G5 Virulence parasitaire

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Parasite Virulence

Of the Pasteur Institute

March 2009

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et de l'enseignement supérieur

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Evaluation report

Research unit :

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Of the Pasteur Institute

Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

mars 2009

Evaluation report

The research unit :

Name of the research unit : Parasite Virulence

Requested label : UMR_S INSERM

N° in case of renewal :

Head of the research unit : M. Gerald SPAETH

University or school :

none

Other institutions and research organization:

Institut Pasteur

INSERM

CNRS URA2581

Date of the visit :

March 12, 2009

Members of the visiting committee

Chairman of the commitee :

Mr Christian DOERIG, University of Glasgow, UK and EPFL, Lausanne, Switzerland

Other committee members :

Mr Theo BALTZ, University Bordeaux 2

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

Mr Christophe ROGIER, INSERM CSS representative

Observers

AERES scientific representative:

Mr Nicolas GLAICHENHAUS

University or school representative:

Mr Alain ISRAEL, Institut Pasteur

Research organization representative :

Ms. Christine TUFFEREAU, INSERM

Evaluation report

1 • Short presentation of the research unit

- Total number of lab members : 10 including
  - 1 full time researcher from the Pasteur Institute
  - 1 postdoctoral fellow
  - 2 PhD students, both with a fellowship
  - 2 engineers, 4 technicians and administrative assistants, including 2 on short term contract
- Number of HDR : 1
- Number of publishing lab members : 2 out of 2

Of note, one INSERM junior researcher from the research unit will leave next year.

2 • Preparation and execution of the visit

Time : from 13:00 to 13 :15
Time length : 15 minutes
Door-closed meeting : Committee members and AERES representative

Time : from 13 :15 to 13 :45
Time length: 30 minutes including questions
Presentation by the head of the lab : past activity and projects

Time : from 13 :45 to 15:30
Time length: 105 minutes including questions
Presentation by lab members: past activity and projects

Time : from 15 :30 to 15 :45
Coffee Break

Time : from 15 :45 to 16 :15
Time length : 30 minutes
Three meetings at the same time

- Meeting with PhD students and postdoctoral fellows
- Meeting with engineers, technicians and administrative assistants
- Meeting with researchers with permanent position

Time : from 16 :15 to 16 :30

Time length : 15 minutes

Door-closed meeting : Committee members, AERES representative, Institut Pasteur and INSERM representatives

Time : from 16 :30 to 17 :30

Time length : 60 minutes

Door-closed meeting : Committee members, AERES representative

Quality of the documents provided, the oral presentations and the organisation of the site visits : The dossier is clearly written and well structured, despite a few "approximations", and the visit was well organised. All oral presentations by lab members, and the responses to the questions of the visiting committee, were of high quality.

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

Coherence with defined projects and missions : The activities of the lab are for the most part in line with the originally stated objectives, which were centred on several aspects of the biology of three Leishmania MAP kinases (localisation, regulation, function in the life cycle, phosphoproteomics, identification of substrates) and on the quantitative phosphoproteomics of parasites at different stages of their life cycle. However, some recent dispersion is apparent, with significant resources devoted to the detailed characterisation of substrates (e.g. HSP proteins). See below for more details.

Overall scientific quality and proper functioning of the laboratory : Overall, the objectives are scientifically perfectly sound, and significant progress has been achieved. This is the first project on phosphoproteomics of trypanosomatids, and is likely to provide novel advances in the field of signalling in parasites. From the interviews the evaluation team had with the personnel, the lab appears to function fully satisfactorily. The PI has established an efficient system to monitor progress of team members (monthly person-person discussion of a written report).

National and European renown in scientific circles : The coordination of an FP7 project by the unit director gives high visibility to the team in the field of "trypanosomatidology". However, the team is not yet a major leader in the Leishmania signalling community, mostly because of the scarcity of its publication record on the subject (2 papers; this is understandable in view of the relatively recent coming of the team into this field, but must be corrected). A quick bibliometric analysis on the ISI server identifies another foreign laboratory group as the current leader in Leishmania MAPK research.

Final assessment of the previous research program and the overall heading of the laboratory : Objectives for the next four years are sound and work has already provided interesting data. The approaches are not particularly original, as the project consists essentially of the application of well established approaches (transgene expression, phosphoproteomics…) to this particular system. However, the novelty resides in the fact that (to the knowledge of the evaluation team) this is the first phosphoproteomics investigation in trypanosomatids. The encouraging results obtained so far are likely to be expanded, and the project has a very good potential.

Degree of laboratory integration into its setting : The unit director runs the Pasteur Seminar series, and coordinates a Pasteur internal collaborative project (PTR), attesting good integration within the Pasteur Institute. Excellent idea to start thinking of merging trypanosomatid-related FP7 projects into a NoE.

Reputation among and involvement with socio-economic partners : Difficult to assess in view of the recent coming of the team in the field. Two SMEs are members of the FP7 consortium coordinated by the head of the unit.

Involvement in training by and for research : In addition to Masters (2) and PhD (2) students, the lab hosted several short-term trainees, notably from Iran and Hong-Kong.

Scientific production : publications, conferences and seminars, patents, licences, contracts, etc.; Scant publication record since establishment of the lab in 2005 (essentially 2 papers in relatively specialised journals). Apparently things will improve in the short term, with manuscripts submitted or in preparation.

Development and maintenance of partnerships with the socio-economic sphere : Two SMEs in the FP7 project coordinated by the applicant.

Functional knowledge production intended for end users of research findings, technology transfer, and socio-economic application of research results : The project is essentially in fundamental research; potential application form the collaboration with SMEs in the FP7 project, but it is too early to assess impact at this stage.

Quality, originality, emerging topics, risk-taking :

- Quality: the science is overall satisfactory (see above for details).
- Originality: Leishmania MAPK family under investigation by other groups since the 1990's, but not the 3 enzymes selected by the team. Application of quantitative phosphoproteomics methods to Leishmania is novel.
- Emerging topics: As mentioned above, the team is pioneering phosphoproteomic analysis of trypanosomatids.
- Risk taking: relatively low risk project - the thrust of the project is to apply well-established techniques in transgenesis and phosphoproteomics to Leishmania. Clearly, a phosphoproteomics approach is bound to yield results.

Assessment of scientific outlook : Care should be taken not to fall into too much dispersion, esp. with biochemical and genetic downstream analysis of amastigote-specific phosphoproteins (Objective 3 of Axis 2 (P. 57), which may cause to divert resources from the main project.

Necessary development and change : improve publication record.

Degree of fit between goals and means. Adequate, in large part thanks to easy local access to the means provided by local technological platforms (proteomics, structural biology..)

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

- Management :

Excellent capacity to raise funds for his research and team and to develop new partnerships. Regular meetings within the unit and with other partners of the Pasteur Institut. The PI stimulates training of his personnal and his promotion and is commited in the respect of health and safety regulations.

- Human ressources :

All personnel appears happy to be part of the team, and of the relations with the PI.

- Communication :

Excellent within the team and the scientific community.

6 • Recommendations and advice

— Strong points :

Good network of collaborators, esp. in the FP7 project.

Accumulating expertise in parasite phosphoproteomics.

Enthusiasm of the PI and team.

Significant funding from various sources.

— What needs to be improved :

Major weak point: the output of the team (as quantified by publications) does not reflect the available resources.

— Recommendations :

Place high priority on improving the publication output.

Avoid dispersion: focus on MAPK biology.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Le 14 avril 2009

Alain Israël
Directeur de l'évaluation scientifique
Institut Pasteur

Mr le président de l'AERES

INSTITUT PASTEUR

Commentaires de Gerald Späth, Ph.D.
Chef de Laboratoire
Head, G5 Virulence Parasitaire
Director, FP7 LEISHDRUG consortium

Paris, April 10th 2009

Object: Response to AERES evaluation EVAL-0755366A-S2100024730-UR-RPRELIM (2).doc

Dear committee members, dear representatives,

In line with the AERES statute, I am responding with this letter to the evaluation report.

First, I want to thank you for your time and efforts spent to evaluate our team, and I highly appreciate your comments and constructive criticism.

I was very happy to read that the team, the management of the laboratory, the

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presentations, and the overall organization of the evaluation day were considered to be of high quality.

Likewise, I appreciated that the committee recognized that significant progress has been made during the first three years since the creation of our research team, and that our phosphoproteomic approach towards trypanosomatid signalling is novel in the field of molecular parasitology and has a good potential to yield important results, some of which have been presented during the evaluation day (e.g. identification of a novel amastigote-specific heat shock complex, identification of the very first *Leishmania* MAPK substrate through quantitative 2D-DIGE).

The major criticism consisted in the low scientific output as judged by the publication record. As noted in the evaluation report, this results from our recent coming into the field of trypanosomatid signalling, and the efforts required to establish cutting edge quantitative phosphoproteomics in our laboratory. The limited scientific output, with two published papers on *Leishmania* MAPKs and phosphoproteomics, is clearly a problem of timing, as we have currently two more manuscripts submitted in high impact journals (Morales et al., resubmission for Science Magazine is in preparation; Morales et al., submitted to PloS Pathogens). In addition, one review and three collaboration papers have been already published, are in press, or under revision in 2009 (Rotureau et al and Späth, Cell. Microbiol. 2009 Feb 4 [Epub ahead of print]; Späth et al, Plos Pathogens 2009, in press; Peduto et al, J. Immunol, 2009, in press; Filipe Dos Santos, et al, Cell Host Microbes, in revision). More important, three team members are currently working on four additional manuscripts. Abstracts for these projects have been presented on recent international meetings, or are accepted for presentation this spring. Thus, I am very confident that this major criticism is rectified shortly.

While the criticism of low scientific output in terms of publications is justified, I am surprised that oral and poster presentations (the first step towards publication) are not taken into account in the evaluation of our scientific output. I would wish that this very important parameter of scientific communication, interaction, and output would be acknowledged in the report, especially as the evaluation report itself eludes to the fact

that the limited number of publications results from our recent coming into the field of trypanosomatid signalling and thus is a timing problem.

I do not agree with the statement that *"The approaches are not particularly original, as the project consists essentially of the application of well established approaches"*, which is in direct contradiction to the statement in the same report that *"This is the first project on phosphoproteomics of trypanosomatids, and is likely to provide novel advances in the field of signalling in parasites"*, and that *"the novelty resides in the fact that (to the knowledge of the evaluation team) this is the first phosphoproteomics investigation in trypanosomatids"*. The adaptation of the phosphoprotemic approach to *Leishmania*, the implementation of 2D-DIGE, and the application of these techniques on parasite MAPK biology was very challenging and has never been done before. In addition, while phosphoproteomic approaches may be well established in other Institutions, our analysis is the first phosphoproteomic study of this kind done at the Institut Pasteur and initiated a new focus of the IP Proteomics platform on phosphorylation, which exclusively relies on our input. In addition, the combination of 2D and Blue native electrophoresis with in-gel kinase activity assays to reveal kinase-substrate relationships at a proteomic level is novel and to our knowledge has not been applied previously. I would wish that these new technical developments, their combination in the same laboratory, and their application on the study of *in situ* kinase activities may be appropriately acknowledged in the report.

Finally, concerns were raised that our recent interest in *Leishmania* HSP phosphorylation and function may lead to dispersion of our efforts. I will make sure to guard against any dispersion and decided to pursue any work directly linked to *Leishmania* HSPs in collaboration with our partner Joachim Clos from the Berhard Nocht Institute, Hamburg, and other partners. However, in other organisms there is an intricate relationship between the foldosome complex we identified in *Leishmania* amastigotes and the activity state of various protein kinases, including MAPKs. We will therefore focus part of our research on this interaction, potential regulatory functions of HSPs on MAPK activity, and the identification of putative heat shock kinases that phosphorylate these HSPs in a stage-specific manner (some of which are likely to be MAPKs).

Thank you very much again for your efforts, your support, and your consideration,

Sincerely,

Gerald F. Späth, Ph.D.