

SIMPA - Stress immunité pathogènes

Rapport Hcéres

► **To cite this version:**

Rapport d'évaluation d'une entité de recherche. SIMPA - Stress immunité pathogènes. 2012, Université de Lorraine. hceres-02029964

HAL Id: hceres-02029964

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Submitted on 20 Feb 2019

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

Research Units Department

AERES report on unit:

Stress Immunity Pathogens

SIMPA

Under the supervision of the following
institutions and research bodies:

University of Lorraine



January 2012



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



| Unit

Name of unit:	Stress Immunity Pathogens
Acronym of unit:	SIMPA
Label requested:	EA
Present no.:	JE2537
Name of Director (2009-2012):	Mr Jean-Pol FRIPPIAT
Name of project leader (2013-2017):	Mr Jean-Pol FRIPPIAT

| Members of the committee of experts

Chair:	Mr Michel COGNÉ, Limoges
Experts:	Ms Marianne COGOLI-CREUTER, Zürich, Switzerland
	Mr Philippe LANGELLA, Jouy-en-Josas
	Mr Michel NEUNLIST, Nantes
	Mr Jean-Michel ROSSIGNOL, Saint-Quentin
	Mr Michel SALZET, Lille (CNU representative)
	Mr Pierre-Paul VIDAL, Paris



| Representatives present during the visit

Scientific Delegate representing AERES:

Mr Joost VAN MEERWIJK

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

Mr Jean-Louis GUÉANT, University of Lorraine

Mr Pierre MUTZENHARDT, University of Lorraine



| Report

1 • Introduction

Date and conduct of visit:

The site-visit of the full evaluation committee took place on January 17th 2012. First, the unit's director presented its global activities followed by presentations by the three project leaders. Then, PhD-students and postdoctoral fellows; engineers, technicians and administrative assistants; and staff scientists met with the committee members in three parallel meetings. In a closed-door session, the committee discussed with the unit's director and the two other project leaders. Finally, the representatives of the University exposed its scientific policy and discussed with the committee-members. The visit ended with a closed-door meeting of the committee.

History and geographical location of the unit, and overall description of its field and activities:

The laboratory recently moved from the Faculty of Sciences to the Faculty of Medicine in Nancy. The five-year project proposes that the "Jeune Equipe" headed by Mr FRIPPIAT will be joined by microbiologists and neurobiologists to form the new unit which will work on "stress, immunity, and pathogens".

Management team:

Mr Jean-Pol FRIPPIAT, director.



Unit workforce:

Workforce	Number on 06/30/2011*	Number on 01/01/2013*	2013-2017 Number of producers**
N1: Professors or assistant professors	3	10	10
N2: EPST or EPIC researchers	0	0	0
N3: Other professors and researchers	0	4	3
N4: Engineers, technicians and administrative staff *on a permanent position	0.5	2.4	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0.5		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	2		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	1	4	
TOTAL N1 to N7	9	16.4	13

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

<http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation>.



2 • Assessment of the unit

Overall opinion on the unit:

The production of the three different research groups forming the EA "Stress, Immunité, Pathogènes" is quite heterogeneous. The overall project needs to be more precisely defined, especially regarding the internal collaborations.

Strengths and opportunities:

The main project of Mr Fripiat is original and carried out by an enthusiastic leader. It allowed some good publications and was repeatedly supported by the CNES, yielding some attractiveness towards the researchers from other disciplines that now propose to join the team.

The project to be investigated by the newly formed interdisciplinary team can lead to interesting findings on the effect of gravitational stress on the humoral immune system and on microorganisms. These new people joining Fripiat's team bring a good technological level and good will.

The overall atmosphere of the team appears good for researchers, technicians, and students

Weaknesses and risks:

Dispersion is a first risk. It is necessary to analyze more finely the different levels of physical or psychological stress that are associated to space flights as well as mild chronic stress encountered in the daily life and to avoid any confusion between the different issues studied.

Contracting with CNES brings money but might carry its own risk. For its claimed intent to broadly study immunity "under stress conditions" and not only under different gravity conditions (low and high gravity), the team has to define more general scientific questions and to show that it is able to compete with the multiple groups studying "stress" worldwide.

Microbiological and neurology projects dealing with stress are not sufficiently based on preliminary studies and include many unrelated projects.

Recommendations:

The team should focus on a more limited number of projects, conceivably restricted to those with preliminary evidence.

In projects associating microbiologists, immunomonitoring should include evaluation of innate immunity and the link between innate and adaptive immunity.

Mid-term perspectives should include projects of new links (or even association) with the other teams of the local "health and biology" Pole.



3 • Detailed assessments

Assessment of scientific quality and production:

The scientific production of the three teams forming the new EA is heterogeneous with some good papers. All members of the team are producers.

Assessment of the unit's integration into its environment:

The unit is supported by the Lorraine University which recently provided new lab space in close proximity with the other labs of the Health and biology pole. It has contracts with the CNES and has already set up an industrial partnership, altogether finding support for its project (but additional funding will have to be obtained for new projects requiring transcriptomics, RNA sequencing or genomics).

Scientific relationships with the other labs in the close environment would deserve to be expanded. They already allow sharing some equipment such as flow-cytometers.

Beyond Nancy, the group is well integrated in the French community of labs collaborating with CNES about health and biology. It thus contributes to defending French participation of biological research activities within the European Space agency. Mr FRIPPIAT succeeded in finding funding from CNES, ANR and from an industrial partner (for a CIFRE contract). He now has a reputation for his work on B cells among those people studying immunity in microgravity conditions but the attractiveness of the team is still limited.

Assessment of the research unit's reputation and drawing power:

International reputation as manifested by invitations to meetings is still limited.

Mr FRIPPIAT received the "Grand Prix de la Recherche AAUL" in 2011

The team is involved in national and international programs under the auspices of CNES.

Assessment of the unit's governance and life:

Governance of the future unit seems to be clearly defined and accepted by all members. The group is well managed and all group members acknowledge the scientific leadership of Mr FRIPPIAT. Internal scientific meeting associating the 3 groups will have to be held on a weekly basis. Most unit members are teaching and are strongly involved into educational activities.

Assessment of the strategy and 5-year project:

The long-term scientific project is still vaguely defined and will need to be clarified in order to make choices and allocate means to the most innovative and sound projects.

Assessment of the unit's involvement in training:

All lab members are strongly involved into educational activities. The unit includes a number of doctoral students. Care should be taken to their future development and careers.



4 • Project-by-project analysis

Project 1:

Effects of gravitational and chronic stresses on systemic and intestinal immunity

Name of project leader:

Mr Jean-Pol FRIPPIAT

Workforce

Workforce in Full-time Equivalents	06/30/2011	01/01/2013
FTE for professors or assistant professors	3 x 0.5	3 x 0.5
FTE for EPST and EPIC researchers	0	0
FTE for engineers, technicians and administrative staff on a permanent position	0.1	2.4 shared between the 3 projects
FTE for engineers, technicians and administrative staff on a non-permanent position	0.1	
FTE for postdocs having spent at least 12 months in the unity	1	
FTE for doctoral students,	2	
TOTAL	4.7	2.3

• Detailed assessments

Assessment of scientific quality and production:

This project is original and well supported by CNES through an ANR project and renewed contracts. Although preliminary, the observations made by the group about potential alterations of the *pleurodele* humoral immune response after a space flight have allowed publications in *Faseb Journal* and in more specialized journals. These data had some impact in the community of scientists studying immunity under microgravity conditions. The team is the only one that has immunized animals onboard a space station. So far only a few results are available on the influence of microgravity on the humoral immune system. Thus the investigations of this team are important.

The Principal investigator has a project selected by ESA for a space flight entitled "The antibody V(D)J recombination machinery in normal and altered gravity" which has been evaluated by an international peer review team as "excellent". The research team is international (F, D and USA).

The members of the visiting committee feel that the main risk is that too many projects are being pursued.

Conclusion:

Globally, this team seems to occupy a well-defined niche which gives it some visibility. It has to go more in depth into a more limited number of well-defined questions, avoiding any confusion between the different types of "stress" that could impact the measured parameters. The intersection with microbiologists can be fruitful provided that innate and not only adaptive immunity is taken into account in the phenotypic analysis of animals studied.



Project 2: Effects of gravitational and chronic stresses on microbiota and pathogens

Name of project leader: Mr Alain LOZNIIEWSKI

Workforce

Workforce in Full-time Equivalents	06/30/2011	01/01/2013
FTE for professors or assistant professors	5 x 0.3*	6 x 0.3*
FTE for EPST and EPIC researchers	0	0
FTE for engineers, technicians and administrative staff on a permanent position	0.9	2.4 shared between the 3 projects
FTE for engineers, technicians and administrative staff on a non-permanent position	0	
FTE for postdocs having spent at least 12 months in the unity	0	
FTE for doctoral students	2	
TOTAL	4.4	2.6

* Because they are hospital practitioners

• Detailed assessments

Comments on the Microbiology project:

The Microbiology project is divided in three very different sub-projects (mycology, virology and bacteriology) and includes one clinical trial.

- **Mycology:**

Two model fungi organisms, *Fusarium solani* and *Exophila dermatidis*, will be studied. These projects already led to several good publications demonstrating that the group has good expertise in this domain. However, the perspectives should be more precise in terms of the transcriptomics approach. The "human-made conditions" to be compared to gravitational stresses should also be defined.

- **Virology:**

The researchers have a good expertise in medical virology and on some aspects of fundamental virology on HCV. The study of relationship between the variability of the S protein on HBV clearance is an interesting project but the putative link with the chronic mild stress is questionable. Moreover, the committee raises the question of financing such expensive projects without preliminary results.

- **Bacteriology:**

The group has a good expertise on the antibiotics resistance of commensal bacteria. The study of the impact of gravitational stress and chronic mild stress on the intestinal microbiota and genetic exchanges is very ambitious. It is also speculative, as no evidence of dysbiosis due to the types of stress has been clearly shown. Numerous recent data published on stress and microbiota should be better taken into account in the design of this project. Some preliminary experiments should be performed using pyrosequencing in order to validate the dysbiosis hypothesis. After such potential validation, some expression approaches should be followed in order to go beyond the simple observation.



The impact of dysbiosis upon the gut-brain axis should also be considered. The strategy chosen to measure genetic exchanges is attractive but will reflect only a minor part of the potential exchanges.

The clinical study on the impact of chronic stress on the colonization by multi-drug resistant bacteria should stay in the frame of clinical research.

Conclusion:

The proposed projects should be centered in the near future around a limited number of model-organisms and focused on stresses more specific of the organisms of interest. More mechanistic approaches should also be developed.

Adaptive and innate immunity should also be better integrated in the projects related to microbiota and the gut-brain axis.



Project 3:

Evaluation of gravitational and chronic stresses and potential implication of the cerebellum in the modulation of immunity.

Name of project leader: Ms Catherine STRAZIELLE

Workforce

Workforce in Full-time Equivalent	06/30/2011	01/01/2013
FTE for professors or assistant professors	2 x 0.3*	2 x 0.3*
FTE for EPST and EPIC researchers	0	0
FTE for engineers, technicians and administrative staff on a permanent position	0	2.4 shared between the 3 projects
FTE for engineers, technicians and administrative staff on a non-permanent position	0	
FTE for postdocs having spent at least 12 months in the unity	0	
FTE for doctoral students	4	
TOTAL	4.6	1.4

* Because they are hospital practitioners

• Detailed assessments

The project deals about the evaluation of the gravitational and chronic stresses and the potential of the implication of the cerebellum in modulation of immunity. The part of the project dealing about gravitational stress is interesting, timely and with an important impact for the scientific community. The research of some biological markers in plasma like ACTH, cortisone, and biogenic amines in nervous system is logic and the link with the neuro-immune response is clear. It can be noticed that evaluation on the Nitric oxide synthetases (NOs) will be pertinent and the investigation of activated microglia versus macrophage-infiltration would offer a better opportunity to correlate brain-immune cross-talk in such stress conditions.

A few suggestions can be offered:

- 1- To study the interplay between innate and adaptive responses by focusing on the cooperation between antigen-presenting cells and T lymphocytes.
- 2- To take advantage of the fact that the unit is involved in a CNES group of laboratories studying the effect of microgravity in mice, to improve the quantification of the mutant behavior that will be used in the project.
- 3- To investigate cerebellum structures, which are specifically involved in the processing of the vestibular information: the floccular and nodular lobe (lesion, stimulation, receptor dosages etc..).

Conclusion:

Based on its past activity, the team should be able to deal with the evaluation of chronic stresses and their impact on neurophysiology. Studying the potential link between cerebellum function and immunity appears to be "high-risk" and would need stronger preliminary evidence.



5 • Grading

Once the visits for the 2011-2012 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 four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

Overall assessment of the unit "Stress Immunity Pathogens (SIMPA)":

Unité dont la production, le rayonnement, l'organisation, l'animation et le projet sont bons, mais pourraient être améliorés.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
B	B	B	B



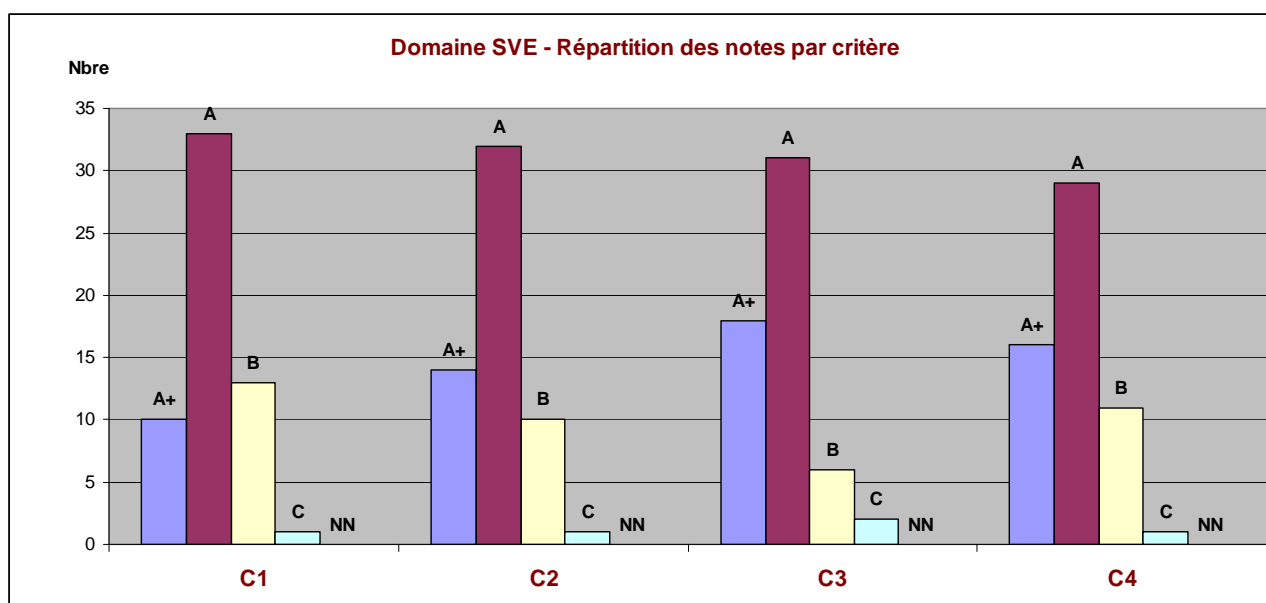
6 • Statistics per field

Notes

Critères	C1	C2	C3	C4
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-





7 • Supervising bodies' general comments

L'Administrateur Provisoire
Jean-Pierre Finance

à

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Objet : rapport d'évaluation de l' EA SIMPA
Référence du document : C2013-EV-0542493S-S2PUR130004766-RT

Monsieur le Directeur,

Vous m'avez transmis le 4 mars dernier le rapport d'évaluation de l'Equipe d'Accueil « Stress, Immunité, Pathogènes » et je vous en remercie.

Je vous prie de trouver ci-dessous les éléments de réponse de Monsieur J.P. Fripiat, directeur de l'unité.

En tant que tutelle du laboratoire nous prenons bonne note des recommandations du Comité d'évaluation. L'université de Lorraine et le CNES ont de multiples collaborations et partenariats. Le partenariat avec une partie des collègues de l'unité SIMPA est historique et bien intégré à la politique scientifique de l'unité.

Je vous prie d'agréer, cher collègue, l'expression de mes sentiments distingués.

L'Administrateur Provisoire



Jean-Pierre Finance

OBSERVATIONS DU DIRECTEUR DE L'EA SIMPA:

Chers membres du comité de visite AERES,

Les membres de la future EA SIMPA vous remercient de l'intérêt que vous avez porté à nos travaux.

Nous sommes conscients qu'à l'heure actuelle, et comme l'indique votre rapport, notre projet de recherche peut sembler 'dispersé' du fait de la jeunesse des rapprochements entrepris. En effet, JE2537 a été créée en janvier 2009, les bactériologistes s'en sont rapprochés en 2010 suivis tout récemment par les neurobiologistes, les mycologues et les virologues (dont certains ne sont d'ailleurs pas encore sur site). Ces mouvements de personnes très récents, mais très prometteurs pour nous et pour notre Université, couplés à nos importantes charges pédagogiques et hospitalières, ne nous ont pas permis pour l'heure d'afficher une organisation scientifique aussi homogène que dans une unité qui existerait depuis plusieurs plans quadriennaux.

La jeunesse de ces rapprochements explique également le manque de résultats préliminaires sur certains points du projet. Ce problème disparaîtra naturellement puisque les trois équipes ont déjà débuté ensemble les projets présentés.

Nos réunions de laboratoire qui ont pour l'instant lieu tous les 15 jours mais qui deviendront, comme vous le suggérez, hebdomadaires, ont justement pour but 1) de stabiliser cet ensemble en travaillant sur le recentrage/recadrage de certaines parties du projet et 2) de renforcer les interactions internes, ce qui sera facile vu l'ambiance constructive qui règne au laboratoire et que vous avez pu constater. Nous sommes donc tout à fait conscients que ces points sont indispensables i) au développement de notre laboratoire mais aussi pour ii) renforcer notre visibilité/réputation internationale et iii) pouvoir prétendre à des financements plus conséquents.

La notion de stress qui a pu apparaître encore insuffisamment définie sera revue et nous porterons plus d'attention à l'immunité innée. Soyez certains que chaque 'project leader' a bien pris note des conseils prodigués dans votre rapport et saura en tenir compte.

L'ensemble du laboratoire, vous prie de croire, chers membres du comité, en l'assurance de sa considération respectueuse.



J.-P. Fripiat et collègues