Vaccinologie parasitaire

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Laboratory of Parasite Vaccinology

From the

Pasteur Institute

May 2010

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From the

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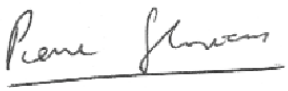
Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur



Pierre Glorieux

May 2010

Research Unit

Name of the research unit : Parasite Vaccinology

Requested label : Pasteur Unit

N° in the case of renewal

Name of the director : Ms. Shirley LONGACRE

Members of the review committee

Committee chairman

M. Michel NUSSENZWEIG, The Rockefeller University, NY, USA

Other committee members

Ms. Deborah SMITH, University of York, UK

M. David ROOS, University of Philadelphia, USA

M. Graham BROWN, University of Melbourne, Parkville, Australia

Ms. Alistair CRAIG, Liverpool School of Tropical Medicine, UK

M. Mike FERGUSON, University of Dundee, UK

M. Neil GOW, University of Aberdeen, UK

M. José RIBEIRO, NIH, Bethesda, USA

M. Mats. WAHLGREN, Karolinska Institutet, Stockholm, Sweden

M. David SIBLEY, Washington University, St. Louis, USA

M. Jérome ESTAQUIER, IMRB, Paris, France

Observers

AERES scientific advisor

M. Nicolas GLAICHENHAUS

University, School and Research Organization representatives

M. Alain ISRAEL, Institut Pasteur

Report

1 • Introduction

- Date and execution of the visit :

This unit was evaluated as part of the Department of Parasitology and Mycology on October 7, 2009.

- Management team :

The head of this team is Ms. Shirley Longacre.

- Staff members (on the basis of the application file submitted to the AERES) :

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

2 • Overall appreciation on the research unit

- Summary

– Strenghts and opportunities

Championship of MSP1 as a malaria vaccine antigen over the course of twenty years, through extensive monkey trials ;

Exploring alternative adjuvant strategies, including the potential of GPI.

– Weaknesses and threats

Other studies around the world have led to the recognition that MSP1 may not be viable as a vaccine candidate ;

The future of these projects within the Institut Pasteur is not clear.

– Recommendations to the head of the research unit

With the impending retirement of team leader, Individuals associated with this laboratory should transition to other groups, as appropriate.

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

INSTITUT PASTEUR

Laboratoire de Vaccinologie
Parasitaire

Paris 30 April 2010

RE: Rebuttal to AERES Evaluation Committee commentaries

To whom it may concern,

This ludicrous document was indeed a distressing travesty of fair, informed, serious scientific evaluation that certainly does no credit to anyone responsible for it. Indeed 30 pages and years of scientific work were granted little more than a dismissive, hatchet job of exactly 59 words, none of which give any indication that anyone ever actually read the report. Nevertheless, below I make a last, probably pointless, effort to joust at these academic windmills before turning to the more fruitful endeavor of creating a biotech enterprise, where something useful may actually get done, based on a serious consideration of real results and applications, quite unlike this shameful excuse for so-called scientific evaluation.

Specific rebuttals

1. "Championship of MSP1 as a malaria vaccine antigen over the course of twenty years, through extensive monkey trials;"

MSP1 is a very big molecule (around 200 kDa) and most of it is polymorphic. Thus the reference to "MSP1" as a vaccine antigen is rather vague to say the least. Do the evaluators mean the whole molecule or only part of it and if so which part(s)? Many people have used different parts of MSP1 as vaccine candidates over the years and it would be reasonable to suppose that that these different parts may not have equal value as vaccine candidates.

Secondly, at least 3 different expression systems (bacteria, yeast, baculovirus-insect cells) have been used to produce the different parts of MSP1. One should also consider that not all expression systems arbitrarily produce equally good recombinant analogs of MSP1 and that this might depend on the protein or part of the protein being expressed.

The molecule we championed was specifically baculovirus expressed MSP1p19 having 2 EGF domains which are notoriously difficult to reproduce in bacteria and yeast. Indeed the superiority of the baculovirus expressed molecule is demonstrated quite clearly for MSP1p19 (Arnot et al. 2008, Clinical and Vaccine Immunology 15, 1345; Reed 2009, Vaccine 27, 1651). I continue to defend the position that the body of preclinical data supporting the vaccine candidacy of baculovirus MSP1p19 is by far the best available anywhere, anytime. I challenge any of the so-called malaria experts who evaluated my dossier to dispute this with data, arguments or anything they wish before an unbiased audience. Indeed during 15 years the Pasteur Institute has invested over €1.000.000 in patent costs and industrial process development for this antigen. One would imagine that there must have been pretty good reasons for this level of support.

2. "Other studies around the world have led to the recognition that MSP1 may not be viable as a vaccine candidate".

What MSP1? What expression system? What studies? Recognition by whom? None of the "MSP1" candidates tested in clinical trials included baculovirus MSP1p19, so on what basis does one conclude that this is not a viable candidate? MSP1p42 produced in bacteria didn't work in clinical trials, but then it never ever worked in preclinical trials either. The only reason for testing this

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molecule in clinical trials was political (supported by GSK, (uses GSK adjuvant), Gates Foundation, NIH etc. who had the funds) rather than scientific. This was the wrong antigen (MSP1p42 is polymorphic), the wrong expression system (bacteria), and the wrong adjuvant (doesn't work in primates with baculovirus-MSP1p19 where other adjuvants do). MSP1p19 alone or fused to AMA1-domain 3 produced in yeast didn't give good results in the clinic. Not surprising, Arnot et al. cited above shows that yeast MSP1p19 was the worst of six antigens tested and baculovirus MSP1p19 the best in preclinical studies.

3. What about the other baculovirus candidates we developed (baculovirus MSP4, MSP5)? Why no comments on these? Did anyone actually read the report? We showed for the first time that MSP5 is myristylated, a rather important finding, which suggests a probable function. Human antibodies to MSP4 and MSP5 antigens are statistically correlated with clinical protection. Antibodies to MSP4 are highly functional in an in vitro test correlated with clinical protection from malaria in endemic regions (see below). Somebody at the Pasteur Institute must have thought the data merited the effort and expense of filing for a patent. Just because this data is not yet published does that mean it is worthless or inexistent? Is it a strength or a weakness? Why? Doesn't it deserve at least some comment?

4. The antibody dependent respiratory burst (ADRB) assay? Why no comment on this? Is it a strength or a weakness or just nothing? Did anyone read about it in the report or perhaps it just doesn't count because not yet published when the report was written? It was in fact recently published in PLoS ONE (Joos et al. 5(3) e9871) with the title: "Clinical protection from falcipaum malaria correlates with neutrophil respiratory bursts induced by merozoites opsonized with human serum antibodies." The abstract conclusion (accepted by referees) states: "This work presents the first clearly demonstrated functional antibody immune correlate of clinical protection from Plasmodium falciparum malaria…." The malaria field has been pleading for just such a test for years. The article has already been viewed over 460 times and downloaded 140 times only 5 weeks after publication. Do these evaluators really consider this so irrelevant as to merit a blank? And what about showing that the baculovirus MSP1p19 and MSP4p20 candidates work particularly well in this test?

5. And what about the patents to which a great deal of effort has been devoted? Is this a strength or a weakness or again just nothing? Or are AERES committees just not interested in applied research? This is indeed somewhat surprising given the numerous government initiatives in favor of innovative biotech start-ups.

6. "Exploring alternative adjuvant strategies, including the potential of GPI." "The future of these projects within the Institut Pasteur is not clear."

This is quite surprising. Indeed it seems that the evaluators must have neglected to notice (or read) that the GPI project was selected and submitted by the Pasteur Direction des Applications de la Recherche et les Relations Industrielles (DARRI) to the highly selective ANR Bio-Emergence program, which chooses projects having already demonstrated proof of principle, with strong potential for industrial applications. My report also noted that the GPI project was subsequently retained for funding by the ANR (one of 21 in France) with the following evaluation:
"Projet innovant répondant potentiellement à une demande importante dans le domaine de la vaccination contre des agents infectieux (médecine humaine et vétérinaire). En effet, à ce jour, les adjuvants disponibles dans le cadre de la vaccination humaine sont rares." In addition the project was labeled by the Pôle de Compétitivité MEDICEN.The financial sheets with the engagement of the Pasteur Institute were signed in September 2009.

Indeed is not vaccine research supposed to be one of the signature interests of the Pasteur Institute? Does not public health to which the Institute so loudly proclaims its engagement require for research to be applied? Do not AERES and Pasteur both risk sinking into irrelevancy with evaluations such as this one? In any case, clearly the vindication of these results must lie elsewhere. So be it.

Shirley LONGACRE

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DIRECTEUR DE L'EVALUATION SCIENTIFIQUE
INSTITUT PASTEUR