinical one in which the two teams collaborate in doing research and patient care combined. The amount of patients taken care of is high and hence the amount of clinical doctors working in the department is high. Nevertheless, the impression after the presentations is that of a good clinical department doing scientific work as much as they can. They have a good national position, while the international recognition is modest. The collaboration with the neighbouring INSERM institute is good, providing the basic science input to the clinical one. What is lacking is a clear focus of what the unit wants to become. In view of the opportunities in France now with the Alzheimer Plan, a sharp focus and joined research effort should be planned and carried out.

4 • Specific appreciation team by team and/or project by project

Team 1 : Cognisciences

This team has its focus on risk factors and biomarkers of AD. The PI is a professor with 77 publications and an H factor of 11. He has been involved in some large scale clinical trials with calcium antagonists and is the PI of a large project called XX.. His future perspectives involve a French center oriented study on plasma biomarkers for AD in the context of the French Plan Alzheimer. This field is highly competitive and despite the huge number of patients seen at the clinical site on a yearly basis the number of projected patients in the study is small. The number of high impact publications with the PI being first or last author are small.

Team 2 : Neuromodulation and Neuronal Plasticity

This team focuses on the management of AD and intervention with non-pharmacological treatments. This team seems to be working in a highly specialized niche area, in which they work together with highly innovative high-tech companies. This field is a difficult one in which the science level is not always high and the yield difficult to ascertain. Despite this they have made some considerable contributions to this field. The research output is modest with publications in low impact journals. The H-factor is 11. The highest impact publications come from international collaborative projects in which they participated, and were not leading.

5 • Appreciation of resources and of the life of the research unit

The unit has access to resources, is involved in several “PHRC”, national programs and European grants. The atmosphere is good and the motivation of the PhD students and clinical doctors is high. There were no specific issues raised by the researchers, technical staff and students who all seem to enjoy working in such a productive medical unit.

6 • Recommendations and advice

— Strong points :

The unit has a good expertise in AD, large clinical sample, motivated doctors, well respected team leaders, good local and national visibility and modest international collaborations.

— Weak points :

The unit is rather small basis for research, despite high number of tenured physicians. Poor access to high-tech diagnostic tools like MRI, PET and CSF analysis. Rather diverse research goals for such a small department. Poor revenues from clinical trials despite high number of patients seen in the clinic. The relevance of labelling clinical psychologists/physicians spending 5 to 10 % of their full time in research "researchers" is questionable.

— Recommendations :

Opportunities : As good clinicians with ample basic science are working next door, the unit should further establish the links with those. The need to focus in research is evident and could strengthen the output of the dept. The management team seems to be in a unique niche but suffers from too little input by themselves; the threat being that they are mainly used for validation of new techniques.

Threats : The biomarker research line moves in a highly competitive field and has little chance of surviving if no focus is applied. More research full time equivalent should be made available from the large amount of tenured positions, in order to enlarge the output. As reflected by the list of papers published by the team, a relatively small number of them are papers where a member of the team is the first or last author, suggesting that an effort has to be made to focus on those projects where the team has the scientific leadership.

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

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 6 avril 2009

DRED 09/n° 136

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'équipe d'accueil « **Maladie d'Alzheimer : facteurs de risques, traitement et prise en charge** » rattachée à mon établissement.

L'Université prend acte des nombreuses critiques soulevées par le comité de visite. En cas de reconnaissance, l'Université veillera à ce que les recommandations faites soient suivies d'effet.

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

Le Président de l'Université

Axel Kahn

Université Paris Descartes 12, rue de l'Ecole de Médecine 75270 Paris Cedex 06
Tél. 33(0) 1 40 46 16 01 Fax 33(0)1 40 46 16 43
Email : axel.kahn@parisdescartes.fr

Research unit : Maladie d'Alzheimer : facteurs de risque, traitement et prise en charge

Requested label : EA
N° in case of renewal :
Head of the research unit : Ms Anne-Sophie RIGAUD

Research Unit Address: Service de Gérontologie 2, Hôpital Broca (AP-HP), 54-56 rue Pascal 75013 Paris
Tel: 331 44 08 35 03
Fax: 33 1 44 08 35 10
Website: www.gerontologie.vermeil.org

Answers to the report from the visiting committee

Written by Anne-Sophie Rigaud and Olivier Hanon

We thank the experts for their thorough investigation of our unit activities and would like to answer several issues raised by their report.

1. Presentation of the unit and 2. Preparation-execution of visit

No comment

3 . Overall appreciation of the activity of the research unit, of its links with local, national and international partners

- *"the international recognition is modest"*.

Although we acknowledge that international recognition should be further developed, we would like to outline our actual contribution in this field:
- We are members of the European Alzheimer Disease Centres which gathers all the expert centres in AD in Europe since the beginning in 2001. In the context of this European network, we participated in the different European trials such as Descripa and Ictus. We were also strongly involved in the Eurocode and DIADEM study. We are also members of gerontonet.
- Pr Hanon is involved in two international study including the Oscar Study (n=26000 patients) and the HYVET (n=3800 patients) study in which he acts as a principal coordinator for France. He is also member of the European society of hypertention and is involved in the teaching course in the Summer school. Recently, Pr Hanon was invited as a speaker in Vietnam in a training course and is involved in the setting-up of health partnership between Vietnam and France.
- In the field of gerontechnology, the team is currently involved in several European projects including the CompanionAble and HCNV Socrates project. The team has been asked to participate in other proposals that have been recently submitted to the EC. Pr Rigaud was also European expert for the Ambient Assisted living call. She is also the principal investigator for France in the therapeutic trial ACC (Wyeth) for France, and for Lilly in GAD in elderly people (phase3).

- *« collaboration with INSERM institute is good ».*

We would like to add that this evolution was recent and will increase with the coming national Programme Hospitalier de Recherche Clinique for which Pr Olivier Hanon is principal investigator.

- *"What is lacking is a clear focus of what the unit wants to become".*

We would like to outline the fact that we know quite well what we want to become. For more than 25 years, the research unit has been working in the field of Alzheimer's disease with two leading issues: diagnosis markers focused on biological markers including genetical markers and vascular risk factors for team 1 and non-pharmacological treatment focused on cognitive stimulation programmes and caregiver support for team 2. We planned to keep working in these issues and to sharpen them: genetical markers for team 1 and cognitive stimulation programmes and gerontechnology for team 2. We would like to emphasize the fact that these two issues are strictly in accordance with both the Plan Alzheimer 2008-2012 and the Paris Descartes University taskforces as stated in the overall University report.

4 . Specific appreciation team by team and/or project by project

- Cognisciences.

- « *Number of patients in the study is small* ».

We would like to emphasize the high number of patients enrolled in our centre in the following on-going studies:
- 600 patients with mild cognitive impairment (MCI) and 1500 patients with Alzheimer's disease are currently enrolled in a longitudinal study assessing vascular factors and cognition
- 600 patients with AD or MCI are currently enrolled in the SIGAL study (in less than 18 months).
- 400 patients will be enrolled in the randomized controlled (COVARAD) study.
- 800 patients will be included in the biomarkers projects (with MRI, CSF, DNA samples) and a 2 years follow-up.

Meanwhile we should go further on and always improve our performance; it seems to us that our enrolment rate is clearly satisfying when we compare it to those in the literature.

- « *number of high impact publications by the PI first or last author* ».

We recently published in high impact journals such as J of Hypertension (2008), Arch Int Med (2009), Eur Heart J (2007, 2009), JAGS (2009) recently accepted.

- Neuromodulation and plasticity

« *research output modest with publications in low impact journals* ».

As stated in the report by the experts « This field is a difficult one in which the science level is not always high", results in this field are still seldom published in journals with high impact factors and thus should be quantified according to this field. Furthermore since the research activity focused on gerontechnology began recently, it took several years to obtain the results and write the papers in this field. However we would like to emphasize that the team activity is dynamic, paper production clearly increases and becomes quite significant since 2 articles are currently in press and 5 are submitted for publication.

5. Appreciation of resources and of the life of the research unit

No comment

6. Recommendations and advice

- Strong points

« *modest international collaborations* ».
We have already discussed this issue in paragraph 3.

- Weak points

- « *Poor access to high-tech diagnostic tools like MRI, PET and CSF analysis*».
Although we do not have an MRI and a PET in the building itself where the unit is currently located (Broca location), we have access to an MRI in Pavillon Achard (Pr Legman-Cochin location)which is less than 500 meters far from our own location. For research purpose, we have also collaboration with (2)in Pitié-Salpétrière hospital (Pr Stephane Lehericy), (3) in Sainte-Anne hospital (Pr Jean-François Meder), (4) in Bichat hospital (Dr Marie-Cecile Feugeas). We also have access to PET (for instance in Orsay) in the context of research studies.
We have easy access to CSF testing which can easily be performed in the department since we have higly trained clinicians in this field including neurologist and rheumatologist. However, although CSF testing is highly contributing in the field of patients diagnosis and treatment follow-up (the latter in clinical trials), we believe that a plasma marker would be easier to use in daily routine.

- "*Rather diverse research goals for such a small department*".
As stated previously in the present document, we would like to outline the fact that our unit has few diversity in terms of goals since it is focused on two issues vascular and biological markers for team 1 and cognitive stimulation programmes and gerontechnology for team 2 in the field of Alzheimer's disease.

- *Poor revenues from clinical trials despite high number of patients seen in the clinic.*
We are not sure that we fully understand this statement. We believe that the experts refer to revenues from clinical trials (with the industry and not academic research)). Activities associated with clinical trials are quite dynamic in the unit. The number of new protocols increased by 7 in 2007 and 2008 and showed a 16% and a 75% increase compared to 2006 and 2005 respectively.
Currently there are 17 clinical trials in the unit. The mean enrolment rate is 89% and allows us to have revenues which are close to foreseen incremental costs i.e. extra costs due to clinical trials (92% for protocols with 84 Keuros for an estimated budget of 92 keuros at the end of 2008). The number of enrolment differs between protocols (between 0 enrolment because of early protocol ending by the promoter and 189 enrolments).
It should be outlined that payment procedure induces a delay between evaluation of incremental costs and actual invoicing of these (payment procedure of overheads at the beginning of the protocol and invoicing of enrolments and incremental costs at the end of the protocol i.e. one to 3 years later). Thus there is an important difference between evaluation of theoretical incremental costs assessed each year and the actual invoicing).
This is the reason why in 2008 we invoiced protocols of which grant agreements had been signed in 2005 and 2006 i.e. 5 agreements (revenues 54,4 keuros) while we have calculated that the annual budget for the on-going 17 protocols was 74,9 keuros.

- *The relevance of labelling clinical psychologists/physicians spending 5 to 10 % of their full time in research "researchers" is questionable.*

We included in our team lists two kinds of professionals:
- Some are actual researchers and have 30 to 100% of time devoted to research. These researchers actually participate in the design, carrying out, results analysis, paper writing and results dissemination. They include V Faucounau, ML Seux, H Lenoir, J de Rotrou, I Cantegreil, E Wenisch, Ya-Huei Wu, Mathilde Riguet, Garance Denis (apart from O Hanon and AS Rigaud).
- Other professionals who are 5% of their full time are mainly clinicians and are involved in patients and families enrolment as well as management of cognitive stimulation programmes for patients and support for families. It is well known that the carrying-out of research that assess cognitive stimulation programmes for patients and their families needs several professionals and cannot be done by one full time researcher for instance. These programmes which are not paid by national

insurance health must clearly be considered as incremental cost (extra costs) induced by research trials and funded by research grants. Thus it seems to us that we should clearly show that some professionals in our team participate 5% of their full time in the research unit activities as shown in the following table).

Name	Numbers of papers in Medline (march 2009)	%research
Rigaud Anne-Sophie (MD, PhD)	82 (rigaud as/rigaud pa/rigaud-monnet as)	50%
Hanon Olivier(MD, PhD)	75	50%
Seux Marie-Laure (MD)	30	30%
Faucounau Véronique (MD)	4 (VF began her activity in the unit one year ago)-2 papers accepted and 5 submitted	100%
Laurence Hugonot-Diener(MD)	21	30%
Florence Latour (MD)	13	20%
Lenoir Hermine (MD)	18 (currently doing a PhD)	50%
Duron Emmanuelle (MD)	6 (currently doing a PhD)	30%
Frédéric Bloch(MD)	9 (currently doing a PhD)	20%
Galdric Orvoen(MD)	Patients enrolment and follow-up	10%
Yann Spivac (MD)	Patients enrolment and follow-up	10%
Jean-Yves Gaubert (MD)	Patients enrolment and follow-up	10%
Catherine Bayle	Patients enrolment and follow-up	5%
Pierre Bert(MD)	21 - Patients enrolment and follow-up	5%
De Rotrou Jocelyne (NP, PhD)	16	30%
Cantegreil Inge (NP, PhD)	7	30%
Wenisch Emilie (P)	8	30%
Moulin Florence (P)	Patients enrolment and follow-up	30%
Martha de Sant'Anna (P)	Patients enrolment and follow-up	30%
Jean-Bernard Mabire (P)	Patients enrolment and follow-up	30%
Ya-Huei Wu (P)	YHW began her activity in the unit one year ago	50%
Mélodie Boulay (P)	MB began her activity in the unit one year ago	50%
Mathilde Riguet (P)	MB began her activity in the unit 6 months ago	50%
Garance Denis (P)	MB began her activity in the unit 6 months ago	50%

Note: the last 4 psychologists who arrived lately in the research unit already have papers accepted and others submitted for publication.

Moreover, we would like to outline that it is our unit policy to stimulate clinicians to be involved strongly in research activities (besides clinical activities).
We would like to emphasize the fact that we gave time for other clinicians (Inge Cantegreil, Hermine Lenoir, Frédéric Bloch) in order to allow them to carry out research activities and do a PhD. Emmanuelle Duron is currently paid by INSERM for one year to do a PhD.

Recommendations

Opportunities:
- *"As good clinicians…..are working next door, the unit should further establish the links with those".*
We are not sure that we fully understand this statement. The researchers and clinicians who are located in the same building, have strong links with weekly meetings. As stated before, we would like to outline the fact that some clinicians, such as Inge Cantegreil, Hermine Lenoir, Frédéric Bloch and currently Emmanuelle Duron, were given time to carry out PhD.

- *"The management team seems to be in a unique niche but suffers from too little input by themselves; the threat being that they are mainly used for validation of new techniques".*

Past experience has shown that techno-push approach ie industrials create technological products that are poorly validated then tentatively provided to end-users is not relevant and led to failure in the recent years. It is clearly not our approach.
We believe in a multidisciplinary approach (including academic teams and industrials) which focuses on the needs of end-users primarily. Apart from our strong links with academic teams in University René Descartes University to which we belong, we would like to emphasize our collaboration with other academic teams both in France and abroad in gerontechnology and AD including clinical teams (Charles-Foix, SAMU 92 Garches, CHU Toulouse and also clinical teams in Spain-La Corugna, Bulgaria-Sofia), end-users (France Alzheimer, Alzheimer Europe), technological teams including (without being exhaustive) Telecom and Management Sud Paris (team HandiCom and Electronics/Physics department (EPH)), ESIEE, TIMC-IMAG Grenoble, University of Evry, INSERM U558, ESIGETEL (Fontainebleau), laboratoire Prism/UVSQ et LISV/UVSQ, ISIR (university Pierre et Marie Curie), Valoria (University of Bretagne Sud) and also academic teams in sociology (Paris 1), in philosophy (Paris 7).

- *"The biomarker research line moves in a highly competitive field and has little chance of surviving if no focus is applied"*.
According to us, the biomarker research is clearly focused with two lines.
The first line is to determine the link between cardio-vascular risk factors including hypertension, dyslipidemia, diabetes, arterial rigidity, atherosclerosis, cardiac arythmia with auricular fibrillation and Alzheimer's disease. These studies are carried out in several national or international cohorts of elderly people. According to us, this goal is sharp and relevant: the team has been working for more than 20 years in this field. Pr Hanon is both geriatrician and cardiologist and measurements of arterial rigidity and echocardiography are easily performed by himself and collaborators inside the unit.
The second line on genetical markers in Alzheimer's disease is also clearly focused as shown in our foreseen study about plasma amyloid peptides as a diagnostic and prognostic biomarker for AD. We can provide evidence that this line is clearly relevant for our team: (1) the team has been working in this field for several years, (2) the on-going SIGAL study on the role of Insulin-like Growth Factor-I system in AD is quite satisfying in terms of enrolment and collaboration with INSERM Jacques Epelbaum and other teams, (3) research in this field with collaboration between clinical and genetical/biological centres at the national level is clearly required in the Plan Alzheimer 2008-2012. Pr O Hanon who has submitted a national trial (PHRC on plasma amyloid peptides as a diagnostic and prognostic biomarker for AD) with other national centres (clinical and genetical) clearly meets the demands of Plan Alzheimer 2008-2012.

- Papers in first and last author.
Out of 75 papers published in medline, Olivier Hanon is first or last author 40 out of 75.
Out of 81 papers published in medline (rigaud AS or rigaud pa or rigaud-Monnet as), Anne-Sophie Rigaud is first or last author 38 out of 82.

We thank the members of the visiting committee and observers of the AERES for considering our answers.

Kind regards
Anne-Sophie Rigaud

April, Friday 2nd, 2009