

Vulnérabilité à l'alcool et dépendance (ERI 24)

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit

ERI 24 – GRAP Research Group on Alcohol and
Pharmacodependences

University of Amiens



February 2009



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Evaluation report

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Pharmacodependences

University of Amiens



Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

February 2009



Evaluation report)

The research unit :

Name of the research unit : ERI 24 – GRAP Research Group on Alcohol & Pharmacodependences

Requested label : UMR_S INSERM

N° in case of renewal : INSERM ERI 24

Head of the research unit : M. Mickael NAASSILA

University or school :

University of Amiens

Other institutions and research organization:

INSERM

Date of the visit :

January 14, 2009



Members of the visiting committee

Chairman of the committee :

M. Esa R. KORPI, Institute of Biomedicine, Helsinki, Finland

Other committee members :

M. Jean-Pol TASSIN, Collège de France, Paris

M. Rainer SPANAGEL, Central Institute of Mental Health, Mannheim, Germany

Ms. Brigitte KIEFFER, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch, France (not present)

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

M. Laurent NAUDON, Paris, INSERM representative

M. Luc ROCHETTE, CNU representative (not present the day of the visit)

Observers

AERES scientific representative:

M. Pierre-Hervé LUPPI

University or school representative:

M. Georges FAURE, University of Amiens

M. Saïd KAMEL, University of Amiens

Research organization representative :

Ms. Catherine LABBE-JULLIE, INSERM



Evaluation report



1 • Short presentation of the research unit

- Total number of lab members : 10 including
 - 5 researchers with teaching duties,
 - 1 postdoctoral fellows (1 will be recruited)
 - engineers, technicians and administrative assistants : 1 secretary, 1 technician will be recruited
 - 4 PhD students, all with a fellowship (3 from the region and one from MILDT)
- Numbers of HDR : 3
- Numbers of PhD students who have obtained their PhD during the past 4 years : 4 (2 MDs continue at the Pinel Hospital, 2 as postdocs in the USA)
- Numbers of lab members who have been granted a PEDR : 2
- Numbers of “publishing” lab members : 4 out of 5

The research agenda of the Unit ranges from preclinical animal models to treatment of acute alcoholic liver disease and prognostics of detoxification treatment of alcoholics. The common aim for each part-project will be the “adolescent alcohol abuse”, its effects on later vulnerability of alcoholism, brain neurochemistry and gene regulation.

2 • Preparation and execution of the visit

The visiting committee obtained the written report of the past activity (2004-2007-present) of the Unit and the description of the project to be funded (2010-2013) well ahead of the visit. The members had thoroughly got acquainted with the material. The task was further clarified at the start of the visit by the AERES representative. The leader of the Unit and three group leaders gave reviews of their past results and future plans, which was helped by the booklet containing the slides. The committee met with the University presidents and representatives of the Regional Council, which helped to understand the significance of the Unit and the basis of the support the Unit has received. Finally, a guided lab tour was given with the opportunity to talk to most of the lab members. The preparation and execution of the visit was carried out professionally maintaining a relaxed but critical atmosphere.

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

The previous director of the Unit is presently on leave, but the transition of the leadership to the new young director has been smooth, well organized and managed. The members appeared full of positive energy, and it seems that an open scientific discussion prevails between the leaders, postdocs and preclinical and clinical students. The group has established a solid publication record on long-term effects of alcohol early life



consumption, but the final breakthrough into the highest profile journal is still awaited. It should be kept in mind that the Unit consists of young scientists, who have also quite large teaching loads. They need to establish themselves stronger internationally, for which they certainly have the potential. The members and PhD students of the Unit participate in French neuroscience and addiction meetings, and the leaders are active also at European and world level in alcohol addiction. There is still more room for international scientific collaborations, which will likely speed up as all the methodology is soon routinely set-up by this young and growing Unit. More active research contacts with drug and diagnostic industry should be encouraged.

Importantly, the expertise of the Unit has already been used in planning the alcohol policy and education in Picardie region, e.g., in regard to recommendations for restricted alcohol consumption during pregnancy. This is not very common for any basic science unit.

In recent years, regular alcohol consumption and especially binge drinking has become a mass phenomenon among adolescent people within most European countries. We have only limited information on the modulating factors of alcohol bingeing. Despite some evidence for increased impulsivity, impairments in spatial working memory and impaired emotional learning resulting from alcohol bingeing, only very limited knowledge exists about the health consequences of alcohol bingeing in the life-span perspective. However, we are expecting major health consequences, enhanced mortality rates, and an increase in the number of alcohol-dependent individuals within the next decades due to current alcohol bingeing among young people. Therefore, this is obviously a very important research topic in France and other European countries, and is in fact at the highest priority level of the European Commission. Our society would very much appreciate if the understanding and diminishing of the adolescent binge drinking and related harms could progress by utilizing the results and interpretations from the research proposed by this research Unit.

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

The plans of the Unit have been formulated so that all the functions would support one main goal, i.e. the mechanisms of adolescent alcohol drinking on vulnerability and persistence of the effects on later drinking and behaviour. Even if we here separate the description of research activities into three parts, the Unit is led scientifically as one integrated preclinical-clinical project.

The basic neuroscience part of the Unit involves alcohol-related behavioural models (binge drinking model and alcohol vapour inhalation), neurochemistry of neurotransmitter receptors, brain regional localization of neuronal activation, coupled with important novel electrophysiological experiments on brain slices. The bulk of the recent research by the Unit deals with neuroscience issues (especially the roles of specific adenosine and cannabinoid receptors), with publications in peer-reviewed international journals with high to medium impact. The research quality is very good, but would still need a final breakthrough in the highest profile journals. The senior members of the Unit are well known in the biomedical alcohol field. The behavioural models will make it possible to study various phases of alcohol addiction, and the future plan to become a leading laboratory in France and Europe rests mostly on these techniques and on the expertise of using them to study the effects of adolescent alcohol binge drinking, dependence and relapse. Importantly, the Unit has demonstrated that multiple binge drinking of alcohol results in increased alcohol intake and alcohol preference in the adulthood, whereas multiple binge drinking in the adulthood fails to alter later alcohol intake or preference. These findings will be followed by experiments comparing adolescent and adult brains in their sensitivities to long-term alcohol-induced changes, e.g. in activities of neuronal circuits in key brain regions, using especially the immediate early gene expression immunohistochemistry, and the whole methodological arsenal the Unit has. Perhaps, scientifically the most exciting study was done on the regulation of the brain stem respiratory neuronal circuits and the long-term depression of the circuit by fetal alcohol exposure. This large study using e.g. extracellular recording of specific neurons in the medulla revealed that fetal alcohol exposure changes the hypoxia-induced respiratory facilitation to long-term depression. The study is now accepted in a journal with a high impact factor, and will certainly be followed by other research groups to establish the mechanisms of persistent modulation.



Genetic and treatment studies on alcohol-induced hepatitis using glucocorticoid steroids and agents increasing antioxidant capacity, such as N-acetyl-cysteine, in patients have been carried out at the Hepato-Gastroenterology of University Hospital of Amiens. The preliminary results of this ongoing study were impressive, as the anti-oxidant add-on treatment further reduced the mortality as compared to steroid alone from about 23 to 7% during the first month of treatment. Alcohol-induced hepatitis was associated with higher frequency of TNF-alpha 308-GG allele, but this polymorphism was not prognostic for lethality. Future experiments of the liver group will focus on the significance of cannabinoid receptors, which are known to be increased in animal models of liver cirrhoses.

Life event analysis coupled with analyses of genetic polymorphisms in alcohol-dependent patients during various phases of detoxification may importantly allow the risk assessment of early alcohol consumption on seriousness of later life dependence. The idea is to identify early prognostic markers for good therapeutic outcome during withdrawal and abstinence. This research is carried in the alcohol withdrawal unit, SESAME unit of the psychiatric Pinel hospital, with two senior MD/Psychiatry researchers and two interns. However, the psychiatric experiments are in an early phase, and although potentially important, much more thought, expertise and collaborations (e.g., brain imaging studies) would be needed to fully benefit from the patient population of 200 to be examined. In addition, some translational components have to be developed and implemented within the next 3-5 years. Human laboratory approaches to alcohol addiction research will finally be the key to translate the preclinical findings of the Unit into medication and treatment development. Thus, even a closer collaboration with the clinicians is warranted and a stronger focus on intervention strategies of adolescent alcohol use/abuse is needed.

Finally, describing the devoted spirit of the Unit to work for the common goal of finding clinically significant mechanisms of early alcohol exposure on later life alcohol dependence, the exciting research on respiratory mechanisms has been decided to be stopped, and replaced by electrophysiological studies on scarcely studied connections between the ventral hippocampus, frontal cortex and nucleus accumbens in the model systems. This decision underlines the management skills of the director and leads to much sharper research focus of the Unit. Particularly important will be the model experiments using alcohol vapour exposure to induce clinically relevant alcohol dependence. This methodology is already in use, and only a couple of other laboratories worldwide are able to do similar experiments. These experiments will undoubtedly have the potential for breakthrough findings, when coupled to the behavioural models mentioned above to answer the question: How does adolescent alcohol exposure affect the major brain pathways involved in motivated behaviour? Although these experiments are very demanding and risky, the Unit has the technical expertise to perform the experiments, especially as more postdocs are planned to be recruited.

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

The Unit has about 500 m² space for labs and offices, as well as a closely-situated new facility for behavioral experiments. The space is excellent for the purpose and the Unit can well realize its planned recruitments in the same space. The lab is equipped e.g. with two electrophysiological set-ups, image analysis system for quantification densities of autoradiographs and cell counts of immunostainings for activated neuronal cells, alcohol analyzer, vapour inhalation chambers and operant chambers. The space for clinical experiments in the hospital is a few minutes drive away.

The members of the Unit are well organized and close to each other for immediate exchange of ideas. Overall, the group leaders and students know well the goals of the Unit. All senior members are teaching in basic neuroscience and addiction courses, and at least one of them has contact teaching for about 200 h per year, allowing perhaps too little time for research. The throughput of PhD theses has been steady, and the new doctors have found appropriate postdoc positions within the basic field or in the clinical specialties. It is very important for the PhD students that everyone who contributes to the studies will have an option for authorship in articles.



In addition to the support from INSERM, the Unit has a strong regional and university support and it has been selected on the basis of earlier competition. The regional support has made it possible to get the state-of-the-art equipment, described above. Also, the grants to PhD students are coming from the regional funds. Even if the lab space is presently adequate for the planned experiments, there are plans to move the Unit to a new medical centre, due in 2012. The new location would certainly make it possible to benefit from various modern infrastructures, such proteomics analyses of the brain samples. What is more, in the new medical center preclinical researchers and clinicians will work next door further catalysing these important interactions.

6 • Recommendations and advice

– Strong points :

- a coherent and enthusiastic unit with one main scientific goal. However, the unit is also internally diverse enough, which facilitates translational medicine
- a promising set of alcohol research-related methodologies, providing an important asset for collaborations in the future
- significant involvement in societal planning for reducing alcohol-related harm

– Weak points :

- collaborative efforts are not well planned
- scientific articles should have more impact, which seems to be the future aim (Note that the leading journal in alcohol research field, *ACER*, has an impact factor of about 3, and that the team is young being in its present form less than two years)

– Recommendations :

- there is a need for focusing the research goal (a process which has already started). This would allow deepening the basic science questions, which should then lead to higher impact publications of cutting edge findings
- get on quickly with the recruitment of more postdocs, since internationally competitive research needs more projects with higher risks of failure
- if possible, keep lab meetings in English to boost the language and communication skills of the students, and keep them more frequently, preferably weekly

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	B	A	A



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Mickaël NAASSILA
Directeur Unité INSERM ERI 24
Professeur Faculté de Pharmacie
Président Task Force Alcool de Picardie

URL: <http://www.u-picardie.fr/decouverte/sante/pagesliees/grap/>

Amiens, le vendredi 27 mars 2009

Objet : Observations de portée générale sur le rapport d'évaluation

L'ensemble des membres de l'équipe INSERM ERI 24 s'accorde à reconnaître que dans sa globalité le rapport d'évaluation retranscrit bien les points faibles et les points forts de l'équipe.

En réponse aux recommandations et conseils émis dans le rapport :

*En ce qui concerne le recentrage de nos objectifs de recherche, et comme il est mentionné dans le rapport, ce processus a déjà été initié. Nos objectifs sont d'étudier les mécanismes impliqués dans la vulnérabilité à l'alcoolodépendance induite par une exposition à l'alcool à l'adolescence. L'élucidation des mécanismes cellulaires et moléculaires de cette vulnérabilité nous permettra d'envisager de nouvelles pistes thérapeutiques et/ou de prévention. L'impact des résultats attendus assurera des publications de niveau élevé et contribuera à l'élaboration des messages de santé publique.

*En ce qui concerne le recrutement des post-docs, nous avons obtenu du Conseil régional de Picardie l'attribution de deux nouvelles positions, ce qui nous amènera en 2009 à un total de trois post-doctorants. Ces trois chercheurs ont pour mission de développer des approches innovantes permettant un questionnement scientifique plus approfondi.

*En ce qui concerne les réunions de laboratoire en langue anglaise, elles ont été mises en place sur une base hebdomadaire depuis le 1^{er} janvier 2009, date d'arrivée du premier post-doc d'origine étrangère.

Points faibles :

*Nous sommes tout à fait conscients du caractère impératif à développer davantage de collaborations et nous avons lancé plusieurs programmes depuis janvier 2009 :

En tant que coordinateur j'ai déposé un projet européen INTERREG IVA qui comprend deux équipes de recherche en neurosciences d'Amiens (INSERM ERI24 et UMR 8160) et les Universités de Rouen et du Sussex (UK). Dans ce projet sont prévues des études d'imagerie cérébrale comme il a été suggéré par les experts du comité de visite AERES.

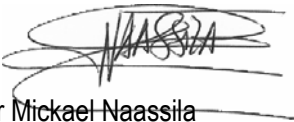
Nous avons aussi déposé un projet européen ERAB en association avec les Universités de Caen et de Louvain (Belgique) ; et pour lequel je suis coordinateur.

Un projet ANR avec l'Université de Caen et dont je suis le porteur a été soumis en 2009. Au niveau régional, nous collaborons avec deux équipes CNRS (UMR 6219 et 6022) de l'Université de Picardie sur un projet de type structurant.

Enfin, ma participation au prochain comité de direction de la société européenne de recherche sur l'alcoolisme (ESBRA) à partir de cette année, me permettra d'établir de nouvelles collaborations.

*Nous sommes également conscients que la qualité et le niveau des publications restent à améliorer et notre dernière publication (AJRCCM, facteur d'impact : 9.1) ainsi qu'une autre en révision dans Biological Psychiatry (facteur d'impact : 8.5), en attestent. D'autre part nous publions régulièrement dans le meilleur journal dans le domaine de l'alcoolisme (ACER). Enfin il faut souligner que notre équipe a été créée en 2007 et c'est aussi par l'arrivée des post-doctorants et la mise en place de nouvelles méthodologies compétitives maintenant opérationnelles que le niveau de publication évoluera rapidement vers l'excellence, comme les experts l'ont conseillé.

Comme il a été souligné dans le rapport, notre équipe est jeune, dynamique et enthousiaste. Elle a développé des outils qui lui permettent d'être très compétitive au niveau international et c'est la seule en France à travailler exclusivement sur la dépendance à l'alcool avec des approches pré-cliniques et cliniques. Les effets à court terme et à long terme des ivresses répétées (« binge drinking ») à l'adolescence est une thématique de recherche qui est prioritaire ; la lutte contre ce phénomène de masse est à l'heure actuelle une des priorités du nouveau plan gouvernemental de lutte contre les drogues et les toxicomanies (MiLDT) 2008-2011. C'est aussi la seule équipe à disposer du modèle d'induction de l'alcoolodépendance chez l'animal qui se rapproche le plus de la clinique. Au niveau sociétal, elle joue aussi un rôle important dans la lutte contre les méfaits de la consommation abusive d'alcool au travers notamment de mon engagement auprès des pouvoirs publics avec la présidence de la Task Force Alcool de Picardie (Mise en place d'actions innovantes dans la lutte contre les méfaits de la consommation d'alcool notamment chez les jeunes et les femmes enceintes).



Pr Mickael Naassila