MEPPOT - Médecine personnalisée, pharmacogénomique, optimisation thérapeutique

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Médecine Personnalisée, Pharmacogénomique, Optimisation Thérapeutique

MEPPOT

Under the supervision of the following institutions and research bodies:

Université Paris 5 - Paris Descartes

Institut National de la Santé et de la Recherche Médicale

February 2013

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

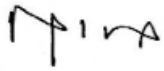
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report received the following grades:

- Grading table of the unit: Médecine Personnalisée, Pharmacogénomique, Optimisation Thérapeutique

C1	C2	C3	C4	C5	C6
A+	A+	A+	A	A+	A

Evaluation report

Unit name:	Médecine Personnalisée, Pharmacogénomique, Optimisation Thérapeutique
Unit acronym:	MEPPOT
Label requested:	UMR_S
Present no.:	UMR-S 775
Name of Director (2012-2013):	Mr Pierre LAURENT-PUIG
Name of Project Leader (2014-2018):	Mr Pierre LAURENT-PUIG

Expert committee members

Chair:	Mr Juan IOVANNA, Université d'Aix Marseille
Experts:	Mr Jean-Noel FREUND, Université de Strasbourg
	Mr Paul HOFMAN, Université Nice Sophia Antipolis
	Mr François-Xavier MAQUART, Université de Reims
	Mr Pierre MARQUET, Université de Limoges
	Mr Arnaud ROTH, Université de Genève, Switzerland

Scientific delegate representing the AERES:

Mr Daniel OLIVE

Representative(s) of the unit's supervising institutions and bodies:

Mr Frédéric DARDEL, Université Paris Descartes

Ms Marie Josèphe LEROY-ZAMIA, INSERM

1 • Introduction

History and geographical location of the unit

This single Team Unit project is in the continuity of the previous U775. The Unit is located at the "Centre Universitaire des Saints-Pères" but some MDs are also working in Hôpital Européen Georges Pompidou.

Management team

The proposed director, Mr Pierre LAURENT-PUIG, PUPH, is the current director of the Unit 775. He has a strong experience in team management, he is well recognized at the national and international level for his studies, and he has the support of all the members of the project.

AERES nomenclature: **SVE1**

Unit workforce

Unit workforce	**Number as at 30/06/2012**	**Number as at 01/01/2014**	2014-2018 **Number of project producers**
N1: Permanent professors and similar positions	9	8	
N2: Permanent researchers from Institutions and similar positions	1	2	
N3: Other permanent staff (without research duties)	0	0	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	0	0	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	0	0	
N6: Other contractual staff (without research duties)	0	0	
TOTAL N1 to N6	**10**	**10**	

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	19	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit*	3	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	9	

2 • Assessment of the unit

Strengths and opportunities

This is a team with a clear goal on translational research. They have the expertise, the tools and the necessary biological resources to perform their projects.

They have made an important contribution by discovering the inefficiency of the anti-EGFR antibodies in patients carrying a mutation in the Kras in colon cancer. These results are of major clinical interest and are used in national and international recommendations to select responsive patients.

They have published 101 original papers (Lancet Oncol, Cancer Res, Clin Cancer Res, Blood, PNAS, Hum J Genet, Gut, Hepatology, etc), including 5 JCO (Mr Pierre LAURENT-PUIG was first or last author on 4 of them). Their papers have been cited more than 2450 times during the last 5 years.

An original projet on microfluidics, well integrated in the global project of the Unit, has started more than one year ago and is a great methodological opportunity for this team.

The team has developed valuable on-site inter-disciplinary collaborations (with mathematicians), thus providing original tools for data-mining.

Through their participation to national and european programs (CIT Ligue contre le Cancer; PETTAC-8), the team has a privileged access to large collections of annotated human samples and clinical data.

The group has an excellent activity of technology transfer assessed by 6 patents and a number of collaborations with private companies. They have a noticeable capacity to obtain fundings through public and private research contracts (more than 3 M€ over the last 4 years).

Weaknesses and threats

Although the projects on cancer and anticoagulants/immunosuppressors represent the natural evolution of the previous studies, attention should be paid for the next five-year period to keep the balance and complementarity between these subprojects within the single-team unit.

Although one MCU-PH obtained the HDR (habilitation to supervise research) during the last 4-year period, the number of HDR in the lab is still relatively low (5).

There is a lack of a defined recruitment strategy for full time researchers at the EPST (Inserm or CNRS).

12 of 20 technicians have temporary (CDD) contracts, which means that they will have to leave soon or be proposed a permanent contract. Also, two tenured technicians will retire over the next few years.

A MCU physicist has been recruited during the last years in relation with the development of the microfluidic project but, for career reasons, he intends to leave the University. This is a major risk for this aspect of the project.

Some basic aspects of the project, particularly those involving miRNA, TWIST1, ER Stress and autophagy, are very competitive and will be studied in collaboration with different other partners. This could be a risk since these research topics are internationaly competitive. It is recommended to recruit specialists in the field.

Recommendations

A careful thought within the lab is needed to reinforce (with PhD or post doc students) the pharmacogenetics and immunosuppressive drugs subprojects, and/or priorize the main project on anticancer drugs.

The unit may consider enlarging its domains of competence in the field of molecular biology to be more independent in some of its highly competitive projects.

The unit should increase its capacity of supervising doctoral students by having other members passing their HDR.

The unit should set up a plan to prepare young researchers for the CNRS and/or INSERM full-time researcher carreer (and competition for admission).

The technical competences and workforce are fragile, owing to many temporary contracts and the close retirement of two tenured persons.

3 • Detailed assessments

Assessment of scientific quality and outputs

This is a large group that is working on a broad spectrum of translational and fundamental scientific projects ranging from pharmacogenomics and genomics to the development of alternative therapeutic approaches and, more recently has been developing original nanotechnology approaches. This is one of the most prominent teams on pharmacogenomics at the French level. They have established several polymorphisms associated to the variability in the response to anticoagulants and immunosupressive drugs. They have participated to a collaborative initiative to develop a Chip containig 16000 polymorphisms and they are leading large prospective French and European projects on colon cancer through 5 multicenter cooperative groups, with the goal to predict individual patient response to the treaments. They are supported by the CIT program of "La Ligue contre le Cancer" to characterize colon cancer samples at genetic and transcriptomic levels, with the goal to classify as homogeneously as possible these patients in order to develop personalized treatments. In the last 4 years, they have made an important contribution by discovering the inefficiency of the anti-EGFR antibodies in colon cancer patients carrying a mutation in the Kras gene. These results are of major clinical interest and are currently used in national and international recommendations to select responsive patients.

Concerning the most fondamental projects, the team has developed an original strategy of gene therapy for lung tumors by transfecting both an improved mutant of the CYP2B6 enzyme named CYP2B6TM and NADPH reductase (RED), which sentizises to treatments with cyclophosphamide. The preclinical results using a lentiviral vector seems to be promising. The team has found a link between the activation of the EGF-dependent pathway with the activation of TWIST1 and bad prognosis in lung cancer. They have found an miRNA as a promising marker of sensitivity to anti-EGFR treatment in colon carcinoma. They have also found data about the obesogenic role of some ambient contaminants such as TCDD and MEHP. Finally, a direct link between the treatment with ciclosporin, TEM, ER stress and autophagy and its nephrotoxicity has been established. The team developed a kit that is presently commercialized by a company to detect the levels of 23 isoforms of human CYP by RT-PCR that can be used to determine the toxicity of compounds and drugs.

The team is developing new and original techniques, in particular through the recruitment of a CR1 who has skills in microfluidics.

The group has published 101 original papers, some in top-ranking journals, 39 reviews and 15 letters. Together, these works have been cited 2450 times. Remarkably, all these projects are very productive in terms of publications and some of these results have been protected by patents (6 during the last 5 years). All the members of the team have delivered constant high quality results. The papers were published in good journals (*J Immunol, Cancer Res (x3), Clin Cancer Res (x2), Am J Gastro, Autophagy, Am J Transpl, Diabetes, Clin Pharmacol Ther (x2), J Proteome Res, J Thromb Haemostas, Cell Death Diff, Lab on Chip, Hum Mol Genet, Am J Kidney Dis, Int J Cancer (x6), Ann Oncol*) to very good journals (*PNAS, Blood, Gut (x2), Hepatology, J Hepatol, Ann Neurology*), and some in even excellent journals in the field of clinical oncology (*5 JCO, of which 4 as a first of last author, one Lancet Oncology in collaboration*). They have presented their results in 69 international and 29 national scientific meetings since 2008.

The group has also an excellent activity of technology transfer assessed by 6 patents and an impressive number of collaborations with private companies such as Servier, Integragen, Sobios, Myriad genetics, Raindance technology.

Assessment of the unit's academic reputation and appeal

The group participates in several international Consortia and has organized scientific meetings. The citation level indicates the recognition of its visibility at the international level. Their seminal contribution to identifying the inefficiency to anti-EGFR antibodies in colon cancer patients carrying the Kras mutation is widely recognized.

Mr Pierre LAURENT-PUIG is recognized as an international expert and leader in the field of pharmacogenetics and cancer. He participates to several scientific committees in France (INCa, Ligue contre le Cancer, Fédération Ftrançaise de Cancérologie Digestive, FFCD).

Other members of the team also participate to scientific committees and have been involved in national programs of evaluation and strategic plans. Two scientists of the team are members of Inserm specialized scientific committees for the current 4-year period.

The team leader was invited to give conferences in 23 international and 31 national scientific meetings. The other team members attended 27 international and 24 national conferences as speakers.

The quality of the research conducted in this Unit led to a number of French and International external fundings.

Assessment of the unit's interaction with the social, economic and cultural environment

The team leader is the president of the PETACC08 clinical trial which includes 2400 patients, and participates in the project Biointelligence coordinated by Dassault Systems and supported by OSEO. Five team projects have been supported by ANR (about 1.4 M€) and nine by INCa/Canceropole Ile-de-France (about 900 k€). The team also have had 16 scientific collaborations that all resulted in publications, and industrial collaborations with Servier, Integragen, Sobios, Myriad Genetics and Raindance technologies, some of which also also gave rise to scientific publications. The group has also an excellent activity of technology transfer assessed by 6 patents.

They organized the FFCD meeting from 2000 to present, the EORTIC on translational research in Paris in 2012, and organized or participated to the organisation of the European Science Foundation meeting in Spain in 2007, 2008 and 2010.

The team leader is head of the SIRIC for the project "Cancer Research and personalized medecine" that includes 22 research units and has been endowed with 7.5 M€.

Assessment of the unit's organisation and life

The laboratory space is 120 m^2 and an additional space of 140 m^2, which is shared with the INSERM U747, 145 m^2 of offices and a rest room of 20 m^2. The committee visited the laboratory and concluded that the team need more surface area for developing their current project. Concerning the organisation of the laboratory, no special problems were detected by the committee, the communication between people is easy, health and safety issues are taken into account, responsabilities are well defined, the council of the laboratory is meeting regularly.

All people, including researchers, technicians and students seem to be very happy to work in the laboratory. Mr Pierre LAURENT-PUIG is clearly "the leader" of this team.

The committee found that 12 over the 20 technicians are contracted and payed on their own research contracts. There are almost no post-doc and the leader is well aware of this problem.

The committee noticed a problem concerning the management of the numerous grants obtained by the lab that needs to be improved. The authorities acknowledged this problem and will try to resolve it.

Assessment of the unit's involvement in training through research

Within the Unit, 8 members are Professors or Assistant Professors, and their duties include teaching per status.

Good activity of training PhD students: 10 students have obtained their PhD degree over the last 4-year period, among them 7 are currently MCU-PH, PU, SUP or are working at the AP-HP, 2 are pursuing postdoctoral studies abroad and 1 continues with medical studies. 10 PhD students are currently trained in the lab. Members of the Unit have also participated to the training of 35 Master students.

Two foreign researchers (Israel, Brazil) have joined the lab for a training period of 8 months and 2 months, respectively.

Remarkably, all PhD students of the laboratory published from 1 to 21 papers during the last 4 years period, with a median of 7 papers, which is really exceptional.

Team members are the national coordinators of the master 2 degree (M2) in "Toxicologie humaine, evaluations des risques, vigilances"; coordinators of 2 teaching units (UE) into the M1 of biology: "Metabolisme des xenobiotiques et implications en pharmacocinetique et toxicologie; immunologie, genetique et médicaments"; they participate in the organisation of "Ecole thematique analyse du genome tumoral"; they are members of the "conseil scientifique et bureau de l'ED Médicament"; finally, they are the coordinators of the "module biologie fondamentale IFSI Paris Descartes".

Assessment of the five-year plan and strategy

The project is entitled "Medicine Personalisée, Pharmacogénomique, Optimisation Thérapeutique" (MEPPOT). In general the project is the continuation of previous works.

Part 1 of the project aims at understanding :

i) the pharmacogenomics of the resistance to anticoagulants (anti-Vitamin K and new oral anticoagulants) ;

ii) the pharmacogenomics or nephrotoxicity of immunosuppressors (role of ER stress in calcineurin nephrotocixity, development of an algorithm for thiopurins dose optimization and identification of specific markers by candidate genes and RNA pan-expression analysis);

iii) the mechanisms of resistance to anticancer drugs (miRNA has-mir31-3p associated to ERGFR resistance, identification of minor cellular subgroups in 3-wt (Kras, Nras and Braf) tumors by "PCR in droplets").

Part 2 aims i/ to understand the role of cytochromes p450 on the metabolism of inhibitors of tyrosine kinases and ii/ to understand the role of reactivation of TWIST1 (EMT activation) expression in lung cancer during the treatments against EGFR as target).

Part 3 is entitled "simulation of the resistance to the targeted therapies by microfluidic" and aims to develop an approach concerning the analysis of single cells by a microfluidic approach using the resistance to EGFR-targeted treatments as a model. The next part of this project is to study the mutations of the circulating DNA of patients included in a PHRC-funded trial which will include 250 colon cancer patients at the time of recurrence, using the same technical approach.

Part 4 of the project aims to develop novel therapeutic approaches based on the developed CYP2B6TM-RED lentivirus on lung and ORL cancers (i/ analysis of its bystander and its immunomodulatory effects, ii/ inclusion of a miRNA-sequence into the vector to limit its biodistribution, iii/ test of other drugs that may be metabolized by CYP2B6TM and RED, iv/ combination with in vaccine-based therapeutic strategies to enhance the immunological response).

This is a dynamic team headed by a solid and imaginative group leader with long standing track record on pharmacogenetics. This team have a very valuable know-how, appropriate national and international collaborations, including with several companies, and they have delivered constant high quality results in their field with a singular translational interest. An excellent exemple is their recent contribution by discovering the inefficiency of the anti-EGFR antibodies in patients carrying a mutation in the Kras in colon cancer by the fact that these results are used in national and international recommendations to select responsive patients.

The new project is in fact the continuity of the previous work, it is based on solid preliminary data, and they have interesting and original biobanks necessary for the project. Their projects have very clear translational as well as cognitive impacts in the fields of colon and lung cancer. Finally, they show a global move to clinically relevant questions that fit with the missions of INSERM.

Competences, expertises, techniques and facilities, including the sophisticated machines and tools necessary for the more recent microfluidic approach, required for the new projects are already largely mastered in the laboratory, or through ongoing and pertinent local and international collaborations. All the members of the visiting committee are convinced that all aspects of the project are realistic and feasible.

4 • Conduct of the visit

Visit date:

Start: February 1st, 2013 at 9.00h.

End: Feburary 1st, 2013 at 18.00h.

Visit site:

Institution: UFR biomedicale des SAINTS-PERES

Address: 45, rue des Saint-Pères, 75006 Paris

The review took place on February 1th 2013 at the present site of implantation of the Unit (UFR biomedicale des SAINTS-PERES). Oral presentations describing past and future research programs of the unit were made by the proposed director (Mr Pierre LAURENT-PUIG) and by the 5 project leaders participating in the new project. The visiting committee visited the Unit and also met separately (in the absence of the direction/team leaders), with the technical staff, researchers with permanent positions, non-permanent lab members (Students, Post-docs) and the representatives of institutional authorities (Paris Descartes University, UFR biomedical Saints-Peres and Inserm). All members of the committee were present from the beginning to the end of this visit and have participated to the final discussion on the report that took place at the end of the visit. They have also returned independently their argued comments to the chairman.

5 • Statistics by field: SVE on 10/06/2013

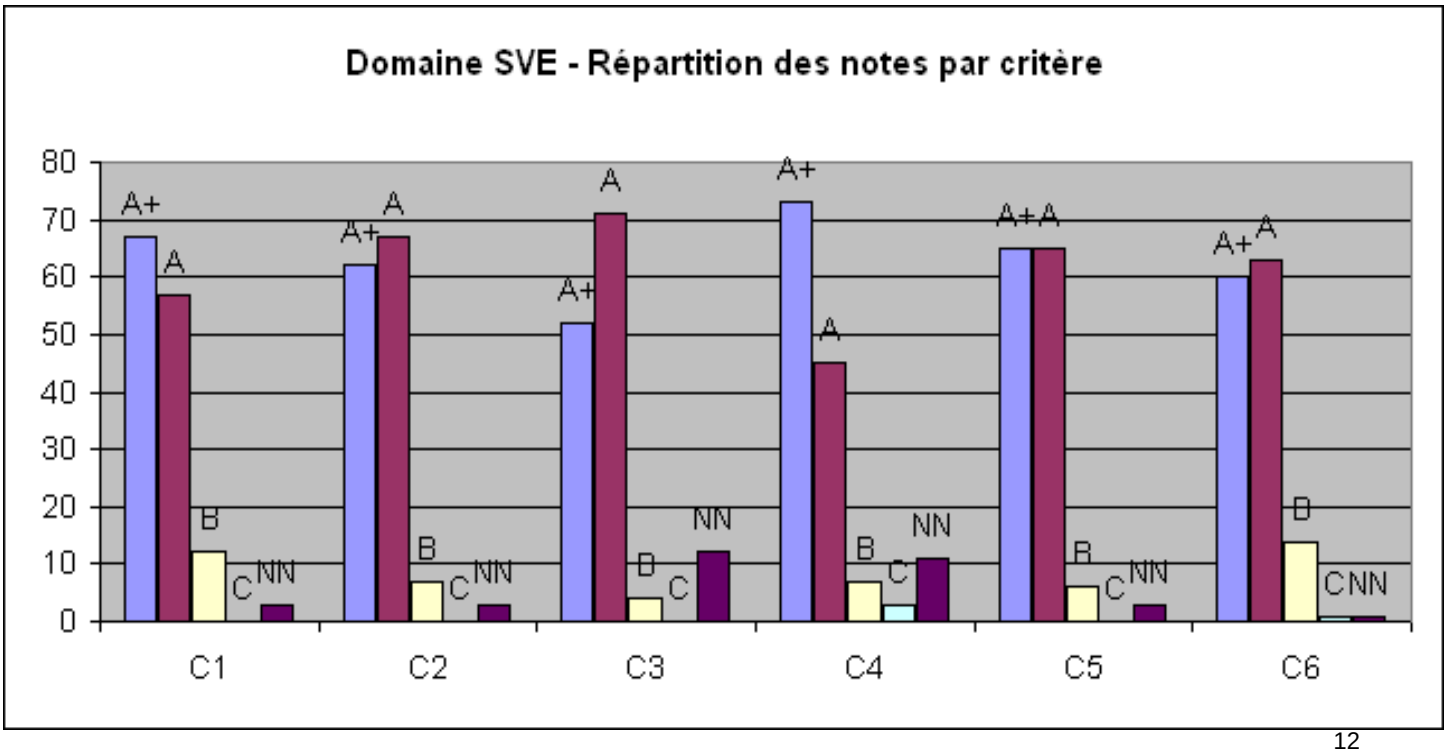
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



6 • Supervising bodies' general comments

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 29.03.2013

Vos ref : S2PUR140006271 –
Médecine personnalisée,
Pharmacogénomique, Optimisation
thérapeutique - 0751721N

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de
l'Enseignement Supérieur
20, rue Vivienne
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Médecine Personnalisée, Pharmacogénomique, Optimisation thérapeutique»

Vous trouverez ci-joint les réponses du Directeur de l'unité, Pierre LAURENT-PUIG, auxquelles le Président et moi-même n'avons aucune remarque particulière à rajouter.

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

Le Vice Président du Conseil Scientifique

Stefano Marullo, DM, DesSci

Université Paris Descartes, Vice-présidence du conseil scientifique, 12 rue de l'école de médecine, 75170 PARIS cedex 06
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General observations

1/ Our team has always maintained an equilibrium between cancer and anticoagulants and immunosuppressor since they are both closely associated to hospital laboratory (leaded by two members of our team).

2/The number of HDR for 2014 is 7 and not 5 as reported. This number will increase to 9 before the end of the year.

3/ Since the writing of our project, the physicist intent to stay in our team and we are developing collaborations with physicists from the ESPCI, the Max Planck Institute and Paris Polytechniques school in order to reinforce this aspect of our project.

4/We have a strong interaction with medical and pharmacy school of Paris Descartes University allowing the recruitment of physicians in good agreement with our translational research orientation. Nevertheless we agree that we should increase the number of full time researchers to strengthen the basic research. In this regards, we identified, for the next four years, three potential scientist candidates who graduated their PhD in our team.