



GRAP - Groupe de recherche sur l'alcool et les pharmacodépendances

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Research Group on Alcohol and

Pharmacodependences (GRAP)

From the

University of Amiens

March 2011



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

Section des Unités de recherche

AERES report on the research unit

Research Group on Alcohol and Pharmacodependences (GRAP)

From the University of Amiens

Le Président de l'AERES

Didier Houssin

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2011



Research Unit

Name of the research unit: Research Group on Alcohol and Pharmacodependences

Requested label: UMR_S INSERM

N° in the case of renewal: INSERM ERI 24

Name of the director: Mr. Mickaël NAASSILA

Members of the review committee

Committee chairman:

Mrs. Véronique DEROCHE-GAMONET, University of Bordeaux 2, Bordeaux

Other committee members:

Mr. Henri-Jean AUBIN, Hôpital Paul Brousse, Villejuif, France, CNU Representative

Mrs. Consuelo GUERRI, Centro de Investigación, Valencia, Spain

Mr. Nasser HADDJERI, Université de Lyon 1, Lyon, France, INSERM CSS representative

Mr. Wolfgang SOMMER, Central Institute for Mental Health, Mannheim, Germany

Observers

AERES scientific advisor:

Mrs. Thérèse JAY

University, School and Research Organization representatives:

M. Saïd KAMEL, University of Amiens

Mrs. Chantal LASSERRE, INSERM

M. Jean LIENARD, CHU Amiens

M. Michel SLAMA, CHU Amiens

M. Jean-Claude BARBARE, CHU Amiens



Report

1 • Introduction

- Date and execution of the visit

The visit took place on March 8th, 2011 at the Faculty of Pharmacy (University of Picardie, 1 rue des Louvels, Amiens) where the GRAP laboratory is located. The first step was a closed-door meeting of committee members with the AERES representative to agree on the mission and timetable of the visit.

The visiting committee meeting started with a general presentation by the leader of the unit. After this introduction, three researchers presented their past activities and projects. Each presentation was followed by a discussion with the committee members.

Then the committee met with representatives of the University, the Hospital, the regional council and INSERM which help understanding how the unit is integrated within the local policy. In addition, the committee met with the members of the laboratory, i.e. PhD students, post-docs, technicians and administrative officers, and researchers, successively. The committee members had a closed-door meeting at the end of the day.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The GRAP was created in 2004 as a Junior Research Group (2004-2006) and was renewed as an ESPRI in 2007 (2007-2009). Mr. Naassila progressively succeeded to Mrs Daoust and obtained the renewal of the GRAP as an ESPRI for two years (2010-2011). Therefore, with Mr Naassila as director, the GRAP is a young team. The team consistently grew over the last 5 years (3 teacher researchers in 2006 - 10 in 2011) to reach now 20 members.

The GRAP works on alcohol use-related disorders. Their interest focuses on both alcohol-induced physiological (notably hepatitis) and behavioral alterations including alcohol dependence. In particular, the GRAP is interested in studying the influence of early life (perinatal and adolescence) alcohol exposure in the vulnerability to develop alcohol dependence using both preclinical and clinical approaches.

The team, housed in the Faculty of Pharmacy, has about 500 m2 space including laboratories, offices and animal facilities. Clinical experiments are conducted in the hospital which is a few minutes drive away. In 2013, the GRAP will be hosted in new larger facilities currently on built in the hospital, therefore facilitating interactions between preclinicians and clinicians.

- Management team

The unit director is Mr. NAASSILA.



- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	6	7
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	2
N6: Number of Ph.D. students (Form 2.8 of the application file)	5	3
N7: Number of staff members with a HDR or a similar grade	5	5

2 • Overall appreciation on the research unit

- Summary

A common aim for all the researchers in the unit is to study behavioral and somatic consequences of alcohol use. A strong emphasis is put on the vulnerability to alcohol dependence related to adolescence binge drinking. The director of the unit has worked hard over the last 3-4 years to provide his team with strong visibility and anchoring in the local environment (University, regional council, hospital). The strong support (grants and positions) provided to the team by these three local partners demonstrates his effectiveness in this matter. Over the last two years, the team actively worked on increasing its national and international visibility by establishing national and international collaborations. The InterregIVa Alcobinge project coordinated by the head of the unit is exemplary in this context. The team worked also to extend methods and equipments for a more exhaustive and intensive preclinical research on the neurobiological determinants of alcohol dependence. Until recently, the team was exclusively composed of researchers with high loads of teaching and/or clinical activities. A balance is being established with the recruitment of 4 post-docs over the last two years.

Altogether, this work led to recent interesting findings and to an increased impact factor of the publications since the last AERES evaluation, two years ago. Conditions are met now for the team to emerge in the alcohol field.

- Strengths and opportunities

This research group has a strong specificity. Worldwide, it is one of the rare groups working exclusively on alcohol-related disorders. In France, this feature makes it unique. In addition, it combines both clinical and preclinical aspects and aims at covering somatic and behavioral consequences of alcohol consumption. The team has reached a reasonable size (20 people) to make room and name for itself. The director is a very efficient group leader. He shows a great ability to unite people and resources around his ideas.

A strong anchoring in the local environment (University and Hospital). For example, the group leader is responsible of the Neuroscience Axis in the project of SFR in health (Federative Structure of Research). The senior and young lecturers of the team are actively involved in the administrative life of the University (Member of the Scientific Council, active involvement in the recent reform of the University...). The PU-PH and PH are active in the administrative life of the CHU and of the Pinel Psychiatric hospital.



A good integration in the scientific policy of the Region. M NAASSILA is the leader of an InterregIvA project (2009-2013) involving three regional teams and two teams from the University of Sussex (England).

A good integration in the alcohol policy of the Region. M NAASSILA is director of the Picardie alcohol task force. The team is involved in many educational activities. The expertise of the Unit has already been used in planning the alcohol policy and education in the Picardie region.

A strong support of the Regional council and of the University of Picardie. The team received and still receives a very strong support (equipments, PhD and post-docs grants) from the Picardie Regional Council, from the University of Picardie (4 positions obtained over the last 4 years + one University Professor position in 2012) and from the Hospital (support for the clinical research).

The team shows a very strong potential for truly translational research.

- **Weaknesses and threats**

A lack of focus in the research project. Tendency to embark on too many projects;

In addition to his numerous administrative and teaching activities, the head of the unit is the leader of most projects.

The team does not include full time researchers, i.e. without clinical or teaching duties.

Clinical and preclinical projects appear disconnected.

For the four above mentioned reasons, projects could not be accomplished at the level they could be.

- **Recommendations**

It would be advisable to focus on the most innovative projects;

The strong potential for truly translational, or reverse translational research should be fully exploited;

A very efficient group leader but due to his huge load of work, delegating responsibilities is essential, in particular to the other senior researcher of the group; i.e. a senior lecturer who has shown the ability to produce a high level research in leading projects. The committee encourages this lecturer to develop research management activities (grants coordination...);

The recruitment of, at least, one full time senior researcher would be critical;

Increased use of advanced preclinical exploratory methods is a decisive point to increase impact. In this context, the expertise of the senior lecturer (electrophysiology) and of a senior post-doc recently hired by the team and who shows a high level expertise in neurochemistry and molecular biology, are critical. Also the recently initiated strategy of combining mechanistic studies with behavioral studies should be systematically maintained to assure high impact publications.

- Production results

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	6
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	0
A3: Ratio of members who are active in research among staff members $[(A1 + A2)/(N1 + N2)]$	0.86
A4: Number of HDR granted during the past 4 years (Form 2.10 of the application file)	1
A5: Number of PhD granted during the past 4 years (Form 2.9 of the application file)	6

3 • Specific comments

- Appreciation on the results

The team took the last AERES recommendations literally, significantly increasing impact factor in publications, attractivity and international collaborations over the last 2 years.

At the preclinical level, the group has established a set of behavioral procedures for alcohol exposure [oral, i.p., vapor] and a set of behavioral procedures to evaluate sensitivity to alcohol (CPA, CPP, locomotor effect) and vulnerability to alcohol use (free choice, operant self-administration). They have recently integrated the withdrawal variable in their procedures; a critical dimension in alcohol-induced effects.

Notably, the group has established the intermittent vapor exposure paradigm, which allows studying alcohol-dependence related neuroplasticity. The model has good predictive validity for target identification and validation for treatment approaches towards relapse prevention. They also established a binge-like drinking regimen of alcohol injections which allowed them revealing and studying the specific susceptibility of the adolescent period to this regimen.

Electrophysiology is a strong pillar of the unit. The methodological development of the group in this area is excellent. A very elegant and exhaustive study was conducted on the regulation of the brain stem respiratory neuronal circuits and the long-term depression of the circuit by fetal alcohol exposure. This study was recently published in a high impact factor journal. In an attempt to focus research on alcohol dependence, the choice was made to shift and establish conditions to study synaptic plasticity in hippocampal slices. This goal was successfully reached. The recent publications and results actually demonstrate that the behavioral and electrophysiological procedures are not only effective, but can be successfully combined. Finally, the group has a long and solid expertise in immunohistochemistry and biochemistry as demonstrated in several publications over the last 4 years.

At the clinical level, research in hepatology is a clear added value for the team. The Hepato Gastroenterologist from the Amiens University Hospital who has an impressive publications record in many liver-related clinical areas (32 over the last 5 years) is in direct link with the GRAP activity. He developed very innovative concepts for the treatment of alcohol-related hepatitis.



Over the last 5 years, (2006-2010), the group published 14 papers with an average impact factor of 4.3. This record might appear low at first glance. However, both the team and the researchers composing it are young. In addition, until recently the team was exclusively composed of professors, lecturers and clinicians, all of them having a heavy load of teaching or clinical activities. No doubt that the recent recruitment of post-docs will have a positive impact on this record. The most recent publications (AJRCCM, Neuropsychopharmacology) and results demonstrate their potential for higher impact papers.

The throughput of PhDs is impressive. Over the last 4 years, 7 students defended their thesis after three to four years in the lab. They all found positions as post-docs in basic science (USA or France) or as clinicians.

The researchers, PhD students and post-docs of the Unit regularly participated in national neuroscience and addiction meetings.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

The leaders are regularly invited in national, European and international neuroscience and addiction meetings.

The head of the unit has been recently awarded a NRJ foundation prize (2009) and the Georges de Saint Blanquat prize (IREB, 2010). He regularly serves as an expert for INSERM or European organizations for alcohol-related calls or meetings. He is the French representative in the working group on the diagnostic criteria for alcoholism in the next DSM (DSMV) and a member of the directory board of the ESBRA since 2009.

PhD students from the unit have been awarded for their thesis work : two PhD prizes (The Pierre Fouquet prize in 2009 and in 2010 with a MADP grant in addictology in 2010).

The unit recruited 5 PhD students over the last 5 years and 3 post-docs over the last 2 years; one coming from the alcohol devoted Gallo Center at UCSF (USA). The team is in an active process for establishing additional national and international collaborations with leaders in the field (NIDA).

The group has obtained several grants (InterregIVa, Mildt, Ireb, Picardie Region...) over the last 5 years. The income of still pending grants (2009-2013) is 725 000 euros, including a partnership with a pharmaceutical company (Biocodex). ANR grants have not been obtained so far. The high potential of the team for translational projects should allow rapidly successful applications to ANR calls.

The group is impressively integrated and supported by the local environment (university, hospital, region).

The Unit plays a critical role in guiding the alcohol policy and education in Picardie region, e.g., in regard to recommendations for restricted alcohol consumption during pregnancy and risks associated with binge-drinking in adolescents. This is enough uncommon for a basic science unit to be noticed.

- **Appreciation on the management and life of the research unit**

The group leader efficiently federates people and resources around his ideas. As mentioned in the recommendations, it is the right time for M Naassila to delegate part of his numerous responsibilities to a senior researcher, in particular for what concerns research projects leading and research management.

It appeared that an open scientific discussion prevails between the leader, researchers, postdocs and preclinical and clinical students. The team consistently grew over the last two years. It appeared that a smooth and smart organization took place to assure optimization in both equipment use and project realization, to the satisfaction of the researchers.

The research unit plays a critical role in the structuration of research at the local level. Among others, the group leader is member of the local ethical committee on animal research and is responsible for the animal housing platform.



- **Appreciation on the scientific strategy and the project**

The characteristics of alcohol consumption in adolescence appear to represent a major risk factor for the development of alcohol dependence. From epidemiology to neurobiology, the GRAP aims at studying the psychobiological mechanisms involved in the increased vulnerability to alcohol associated with this critical developmental period.

Some of the projects are very well thought through, are feasible and demonstrate that the team has great potential.

The described methodology to attack the preclinical objectives is correct, including the different ways of alcohol administration (intermittent alcohol treatment, alcohol vapor exposure, two bottles choice, operant self administration, etc) to induce sensitization and dependence to alcohol, and the procedures to assess the targets of these processes.

In particular, the planned electrophysiology experiments address a very important and timely research question. It is one of the strongest parts of the proposal and should be given high priority. The project of studying interactions between hippocampus and accumbens is highly interesting and not well understood in the addiction field.

Pharmacological mapping of the effects of different ligands will contribute very importantly to our understanding of the vapor-induced dependence model, its applicability for research on alcohol addiction and its treatment. This approach should ideally be combined with IEG mapping and electrophysiology for high impact studies.

The immuno-histochemical mapping studies, which in the present form lack focus, may be helpful for guiding electrophysiological studies, pharmacological mapping or proteomics experiments. It should be integrated in the respective projects when justified.

Some of the projects should be given less priority. Despite obvious interest, it is probably premature to engage in studying the combined effects of THC and alcohol or nicotine and alcohol. Similarly, investigating the drug x environment interactions during adolescence appears premature.

Importantly, for preclinical studies, the range of methods to assess alcohol-related responses has been extended by operant procedures. The planned capacity of 20 SA-chambers allows the group to shift the focus on the study of addiction-related phenotypes. The group also plans to build up sufficient capacity to supply vapor exposed animals for several lines of experiments.

Considering the innovative feature of the clinical studies on alcohol-related hepatitis, this research project should be reinforced and translational research should be promoted, when possible. The psychiatric research is still in its infancy but conditions are met for interesting results to be produced.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
GROUPE DE RECHERCHE SUR L'ALCOOL ET LES PHARMACODÉPENDANCES: GRAP	A	A	A	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique



Statistiques de notes globales par domaines scientifiques (État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2_LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	42	5	20	26	36	59	5	17	29	239
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

* les résultats SVE2 ne sont pas définitifs au 06/05/2011.

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
 - SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie
 - SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes
 - SVE1_LS3 Biologie cellulaire, Biologie du développement animal
 - SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie
 - SVE1_LS5 Neurosciences
 - SVE1_LS6 Immunologie, Infectiologie
 - SVE1_LS7 Recherche clinique, Santé publique
- **SVE2 Ecologie, environnement**
 - SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement
 - SVE2_LS9 Sciences et technologies du vivant, Biotechnologie
 - SVE2_LS3 Biologie cellulaire, Biologie du développement végétal

Amiens, le 12 avril 2011

Monsieur le Président

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2011.04.044. GF/SD

Objet : réponse officielle évaluation GRAP

Référence AERES : S2UR120001855 - GROUPE DE RECHERCHE SUR L'ALCOOL ET LES PHARMACODEPENDANCES: GRAP - 0801344B

Monsieur le Président,

Je tiens tout d'abord, au nom de l'Université de Picardie Jules Verne et en particulier au nom du directeur et des membres de l'Unité « Groupe de Recherche sur l'Alcool et les Pharmacodépendances » (GRAP) à vous remercier pour la qualité du rapport d'évaluation ainsi que pour les échanges constructifs que nous avons pu avoir avec le comité lors de la visite du 8 mars 2011.

A la suite de la transmission du rapport d'évaluation, le Directeur, les membres de l'Unité et moi-même tenons à apporter les précisions suivantes :

Concernant les quatre points faibles relevés, nous sommes conscients de la priorité de toujours resserrer un peu plus la thématique et de délaissier certains projets moins prioritaires qui nous ont pourtant été réclamés lors d'expertises de projets ANR (étude de l'interaction avec d'autres drogues comme le cannabis et la nicotine à l'adolescence, étude de l'interaction avec l'environnement). Ces projets seront donc envisagés à plus long terme comme suggéré par le comité.

Comme souligné dans l'expertise nous avons effectivement le projet de développer davantage les études électrophysiologiques et de favoriser les projets transversaux « comportement addictif et plasticité synaptique ». Depuis deux ans nous avons stratégiquement fait le choix de renforcer sur le plan matériel le domaine de l'électrophysiologie et le développement de nouveaux projets nécessiterait cependant le recrutement d'un nouveau chercheur expert en électrophysiologie.

Concernant le deuxième point faible relatif au fait que le directeur d'unité est le responsable de la plupart des projets, ce point a déjà fait l'objet de discussions au sein de l'unité depuis 2010. Un projet ERC a été déposé en 2010 dont le porteur est un post-doc de l'unité. D'autre part, le Dr Olivier Pierrefiche est le porteur du projet que nous allons déposer dans le cadre du prochain appel d'offres de l'ANR sur les projets internationaux avec comme thème « la plasticité synaptique et l'addiction à l'alcool ».

Concernant le troisième point faible, l'unité en est bien sûr consciente mais doit s'adapter à l'absence de chercheurs statutaires. Ce point ne pourra évoluer qu'en concertation avec l'INSERM. A ce titre, l'unité demande la création d'un poste de maître de conférences dans le cadre des chaires d'excellence.

L'attractivité de l'unité est maintenant suffisante pour attirer des chercheurs post-docs de haut niveau avec une expertise spécifique dans le champ des addictions mais les opportunités de recrutement sont très faibles.

Le quatrième et dernier point faible relevé, relatif à la déconnexion entre les projets cliniques et précliniques est inhérent à plusieurs freins que sont par exemple la difficulté à trouver des financements dans le champ de l'alcoolologie en France et l'absence de bons modèles précliniques de la maladie alcoolique du foie.

Nous continuons cependant à travailler sur la mise en place d'un modèle de la maladie alcoolique du foie notamment avec un projet relatif à l'épigénétique aux histones désacétylases et aux endocannabinoïdes. Nous avons tout de même ces deux dernières années développé des projets translationnels :


- 1) « rôle de l'a-synucléine dans les troubles anxio-dépressifs chez le patient alcoolodépendant et dans un modèle animal de la maladie » (souris transgéniques et rats alcoolodépendants)
- 2) « Implication du gène *Adora2* dans l'addiction à l'alcool » avec une étude d'association génétique chez l'Homme et une étude chez des souris transgéniques et une étude des traitements ciblant ce récepteur A2A de l'adénosine chez des rats alcoolodépendants
- 3) « Binge drinking chez l'Homme et chez l'animal, études des atteintes cognitives et émotionnelles et de la vulnérabilité à l'alcoolodépendance ».

Dans ce dernier projet d'envergure européenne et que l'unité coordonne, nous avons particulièrement mis l'accent sur l'aspect translationnel avec une forte complémentarité entre modèles animaux et recherche clinique.

D'autre part nous comptons sur la mise en place de la fédération inter-hospitalière en alcoolologie et addictologie à laquelle l'unité participe activement et qui doit faciliter la mise en place d'études cliniques sur les projets que nous développons.

Je vous prie d'agréer, Monsieur le Président, l'expression de mes sincères salutations.

Le Président de l'Université de
Picardie Jules Verne


Georges FAURÉ



UNIVERSITÉ de Picardie Jules Verne