# Physiopathologie et pharmacotoxicologie placentaire humaine

Rapport Hcéres

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

Department for the evaluation of research units

# AERES Report on Unit:

## Pathophysiology & Pharmacotoxicology of the Human Placenta

## Under the supervision of the following institutions and research bodies:

Université Paris Descartes

Institut national de la santé et de la recherche médicale

January 2013

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

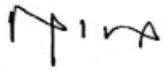
Research Units Department

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: Pathophysiology & Pharmacotoxicology of the Human Placenta

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

# Evaluation report

| | |
|---|---|
| Unit name: | Pathophysiology & Pharmacotoxicology of the Human Placenta |
| Unit acronym: | |
| Label requested : | UMR-S |
| Present no.: | UMR-S 767 |
| Name of Director (2012-2013) : | Ms Danièle EVAIN-BRION |
| Name of Project Leader (2014-2018) : | Mr Thierry FOURNIER |

# Expert Committee members

| | |
|---|---|
| Chair : | Mr Vincent SAPIN, Université d'Auvergne, Clermont-Ferrand |
| Experts : | Ms Nadia ALFAIDY, INSERM, Université Joseph Fourier, Grenoble 1 |
| | Ms Marie-Christine CHABOISSIER, INSERM, Université Nice Sophia-Antipolis |
| | Ms Christine DAMASE-MICHEL, INSERM – Université Paul Sabatier, Toulouse |
| | Mr Martin KNÖFLER, University of Vienna, Vienna, Austria |

## Scientific delegate representing the AERES:

Mr Jean GIRARD

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

Ms Chantal LASSERRE, INSERM

Mr Stefano MARULLO, Université Paris-Descartes

# 1 • Introduction

After its first creation as an INSERM unit in 1995 under the direction of Ms Danièle EVAIN-BRION, the current INSERM Unit was recreated in 2006 (U767 / Normal and Pathological Pregnancy) with the same director. The main research focus of the UMR INSERM S767 is to study the development and functions of the human placenta during normal and pathological (preeclampsia, intra-uterine growth retardation, prematurity) pregnancies. In particular, the team studies the molecular and cellular mechanisms involved in the invasion and differentiation of (villous and extra-villous) trophoblastic cells. The UMR INSERM S767 is located at the « Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes". 300 m2 of research surfaces are devoted to this unit, which has also access to platforms from the IFR and the University.

## AERES nomenclature:

SVE1_LS4

## 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 | 4 | 4 | 3 |
| **N2** : Permanent researchers from Institutions and similar positions | 5 | 6 | 2 |
| **N3** : Other permanent staff (without research duties) | 1 | 1 | |
| **N4**: Autres enseignants-chercheurs (PREM, ECC, etc.) | 1 | 1 | |
| **N5**: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.) | 3 | 2 | |
| **N6** :Other contractual staff (without research duties) | | | |
| **TOTAL N1 à N6** | 14 | 14 | 5 |

| | |
|---|---|
| Percentage of producers | ***100 %*** |

| Unit workforce | Number as at 30/06/2012 | Number as at 01/01/2014 |
|---|---|---|
| Doctoral students | 3 | |
| Theses defended | 10 | |
| Postdoctoral students having spent at least 12 months in the unit | 3 | |
| Number of Research Supervisor Qualifications (HDR) taken | 10 | |
| Qualified research supervisors (with an HDR) or similar positions | 10 | 7 |

# 2 • Assessment of the unit

## Strengths and opportunities:

The internationally recognized expertise in human placental development, physiology and functions (focused on trophoblastic cells) during normal but also pathological pregnancies.

The development of acknowledged cellular models representative of trophoblastic environment and the development of a new model : the perfused cotyledon for the pharmacotoxicology project.

The clinical relevance of the research questions with translational applications to major human pathophysiological pregnancies affecting around 70 000 cases per year (9% of the French annual pregnancies).

The very good exploitation of the scientific work in terms of echographic and biomarkers development.

The strong ability to obtain some important fundings during the last 4 years : 3 ANR projects and private grants.

A central and leader position with the scientific and clinician community working on obstetrics in Paris, with the establishment of a real and functional network based on numerous institutions as RTRS “Pregnancy and Prematurity” and the PremUp Foundation, Labex or Equipex for example.

An important number of publications (145 ACL publications) in the best journals of the specialties “Biology of Reproduction, Obstetrics and Gynecology or Endocrinology”.

The support of the faculty and university and the opportunity of a future evolution of the faculty toward a research centre.

## Weaknesses and threats:

The major weakness is linked to the lack of high rank publications in general journals potentially explained by the highly focused research topic.

The absence of european or international funding networks.

The future move to the new research building occuring during the future 4 years period potentially affecting the team’s life and production.

## Recommendations:

The new scientific fields proposed in the project (pharmacotoxicologic and the oxidative status of the human trophoblastic environment) have to be supported to strengthen up and consolidate the global approach of the unit in terms of placental pathophysiology.

The Unit has to reinforce its network in terms of clinical and scientific collaborations, collections of biological samples related to pregnancies, and socio-economic relations in order to stay among the most acknowledged research laboratories in terms of national and international lisbility.

Due to its expertise, the results obtained and the high level of the projects, the team has to produce some publications that can be submitted to generalist journals with a high international rank, and not to keep publishing in the ones they have been used to, as they belong to the restricted scientific field “Biology of Reproduction, Obstetrics and Gynecology or Endocrinology”.

# 3 • Detailed assessments

## Assessment of scientific quality and outputs:

There are regular publications (145 papers type ACL in the 4 last years) in the best journals of the field "Biology of Reproduction, Obstetrics and Gynecology or Endocrinology", with the 5 most important publications since 2007 listed by the team published in Endocrinology (2), J. Clin Endocrinol. Metab., Am. J Physiol. Cell. Physiol and FASEB.

The (clinical and fundamental) research questions are very original with an important obstetrical relevance and based on an international expertise on placenta. The results are established with specific models (primary cultures, established cell lines, perfused cotyledon) well controlled and validated.

The translational research topics at the clinical research interface led to echographic developments and in vitro diagnosis assays.

There have been no publications in general journals or in journals with high impact factors.

## Assessment of the unit's academic reputation and appeal:

There is an important international academic attractiveness of the team members with 25 guest international conferences participation. The team members belong to the different international committees working on placental science (IFPA, Trophoblast Research Center of Cambridge…) and are members of the editorial board of the journal Placenta.

National and international collaborations are well established to support the different past, present and future projects.

The acknowledgment of the team is attested by obtaining important institutionnal financial support (3 ANR) and private grants.

The team created and organised the first international symposium of the "Francophone Placenta Group" in Geneva (2012) and was designated for the organisation of the Congress of International Federation of Placenta Associations in Paris (2014).

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

This point is excellent in terms of network participation. The Inserm U767 team founded the RTRS "Pregnancy and Prematurity" research and care network. The PremUp foundation was also created by the U767 with other parterns. PremUp organised annual meetings on perinatality with public participation and published numerous press articles, films and interviews.

## Assessment of the unit's organisation and life:

The entity governance is recognised as performant by staff members. This point has been clearly mentioned by both engineers and technician staff, during their interviews.

A regular (monday) meeting was organized for all the team to talk about scientific, administrative and technical aspects.

The need for a future potential help (by a recruitment) was underlined by engineers and technician staff concerning the administrative charge of the future director in order to be able to conduct "as well as before" his scientific team.

## Assessment of the unit's involvement in training through research:

Since 2007, the U767 was in charge and directed : 11 doctoral fellows (Doctoral school ED157 - Génétique, Cellulaire, Immunologie, Infectiologie et Développement), 3 "INSERM welcome (for clinicians)" positions, 18 Master's (3 M1 and 15 M2) research students, 3 BTS and 3 Licence pro. The day-to-day supervision of the PhD students is well done.

Most of the researchers or teaching-researchers (PU, MCF, PU-PH, MCU-PH) are involved in teaching with participation in several Master programs. The unit is involved in several following research courses:

- Reproduction and Development (University Paris 5 and 7);

- UE Vascular Physiology and Pathology: regulation of angiogenesis (University Paris 6);

- Cell Biology, Physiology and Pathology (University Paris 7);

- Scientific seminar in Intra-uterine Growth Retardation for midwives and obstetricians (University Paris 5);

- Training for adults : biotechnology and cell biology technicians (GRETA de Massy).

The team didn't mention any responsiblity in national and international training networks.

## Assessment of the five-year plan and strategy:

The goal of the research project 2014-2018 is globally to obtain better knowledge of human placental development and function in normal and pathological conditions in order to improve early screening and care of the main obstetrical diseases associated with placental dysfunctions with a specific focus on the floating chorionic villous. The study will analyse the impact of the environment within the intervillous space in both physiological and pathological conditions on the formation, integrity, exchange andhormonol fucntions of the chorionic villous, the functional unit of the human placenta.

The project is clearly divived in work packages:

### **WP 1**: Formation of the placental barrier

"Formation of the placental barrier" represents a very interesting working package of the future unit, which has a longstanding and worldwide-recognized expertise in studying mechanisms controlling trophoblast cell fusion which represents the key event in placental barrier formation. Understanding regulation of trophoblast cell fusion is not only fundamental to our understanding of placental function and hence fetal nutrition and wellbeing during normal pregnancy, but also critical to unravel mechanisms involved in the pathogenesis of diseases arising during pregnancy such as preeclampsia, intrauterine growth restriction or trisomy 21. This is of particular relevance to the human health in later life, since it became evident that abnormal fetal growth during pregnancy predisposes to a variety of adult diseases such as hypertension, cardiovascular problems or metabolic disorders.

As mentioned above, researchers of the unit are regarded as leading experts in the field since they unraveled numerous key mechanisms in trophoblast fusion such as the role of cAMP signaling and placental hormones. Importantly, they could also demonstrate that the fusion process and production of different forms of the pregnancy hormone called human chorionic gonadotrophin were impaired in trophoblasts of pregnancies carrying fetuses with trisomy 21. Hence, research of the unit not only investigates basic mechanisms in trophoblast differentiation but also has a strong focus on failures in this process in pathological pregnancies which will likely lead to the identification of novel biomarkers and improvement of diagnostic tools long-term.

The head of this working package has convincingly demonstrated that his expertise, knowledge and current research ideas will lead to further important insights in this particular area of pregnancy research. Besides his excellent publications in the field he gave an outstanding presentation on the current data, ideas, and projects during the AERES evaluation. As part of his PhD thesis he discovered that abnormal hCG (human Chorionic Gonadotropin) signaling impairs trophoblast fusion as occurs in trophoblasts derived from trisomy 21 placentae. He also identified other important regulators of trophoblast cell fusion such as ZO-1 and contributed to our understanding of the mesenchymal-trophoblast cross talk in the placental villus. His recent activities to identify the role of phosphatases and cAMP-dependent macro-complexes controlling trophoblast cell fusion sound very interesting and promising for the future since much remains to be learned about physiological and abnormal trophoblast differentiation.

It is also worthwhile mentioning that during his postdoctoral studies in Oslo, Norway, he produced excellent publications on AKAPs, (A-kinase anchoring proteins) protein-macro complexes controlling and organizing cAMP signaling in a spatial and temporal manner.

The project also presents interesting novel techniques to studying the protein interactions in macro-complexes of the placenta and to analyze trophoblast cell fusion, which are already established in the laboratory. Moreover, the role of different types of phosphodiesterases (PDE), inactivating cAMP, in trophoblast fusion and their potential roles in pregnancy disorders are largely unknown. Unpublished data of the group nicely demonstrated that different enzymes of the PDE family are involved in this fusion process.

In conclusion, the strong expertise in cell- and molecular biology of the placenta supported by excellent collaborations will allow the PI to study AKAPS and other interesting protein assemblies in the setting of physiological and pathological trophoblast function and differentiation which represents a novel and promising research direction of the working package within the next years.

WP2 : Ontogenesis of the placental barrier

This working package will be focused on the ontogenesis of the placental barrier with two parts: (i) the role of the oxygen environment in the trophoblastic differentiation and functions; and (ii) the role of nuclear receptor PPAR gamma (PPAR□□ and its target genes in placental development. Up to date, the redox status of trophoblastic cells is poorly known. For this first axis, the hypothesis is that oxidative/nitrosactive stress inside the trophoblasts due to changes in oxygenation (occurring well established steps of the placental development) may have physiopathological consequences (preeclampsia and IUGR) for trophoblastic differentiation and functions; and for the passage and metabolism of xenobiotics during pregnancy. The second part is based on previous interesting papers of the team identifying the important roles of PPAR□ in trophoblastic functions. The present project will develop the involvements of PPAR□ target genes during human trophoblastic differentiation. They also hypothesized that a dysregulation of PPAR□, HCG and LOX could occur in placental pathologies.

* Strong points:

- The team leader's research has contributed in a fundamental manner to important advances in placental endocrinology. His studies have established the key roles of peptide hormones, such as HCG in the control of trophoblast differentiation and have contributed to the elucidation of current concepts on the role of the transcription factor, PPAR□ in placentation. Recently his team has shown that a hyperglygosylated form of HCG (H-hCG) exists in the placenta with a direct role in the control of trophoblast invasion. As a result of this insightful work concerning HCG and PPAR□, this team became an independent part of the teams working in the field of hCG and PPAR□ in the placenta.

- The new project proposes a large and novel number of hypotheses focusing on the understanding of normal and pathological pregnancies, with an important feasibility in terms of technical and scientific support.

- The team has a strong support from the actual authorities: University, Hospital and Faculty of Pharmacy.

- This redox status project will be supported by the presence of newly recruited teaching-researchers specialized in this field.

* Weak points:

- The committee believes that with the workload that the team (and also unit) leader will have, he won't be able to run day-to-day specific projects and he needs to delegate some of his own proposed projects to young researchers.

- With the proposed new project the unit should consider the development of animal models, a criterion that was missing during the last term.

### WP3: Placental transfer and metabolism of xenobiotics

This is one of the main new research topics of Unit UMR-S767. Placental transfer and metabolism of drugs and environmental toxins (such as benzo[a]pyrene) are studied using ex vivo human perfused placental cotyledon model. In the project, two types of immunosuppressive drugs (tacrolimus and cyclosporine) will be studied. First results have been obtained on tacrolimus which transfer has been evaluated using control placentas and placentas of transplanted women. This approach is completed by in vitro studies using trophoblastic primary cultures eliciting the evaluation of the xenobiotics impact on cell differentiation. Cellular and lipid markers will be characterized by means of a mass spectrometry, especially after long term exposure in placentas from transplant recipients. This topic is strongly supported by the Faculty of Pharmacy as demonstrated by the recruitment of a Professor in Biochemistry, previously working on the model of perfused placental cotyledon. Several fundings support this activity: ANR "Placentox", LFB or Mutuelle generale.

The perfused cotyledon model is simple, elegant and not very expensive. However, it only offers a localised, restricted and fixed view of pregnancy. Nevertheless, it can give first data on drug availability over the placental "filter". One interesting point is that the studies are not only performed on normal placentas but also on placentas from transplant recipients eliciting the study of the impact of the disease and/or the chronic drug use on placental transfer.

### WP4: Translational Research

The first translational theme deals with the study of the maternal blood flow within the intervillous space by two approaches. Indeed, the researchers plane to assess the impacts of perturbations of maternal hemodynamics on the biological properties of the villous trophoblasts by (i) identifying the impact of the shear stress on the biological functions of human syncytiotrophoblasts and by (ii) examining the placental vascularization in normal and pathological pregnancies using ultrafast imaging (micro-Doppler). The second translational theme concerns the identification of biomarkers of abnormal trophoblastic differentiation in placentas with aneuploidy (trisomy 18, 13, 21, Turner syndrome 45X0). This work will be realized using a mixed approach: identification of biomarkers at cellular levels in cultures and after a validation of the candidates at the clinical interface. The feasibility of both projects is excellent due to the biological and obstetrical positions of both teaching-researchers at the hospital. This was also completed by an important competence of both project leaders in terms of scientific and technical fields. The recruitment of patients will be clearly helped by the different collections strategies and tools previously installed.

In addition, since 2006, the director of the unit UMR-S767 INSERM has created and directs the foundation for scientific cooperation on perinatality, PremUP (www.premup.org). PremUP meets two main concerns including a better understanding of fetal growth disorders and provide assistance to patients. PremUP includes 6 maternity and neonatology units type 3 (with 20 000 births and 2500 premature babies) and research centers (10 INSERM units, 1 CNRS unit, 1 INRA unit, 1 IRD unit, 2 Centers for Clinical Investigation and 1 Center for Epidemiological Investigation). In addition, PremUP supports Perinat Collection that was selected in the first call for the projects EQUIPEX. This project allows collecting, preserving and developing large collections of fetal and perinatal samples. These collections are also documented and associated to clinical data and imaging in reproducible conditions. The PremUP foundation and Perinat collection are both unique tools to follow pathological pregnancies, the birth and the childhood and contributes in a unique way to improve the management of perinatal problems, especially those of prematurity. Finally, Prem Up and Perinat Collection are keys actors in structuring the French research from the physiology of human placenta to prematurity.

## Conclusion:

The proposed project has a very important obstetrical relevance, mixing fundamental, clinical and translationnal approaches.

The work already done is of excellent quality, allowing this team to obtain national and international acknowledgment.

The feasibilty of the proposed projects is good due to the previous establisment of scientific, socio-economic and clinical networks.

# 4 • Conduct of the visit

## Visit date:

Start: 29, january, 2013, at 8h30

End: 29, january, 2013, at 17h30

## Conduct or programme of visit:

**Salle Polyvalente of the Faculty of Pharmaceutical and Biological Sciences**

| | |
|---|---|
| 8h30-9h00 | Welcome of the evaluation committee |
| 9h00-9h30 | Meeting with the project manager and the current director of the UMR-S767 |
| | Welcome by le Doyen, M. Jean Michel SCHERRMANN |
| 9h40-10h00 | M. Thierry FOURNIER, project manager **"Overview of the scientific project and strategic approach"** |

**Development and functions of the chorionic villi**
*(talk 15 min + 15 min discussion)*

| | |
|---|---|
| 10h00-10h30 | Mr Guillaume PIDOUX (CR2 INSERM) **"Formation of the placental barrier"** |
| 10h30-11h00 | Mr Thierry FOURNIER (DR2 INSERM) **"Ontogenesis of the placental barrier"** |
| 11h00-11h30 | Ms Sophie GIL (PU) **"Placental transfer and metabolism of xenobiotics"** |
| 11h30-12h00 | Discussion break (coffee, tea, etc,.) |

**Translational research: pathologies and biomarkers**

| | |
|---|---|
| 12h00-12h15 | M. Jean GUIBOURDENCHE (PUPH) **"Biomarkers of trophoblast differentiation in complicated pregnancy of placental origin"** |
| 12h15-12h30 | M. Vassilis TSATSARIS (PUPH) **"Maternal blood flow within the intervillous space"** |
| 12h30-12h45 | General discussion of the clinical research |
| 12h45-13h00 | Ms Danièle EVAIN-BRION (DR1 INSERM), Director of UMR-S767 and of the PremUp foundation **"Interaction with the socioeconomic environment"** |
| | **Conclusion** M. Thierry FOURNIER |
| 13h00-14h00 | Lunch in the salons "du Doyen" |

**Laboratoire UMR-S767**

| | |
|---|---|
| 14h00-14h30 | Poster presentations |
| 14h30-15h00 | Meeting with the engineers and technicians, and with doctoral and post-doctoral fellows |
| 15h00-15h30 | Meeting with "les tutelles" of the unit |
| 15h30-17h30 | Deliberation of the evaluation committee |

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

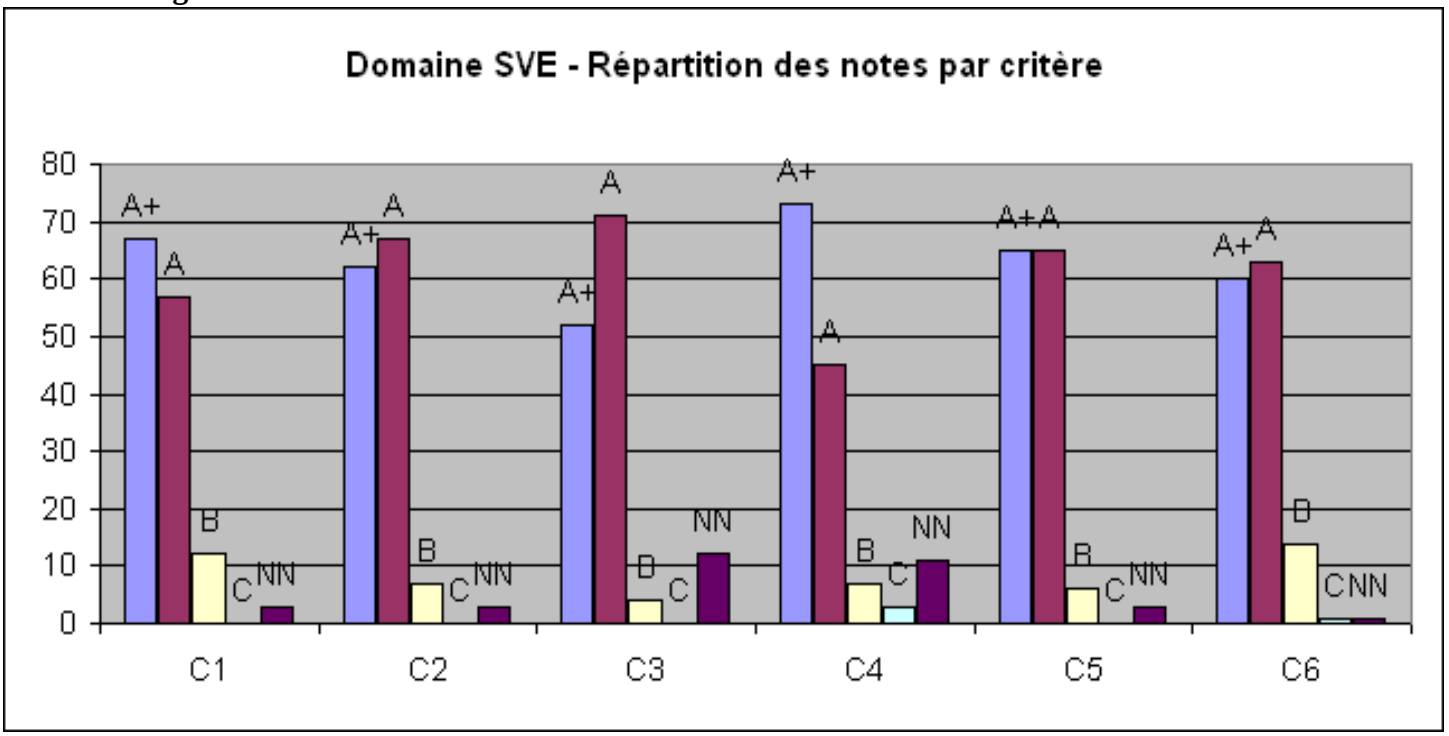
## Grades

| 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 24.04.2013

Vos ref : S2PUR140006289 –
PhysioPathologie et
PharmacoToxicologie Placentaire
Humaine – 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 « PhysioPathologie & PharmacoToxicologie Placentaire Humaine »

Vous trouverez ci-joint les réponses du Directeur de l'Unité, Thierry FOURNIER, auxquelles le Président et moi-même n'avons aucune remarque particulière à apporter.

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
Téléphone: 01 76 53 17 45; Courriel: stefano.marullo@parisdescartes.fr

**UMR-S, Inserm-Paris Descartes**
**PathoPhysiology & Pharmacotoxicology of the Human Placenta**

Re.: comments relative to the AERES report D2014-EV-0751721N-S2PUR140006289-002011-RT

Paris, April 20, 2013

First of all, we would like to thank the committee for their report concerning the evaluation of our research unit and the helpful and positive comments of the referees. We have no general comments on the report, which covers and describes well the activities of our research unit.
We wish nonetheless to bring some insights about the few specific points raised in the three recommendations of the report, and concerning animal models, as developed below.

1/ Research on the pharmacotoxicology of the human placenta currently benefits from financial support (Placentox) from ANR and another proposal is under evaluation. This latter financial support will allow the recruitment of a doctoral and/or a post-doctoral fellow to reinforce research on this topic.
Research on the ontogenesis of the placental barrier and oxidative status of the trophoblast will be reinforced by the recruitment of an AHU in 2014. One funding proposal is under evaluation and will allow recruitment of a post-doctoral fellow to support this theme. In addition a fellowship for a Canadian post doc is under evaluation. We have also posted an offer for a CR position by internal mobility.

These two topics will benefit from the technical expertise of an AI from January 2014 and of a MCU position (September 2014) thanks to the arrival of a PU and a PUPH in the team.

2/ As mentioned in the report, our research is part of the PremUP program (foundation for scientific cooperation, www.premup.org), promoting translational research in perinatology
It will profit specifically from PremUp technical platforms such as the Placental Physiopole and the imaging platform PremIMAGE, from the task force of the PemUp clinical and research network involving 20 000 births per year, and from well-characterized collections of biological samples (Equipex, Perinat Collection).
Our project will be developed in collaboration with the “Pregnancy & Prematurity” teams of the PremUp network, including research teams (INSERM, CNRS, INRA) and care teams in the Paris region (maternity and paediatric units, AP-HP), allowing interactions with clinicians. Active collaboration with obstetric units (Cochin-Port Royal, , Robert Debré, CHIC

Créteil,Kremlin Bicêtre, Antoine Béclère, Armand Trousseau)) will allow us to obtain human placental tissues and blood samples, with the patients' informed consent.
This project will take place on the site of the Faculty of Pharmacy Paris Descartes and will benefit from the technical equipment and expertise of members of Paris Descartes IMTCE: confocal and electronic microscopy (B. Saubamea, IMTCE), and mass spectrometry (O. Laprévote, IMTCE). In addition, we have developed collaborations with teams specialised in proteomics (F. Guillonneau), FRET (P. Vincent), and gap-FRAP (J. Dompierre).
This project will also benefit from our active participation in networks that include many laboratories working in the field (Nuclear receptors group, Peroxysomes & PPARs association, International Francophone placental Group (GfP), French cAMP network (club AMPc), which will share scientific knowledge, techniques, approaches and tools.
In addition, the Unit is in charge of the organization of the International Federation of Placental Association (IFPA) congress in September 2014.
All together this will facilitate collaborations, translational research and international visibility.

3/ Concerning publications, we are currently publishing in specialized journals such as Placenta and in more generalist ones such as Endocrinology, Plos One, Am J Physiol, FASEB J and JCEM for the clinical aspect of our work. We will concentrate our effort to publish in higher ranked journal such as Embo J and JCI for fundamental and clinical studies, respectively.

Concerning the use of animal models:
Due to the specificity of human placentation we have concentrated our effort on the development of original physiological models in order to mimic human placental pathophysiology as closely as possible. We have original *in vitro* models (primary cultures of human placental mesenchymal and trophoblastic cells isolated at different terms of pregnancy) and *ex vivo* models (human perfused placental cotyledon). The *in vivo* approach of our project will be considered in collaboration with Dr Chavatte–Palmer (INRA, RTRS PremUp foundation), who has developed a rabbit model of IUGR.

Thank you for the review process

Sincerely yours,

Dr Thierry Fournier

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Université Paris Descartes - Faculté de Pharmacie, 4 av. de l'Observatoire
75270 Paris Cedex 06
Tél. : (33) 1 53 73 96 03 - Fax : (33) 1 44 07 39 92
thierry.fournier@parisdescartes.fr