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

Section des Unités de recherche

AERES report on the research unit

Génétique et Immunologie des Maladies Parasitaires

From the

Université Aix-Marseille 2

INSERM

March 2011

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

March 2011

Research Unit

Name of the research unit: Genetique et Immunologie des Maladies Parasitaires

Requested label : UMR_S

N° in the case of renewall: U906

Name of the director : M. Alain DESSEIN

Members of the review committee

Committee chairman

M. Gerald SPAETH, University Paris Descartes, Paris, France

Other committee members

M. Rick MAIZELS, University Edinburgh, UK

M. Raymond PIERCE, Université Lille 2, Lille, France

Ms Paola ZACCONE, University of Cambridge, UK

Ms Elena LEVASHINA, University Strasbourg, INSERM CSS representative

Ms. Dominique MAZIER, Unversity Pierre et Marie Curie, Paris, CNU Representative

Observers

AERES scientific advisor

M. David DOMBROWICZ

University, School and Research Organization representatives

M. Pierre CHIAPPETTA, Université Aix-Marseille 2

M. Dominique NOBILE, INSERM

Report

1 • Introduction

- **Date and execution of the visit**

The visit was carried out on March 18th 2011, co-jointly with a visit (by the same committee) to Inserm UMR-MD3. An oral presentation of the project by the current director, senior scientists, presenting the three main research themes, was followed by the presentation of posters by PhD students. After a discussion with the representatives of the University and Inserm, followed by an audition of the personnel (researchers, technicians and students), the committee deliberated.

- **History and geographical localization of the research unit, and brief presentation of its field and scientific activities**

The current unit was created from the former unit (Inserm U 399) at the same site with the same director. The main themes treated have remained the same. The research unit is localized at the Université de la Méditerranée, Faculty of Medicine, Marseille, and is part of the IFR 88 Structural Biology and Microbiology Institute, which synergizes regional efforts on infectious diseases research. The major focus of the unit is the genetic identification of human resistance and susceptibility factors for various severe parasitic diseases, including schistosomiasis, leishmaniasis, and cerebral malaria, and the validation of these factors using immunological approaches.

- **Management team**

The unit is directed by M. Alain DESSEIN and is structured in four thematically distinct teams that are coordinated by senior staff members, including the PI, two research associates (CR1) and one engineer.

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
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	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	3	3

2 • Overall appreciation on the research unit

- **Strenghts and opportunities**

- Creation and maintenance of exceptional and extensive cohorts for field studies in South America, Africa, and Asia;

- Highly interdisciplinary approach based on genetic screens and immunological validation, integrating new approaches including genome wide association studies, and applying common platforms across three major tropical diseases;

- Unique insight into human factors associated with susceptibility/resistance to parasitic diseases;

- Ground-breaking translational approach on diagnosis and prognosis of fibrosis during human viral infection and auto-immune disease;

- Generation of important intellectual property.

- **Weaknesses and threats**

- Very specialized technical expertise and largely descriptive nature of the research projects, with relatively little experimental validation of individual gene effects, which may limit the impact of publications;

- Insufficient personnel for the multitude of projects established, which may impact negatively on project progress and validation through publication;

- Visibility of the unit does not correspond to the impact of the research program. This is documented by the absence of international staff members, international funding and partnership in international networks. This could threaten the international standing of the unit;

- No junior leader is emerging that could take over the unit after retirement of the unit head in 6 years.

- **Recommendations**

- Unit should open to new approaches to further investigate the mechanisms of the most interesting findings obtained in their field studies, for example through recruitment of postdocs and staff members with novel expertise (imaging, cell biology), and by establishing stronger collaborations with laboratories on individual genes of common interest.

- The unit should recruit a strong young leader that would be competitive for independent funding, for example through the ATIP/AVENIR program.

- The unit should play a more leading role on the international scene through active participation in international meetings and the establishment of funded collaborative networks (FP7, Gates etc).

- More international collaborations should be opened up, particularly for the investigation of the roles of the molecular players identified in the genetic studies.

- The visibility of team leaders other than the director should be improved by their participation in more international meetings.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	2
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	2
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	4/4
A4: Number of HDR granted during the past 4 years	1
A5: Number of PhD granted during the past 4 years	7

3 • Specific comments

- **Appreciation on the results**

The unit uses genetic approaches to identify human resistance and susceptibility factors for various severe parasitic diseases, including schistosomiasis, leishmaniasis, and cerebral malaria, and carries out validation of these factors using immunological approaches. The research program is highly relevant and original as it interfaces human genomics and immunology and the unit has established itself as an international leader in this field. The quality of research program is very good as documented by two publications in high impact journals (see below). The results are of high impact as they directly reveal novel susceptibility and resistance genes for the diseases studied in the lab by genetic analysis of various cohorts in South America, Africa, and Asia. Further, these findings are shown to impact on diseases also affecting Europeans such as HCV and systemic sclerosis. Due to the quite unique experimental approach, the projects of the unit generate important new insight into the genetic basis of human suceptibility to parasitic diseases. The potential of these results to shape cutting edge projects is somewhat restricted by the limited impact of mechanistic down-stream analyses. This aspect could be improved by establishing collaborations or by recruting internatioanl scientis with diverse experties.

The publication record is satisfactory and the quality of recent publications is good, with a total of 25 publications, including 19 signed as first or last author by team members, with two publications in high impact journals. However, the publication record shows substantial variations from year to year, with for example only one last author publication from the team in 2010, which to some extent is accounted for by delays imposed by patent procedures. Recent results should be seen in print as soon as possible.

The number of Ph.D. theses generated by the unit is very good with seven theses accomplished since 2006. The quality is fair with 6 out of seven students having published at least one first author paper in medium impact journals.

The stability of current partnerships is very good as judged by common publications. The partnerships are primarily with scientists in endemic countries and involve generation and maintenance of the cohorts, and extensive exchange of personnel including PhD students and other trainees. The quality of partnerships could be further strengthened through international collaborations with leaders in genetics and genomics research, molecular immunology, and cell biology for further functional analyses of identified genes.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

No scientific awards are indicated. Staff members were invited to 11 international meetings/symposia, with 10 invitations for the unit director.

The unit currently hosts two French PhD student, one PhD student from Sudan and two short-term visiting students from Brazil. No high-level scientists or postdocs from abroad were recruited during the past 4 years.

The laboratory successfully competed for national funding with two ANR grants awarded. No major international funding was obtained. The laboratory is not part of any funded international network. International collaborations are largely restricted to cohorts and related structures in endemic areas. One international collaboration involves a laboratory at Rockefeller University although this interaction is not yet documented by publication.

Translation of research results into application is on of the strengths of the reseacrh unit, with patents issued and pending on the diagnosis and prognosis of HCV and scleroderma pathology. The translational character of the research program is further documented through industry-sponsored projects on HCV-dependent fibrosis and anti-schistosomal vaccination.

- **Appreciation on the management and life of the research unit**

The organization of the unit is satisfactory but could be strengthened by recruitment of at least one more staff scientist.

The unit adheres to standard lab practice, including the use of official lab books and the generation of data back ups.

The scientific animation is good and relies on participation to local scientific seminars sponsored by the IFR Microbiology, regular journal clubs, and scientific as well as administrative lab meetings. Students, postdocs and staff members are encouraged to participate at national and international meetings. Unit members are involved in local and regional teaching courses on host-parasite interaction and human genetics, and participate at courses on national levels as well as in disease endemic areas. The unit could play a more important role in scientific animation at the regional level through organization of a seminar series dedicated to parasitology research with national and international speakers. This could be linked to a teaching course on the same subject.

- **Appreciation on the scientific strategy and the project**

The unit proposes a very ambitious transversal research program over the next four years that is based on recent results and uses established genetic and immunological approaches. However, the number of projects is not in good concordance with the manpower available in the unit. Staff members are implicated in a variety of projects, which may limit the feasibility and impact of each single project and delay validation of the research results through publication.

The allocation of ressources is inadequate for the scope and size of the research program. Given the high impact of the series of projects, increasing the focus is not the best option. It is rather recommended to considerably increase the size of the unit through the recruitment of postdocs and staff members with different experties at the senior level (CR1, DR2).

Current projects are cutting edge with respect to the multidisciplinary genetic/immunological approach chosen, the impact of the obtained results to understand human infectious disease, the transversal character of the entire research program investigating similar pathologies across a variety of diseases, and the translational quality of the projects improving vaccination, diagnosis and prognosis of human disease through strong partnerships with industrial partners.

The projects identify new and important molecular players in infection and pathology, and provide interesting new hypotheses that can be tested at the mechanistic level

The originality of the research project could be further strengthened by expanding mechanisitic analyses for some of the main findings through recruitment of senior scientists that bring in novel expertise complementary to the one established in the lab.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
GÉNÉTIQUE ET IMMUNOLOGIE DES MALADIES PARASITAIRES	**A**	**A**	**A**	**A+**	**A**

C1 Qualité scientifique et production
C2 Rayonnement et attractivité, intégration dans l'environnement
C3 Gouvernance et vie du laboratoire
C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Objet : Réponse au rapport d'évaluation - **S2UR120001646 - Génétique et Immunologie des Maladies Parasitaires - 0131843H** - de l'unité Génétique et Immunologie des Maladies Parasitaires

Observations d'Aix-Marseille Université

Aucune observation n'est formulée

En accord avec les deux autres établissements d'Aix-Marseille

Le Président
de l'Université de la Méditerranée

Yvon BERLAND

Le Vice-président du Conseil Scientifique
de l'Université de la Méditerranée

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FACULTE DE MEDECINE
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Laboratoire de Parasitologie-Mycologie

Pr A. Dessein

U 906 Marseille : Answers to the AERES evaluation report.
Pr Alain Dessein.

We thank our colleagues for the time they have spent evaluating our unit. We will do our best to take advantage of their recommendations. We are glad that the committee has recognized the major scientific contributions of our laboratory including the cutting edge science that is being carried out by our group. Below we are insisting on another important aspect of our work that has not been reported by the committee : that is the fact that our findings may directly impact on the diagnosis and the treatment of severe disease in leishmaniasis, schistosomiasis and hepatitis. These successes are important for two reasons: first, because no much has been reported in the diagnosis and treatment of Leishmania and Schistosoma infections for more than twenty years and second, because a major recommendation of our Health Ministry and from Inserm was that our research should be more translational. Finally, we have noticed that some statements in the report may lead to wrong interpretations and we would like to add our comments. The evaluation was very short: (90 min), two committee members were also present at the poster session (less than 30 min). Then there has been no much discussion on the major crucial issues in our field, this was aggravated by the absence of a specialist of Human Genetics in our committee. For these reasons, we think important to highlight a few important issues which, we feel, have not been well understood by the committee.

1. Human Genetics of complex disease is not a descriptive science. The committee did not fully understand the analysis of the genetic basis of complex diseases : Patient selection (which requires an understanding of the local conditions of pathogen transmission and in depth clinical and immunological evaluations of hundreds of subjects), definition of the clinical phenotypes (including hypotheses on the possible molecular mechanisms of disease), identification of resistant and susceptible groups, choice of study design and strategy, complex statistical analysis, molecular evaluation of candidate genes and pathways, are all crucial activities of our genetic studies that are strongly hypothesis driven and are far from a descriptive work. Our recent articles in JEM, J. Clin Investigation and J. Immunol show that very clearly.

2. Much experimental work has been carried out in our unit or in collaboration for the past four years, it seems that the committee has overlooked this. I give below some details on what has been done…

a) We have established a strong collaboration with Dr Gorvel and Dr Meresse at the CIML to perform experimental work (cell biology) on all of the genes identified in our genetic studies on the phagosome project (our major *Leishmania* project). This collaboration is funded by our ANR grant GENLEISHPHAG (120 KE for Gorvel's team). This collaboration has been

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ongoing since 2009 and one publication is in preparation for the journal "Cell". One Ingeneeer from our unit is also spending 70% of his working time performing experimental work under Dr Meresse supervision.
b) Two PhD students and one university Ingeneer have performed experimentals to evaluate how polymorphisms in the IL-2 pathway could affect *Schistosoma* and *Leishmania* infections since we had found that polymorphisms in this pathway aggravate both infections. These investigations also include animal studies in collaboration with Immunologists from Nice (submitted to ANR for funding)
c) More generally of our published genetic studies include experimental work evaluating the functional effects of the studied mutations.
d) Dr. A. Romano, a former PhD student of our laboratory, is undergoing postdoctoral training in D. Sachs Laboratory (NIH), and is working on experimental Leishmaniasis in mice. She will return to our laboratory bringing her expertise and collaborative links.
e) The malaria project did not involve a lot of experimental work. To fill the gap we invited a specialist in experimental malaria (P. Pouvelle to join our team, but this was not approved by the University).
f) With our Australian (Don Mc Manus) and Chinese (Y. Li) colleagues, we have jointly submitted an MRC Australian grant application (800 000 $, pending application) to perform more of this experimental work on hepatic fibrosis and Tregs in schistosomiasis.

Though we agree with the committee that experimental work is essential, it is crucial that we keep working mostly (2/3 of our activity) in endemic populations for the following reasons : Huge number of papers (many in Nature and Science) have been published for the past 30 years on experimental (in animals and in vitro) schistosomiasis and leishmaniasis. In spite of these works, the treatment, the diagnosis and the understanding of the pathogenic mechanisms in severe schistosomiasis, in cutaneous leishmaniasis and in KA (Kala Azar) have made little if no progress. There is not hope for a vaccine against *Schistosoma* or against *Leishmania*, no good diagnosis test for cutaneous leishmaniasis, the treatment of leishmaniasis is the same it was 30 years ago; it is so toxic that it kills the weakest patients. It is so poorly effective that some patients remain invalid for life. Millions of people are still suffering from these diseases as they were 30 years ago. **Then it is urgent to try other approaches especially when (like ours) they have met with some success.** In the past four years, our lab has identified two major pathways in severe hepatic fibrosis in human schistosomiasis and shown that mutations in these pathways **increase altogether the risk of disease by 200- to 300 times. None of these pathways had been revealed by experimental works** (either animal or in vitro work) that also have failed to uncover the strong genetic control exerted on fibrosis. We have extended these findings to other hepatic infections such as HCV and HBV **and we are developing diagnosis and theranostic tests that will be soon used at hospitals for predicting progression to severe disease and providing strong help to the clinicians for the choice of treatment of schistosomiasis but also of fibrosis of other aetiologies. This will impact on the treatment of more than two hundred millions of patients**. There has been many articles in top journals on Th1 (protecting) and Th2 (aggravating) in experimental leishmaniasis but this elegant work provided little understanding to the mechanism of severe cutaneous leishmaniasis (because these patients produce high Th1 response) or of KA (because the patients are immuno-depressed). We were the first to report that resistance to a human infection (leishmaniasis) was associated with high IL-17 and IL-22 responses and not much with IFN-γ; this finding was entirely novel and totally unexpected from experimental work ; **since our publication various reports in other infectious diseases have confirmed the protective role of IL-17 in infections**. Furthermore, Immunogenetics has allowed us to demonstrate that IL-10 was

crucial in suppressing the protective immune response in cutaneous leishmaniasis increasing markedly the risk of lesions. **This finding is presently being applied in the field to improve patient response to the poorly efficient treatment**. Our work on malaria is another example of the usefulness of working in endemic population : while experimental studies in mice indicated Th1 aggravate severe malaria we have shown that Th1 protect Malian Children against severe malaria and that Th2 responses aggravate disease.
Nevertheless, we strongly believe experimental work is crucial to define how mutations exert their effects and we will be careful to increase our collaborations on this aspect. As suggested by the committee, we should also look for the recruitment of at least one or two junior scientist (including A. Romano) who will increase this part of our activity.

3. The size of the project is not as large as it may appear. Nevertheless, we will reduce it until more young scientist will be recruited
Many of our projects are just steps of a few major projects; a given step will not be initiated until the preceding step has been concluded. Most projects have been already started and have yield exciting and good results, a number of these projects are already half way and close to publication (Analysis nof Tregs in schistosomiasis and leishmaniasis, project GENLEISHPHAG). Finally our unit has several specific characteristics that increase the feasibility of our project: our activity and themes are highly integrated, we have high synergy between subprojects which reduces costs and technical investments, and the heavy workload of genotyping is performed offsite on an IBISA platform. We also rely upon the work of our overseas collaborators who are major players in our immunological evaluation (Th17, Tregs).
Nevertheless we shall ensure that the number of projects will not increase and we will delay the projects that have not been started until ongoing projects will be completed and the work will be published. One project has been deleted.

4. The International visibility of the laboratory : We would like to add that:
a) The unit director was one of the very few European scientists to be invited as a speaker at the 2011 Gordon Conference on Tropical Disease (the highest level conference in the field of tropical disease, held every two years).
b) The unit director has been elected as a senior member of the F-1000 university in the section of Immunity and infections.
c) Two of our recent papers were published in high ranking journals ("J.Exp.Med" and "J.Clin.Investigation") and our article in "J of Immunology" (IL-10 in Human leishmaniasis) has been ranked in the top percentile of cited papers for two years.
e) Finally, the term "international" should encompass *all countries*, not just the US and Europe. Our visibility in China, South America (including Brazil), and Africa is very high. This has an important bearing for international collaborations and future economic links. Note that a number of our former PhD students are now heads of institutes and ministers of Health or Education.

5. The replacement of the director of the unit in six years :
This question has not been discussed with the director during the visit. Replacement of the unit director has been anticipated by planning the hiring of two scientists with high expertise in the field and by stimulating the current staff members to demonstrate their capacity to exert this responsibility. On two occasions, the current unit director has attempted to recruit such a brilliant and well respected two young scientists but this was not accepted by the faculty of medicine. In this respect, the comments of the evaluation committee will help us to get the support of the University.

6. Publications in 2010

We have had three patents and two pending patents in 2009 and 2010, this explains why we have only five publications and no major publications in 2010. Four major publications (to be submitted to journals such as Hepatology and JEM) on the Genetics of fibrosis and HCV treatment have been delayed by patent applications and discussions on licensing but these articles will be submitted now. In addition, we are completing three studies for major journals on the Genetics and cell biology of leishmaniasis as well as one important study in malaria. Two papers (one for Cell, one for J Exp Med) have been delayed by ongoing experimental studies (siRNA studies) that required hard work. All of these studies will be published soon in 2011 together with genetic work on Th17 in malaria and leishmaniasis.

7. The number of PhD students in the lab is not 3 but 7

At present, there are seven PhD students working in the laboratory M. Sertorio (full-time in Marseille), S. Oyegue (full-time in Marseille), P. Oliveira (80% of the time in Marseille, 20% of the time in Brazil), M. De Assis Souza (50% of the time in Marseille, 50% of the time in Brazil), C. Accioly Brelaz De Castro (50% of the time in Marseille, 50% of the time in Brazil), Mo. Abdelwaheed (30% of the time in Marseille, 70% of the time in Sudan), and X. Hou (30% of the time in Marseille, 70% of the time in China). All of the students have fellowships (or positions) either from France or from their own country.

8. The number of publications per Thesis is 4.3 (see report) and varies between 2 to 10 publications per PhD thesis. All students are first authors on at least one paper published in a journal with IF > 4 to 6). It makes no much sense to count publications during the thesis itself since most publications on patients in endemic patients and are often delayed until after the thesis because they require longer time to be completed than experimental work performed in Marseille. This production is good, considering that the scientific quality of the work is well controlled and that our reports are known to be very reproducible.

Once again we thank our colleagues for taking on their time to share their experience with us and to advice us on what could be done to improve our projects. We also hope that our remarks will help them to understand better the specificities and high potentials of our Unit.

Professor Alain DESSEIN

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