Infections parasitaires : transmission, physiopathologie et thérapeutiques

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Transmission, Pathogenesis and Therapeutics

From the

Université Aix-Marseille 2

IRD

Service de Santé des Armées

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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: Parasitic Infections: Transmission, Pathogenesis and Therapeutics

Requested label: UMR_MD

N° in the case of renewal:

Name of the director: M. Daniel PARZY

Members of the review committee

Committee chairman:

M. Raymond PIERCE, Université Lille 2, Lille

Other committee members:

Ms Elena LEVASHINA, Université Strasbourg, France

M. Rick MAIZELS, University of Edinburgh, Edinburgh, UK

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

Ms Paola ZACCONE, University of Cambridge, UK

Ms. Dominique MAZIER, Université Pierre et Marie Curie, Paris, CNU representative

Observers

AERES scientific advisor:

M. David DOMBROWICZ

University, School and Research Organization representatives:

M. Jean-Louis MEIGE, Université Aix-Marseille 2

M. Phillipe MAUCLERE, Ministère de la Défense, Paris

Report

1 • Introduction

- **Date and execution of the visit**

The visit was carried out on March 18th 2011, conjointly with a visit (by the same committee) to Inserm UMR 906. An oral presentation of the project by the current director, a senior scientist and the future director, presenting the three main research themes, was followed by the presentation of posters by staff scientists and PhD students. After a discussion with the representatives of the University and of the Army Health Service, 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 UMR-MD3 was previously composed by researchers at the University of Aix-Marseille 2 and the Army Health Service. In 2008 they were joined by 3 researchers from the EA2405 UPS Toulouse 3, but the discrepancy in the evaluation cycle between the Universities of Marseille and Toulouse dictated the withdrawal of these researchers from the current project. However, two researchers at the IRD in Montpellier joined the project in 2010. In addition, two clinicians at the Laveran Military Hospital in Marseille are also members of the unit. Geographically, the UMR-MD3 is now thus split among four sites, the Pharmacy faculty at the University of Aix-Marseille 2 (on 3 floors), the IRBA at the Pharo site in Marseille, the Laveran Military Hospital (parasitology laboratory), Marseille, and at the Pharmacy faculty in Montpellier. The research project is centred on two tropical parasitic diseases, malaria and leishmaniasis, with three main axes: therapeutics, physiopathology (with an emphasis on pulmonary complications of malaria) and transmission (combining studies on the epidemiology of parasite drug resistance, on vectors and on improving diagnostic methods). It should be noted that the National Reference Centre for Malaria at the Laveran Military Hospital forms part of the unit.

- **Management team**

An executive committee composed of 8 members (the Director, 2 co-Directors and the heads of each research group) meets monthly. Its role is to coordinate the research programmes, ensure the coordination between themes, initiate new projects, ensure responsiveness to national and international research funding calls and is responsible for the choice of heavy equipment. A Laboratory Council, comprising all senior researchers and representatives of the students and technicians is involved in the choice of study strategies. The Laboratory Council will be the forum for presentation of projects, experiments and results. Its role will also be to identify specific needs in the UMR and to bring them to the attention of the Executive Committee. The frequency of meetings of the Laboratory Council is not specified. It should be noted that the current director will have to step down within the next mandate due to obligatory retirement. However, his successor has already been designated and agreed upon by all members of the UMR. The evaluation committee considers this to be an extremely positive step.

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	23	21
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	6
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	14	12
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)	12	
N7: Number of staff members with a HDR or a similar grade	21	19

2 • Overall appreciation on the research unit

- **Summary**

The UMR-MD3 has undergone a major reorganization in terms of personnel and research objectives. The research objectives concerning two parasites and three strong themes have improved focus and will contribute to forging a clear identity for the unit, but structural difficulties (fragmentation over four sites, lack of a clear organization into groups) mean that the process of restructuring needs to continue. In particular, firm management will be necessary to ensure that the programmed migration of the ITMSSA researchers of the UMR to the centralized site at Brétigny s/Orge does not lead to disruption. Although the former dispersal of the research effort has been much improved, there is still room for further progress. The collaborations with groups in endemic areas and with industry are strong, but greater participation in internationally funded networks should be sought. This will in turn contribute to improving the quality of publications and the overall visibility of the unit.

- **Strengths and opportunities**

- The new focus on two parasitic diseases and three main themes of research: therapeutics, pathophysiology and transmission, although incomplete (see weaknesses), strengthens the research capabilities of the unit.

- In particular, within the "transmission" theme, the holistic approach encompassing studies on the vector, the parasite and improvements in diagnosis is original and promising.

- The focus on pulmonary complications in malaria (within the physiopathology axis) combines transcriptomics and proteomics applied to study a novel model to explain malarial acute respiratory distress syndrome.

- The ethnopharmacalogical and targeted drug discovery strategies are complementary and have produced results. Clear strategies are in place to allow the screening of potential antimalarials. Moreover, a novel chemoluminescent method for assessment of parasite proliferation has been developed.

- The organisation of well-equiped technical platforms for imagery, transcriptomics, parasite culture, cell culture, animal housing, chemistry and clinical studies represents a major asset to the unit.

- Strong collaborations in the field are focused on two main areas, Kinshasa (RDC), Vietnam and Thailand.

- Active collaborations with industry are a major source of finance (Kalliste, InnoMed), as well as a stimulus for valorisation, such as the development of the Mobile Ultralight Field Laboratory. Seven other contracts or collaborations with industry are in progress and 4 patents have been filed. This represents a particular strength of the unit.

- The Laveran Military Hospital is the national malarial reference centre.

- The presence of a parasitology research unit in Marseille is of local and regional importance (as part of the "Infectiopole Sud"). The project regroups researchers previously distributed between different units and will increase the visibility of the groups concerned.

- The designation of the new director to take over on the retirement of the current director, within the next mandate, will ensure continuity and stability in the management of the unit.

- **Weaknesses and threats**

- The written project was considered by all committee members to be inadequate as a basis for the evaluation of the unit. This may have been partly due to the necessity to write the project months in advance of the evaluation, at a time when the effort to reconstruct and redirect the research activities of the unit were still ongoing. The oral presentation went some way to correcting this, but not completely. The written report was seen as evidence of a failure of management.

- Although the organisation of the unit into research groups is stated (identification of novel natural or synthetic anti-parasitic compounds, therapeutic optimization, physiopathology, entomology, optimisation of control strategies) neither the team leaders, nor their members are clearly identified. A "transversal" organization was privileged in the presentation, but this remains a vague concept.

- The unit is split between four distinct geographic locations, three within Marseille, one in Montpellier. Although the means to overcome this separation have been put in place - regular meetings of the Executive Committee, twice-yearly scientific meetings, an interactive web-site for exchanging data – it remains a threat to the cohesion of the unit.

- Within two to three years the programmed departure of the researchers affiliated to the IMTSSA to a site at Brétigny s/Orge will take place. Although this migration will probably be gradual, it will start in 2013 and will necessarily affect both communication and the continuity of research. This move is clearly seen as destabilizing by some personnel. No administrative problem is posed to students who are registered at the Marseille University Biology and Health Sciences doctoral school. However, here again, the threat is to communication and continuity.

- The research activities of the unit have been considerably focused to concentrate essentially on two parasitic diseases and three main themes, however, within these themes there are a number of different strands that are being pursued. Despite the large number of researchers involved this dispersion of effort is a threat both to cohesion and to the overall quality of work.

- Some proposed projects require a review of strategy. In particular, the proposal to use anti-sense RNA to systematically evaluate genes as targets in Leishmania seems very risky as it is based on questionable data and lacks specific financing. The proposed project concerning the immunogenetics of resistance to malaria appears not to be competitive and has already been dropped (communication of the director).

- The development of novel therapeutics via an ethnopharmacological approach or a target-led (protein kinases) strategy has produced promising results and is backed up by collaborations with 3 french laboratories, but a strategy to carry this research forward to the development of drug candidates from the lead compounds is either lacking or not explicitly set out.

- The publication record of the unit reflects the former dispersion of effort. Numbers of publications in peer-reviewed journals are high, but the majority were not published in leading journals, even within the parasitology field.

- The main research effort reposes on teaching staff and PhD students. There are three full-time IRD researchers and four contractual researchers at the IMTSSA. There are no other post-doctoral researchers or full-time research staff. The unit appears unbalanced in this respect.

- At present, the UMR-MD3 does not appear as a leader in any particular field. It therefore lacks a clear identity and international visibility.

- **Recommendations**

- The unit should continue its current and ongoing process of focusing on strong and identifiable research themes that will allow it to develop international visibility.

- Efforts should be made to ensure publication in higher ranking journals, both within and outside the domain of parasitology, even if this means sacrificing quantity to some extent.

- More full-time post-doctoral or even statutory researchers (this latter is probably unrealisable currently) should be recruited if possible.

- International scientific collaborations (not just in endemic areas) should be developed. This will increase the visibility of the unit and the standard of publications. This can be achieved by becoming involved in internationally-funded multi-centre projects.

- The unit should be organized into individualized teams and ressources allocated accordingly. This seems particularly necessary given the geographic fragmentation of the UMR.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	20
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	3
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	23/24
A4: Number of HDR granted during the past 4 years	Not given
A5: Number of PhD granted during the past 2 years	4

3 • Specific comments

- **Appreciation on the results**

The project presented is composed of three main themes (or axes) and is not broken down into the activities of separate teams, although these are specified in the project (identification of novel natural or synthetic anti-parasitic compounds, therapeutic optimization, physiopathology, entomology, optimisation of control strategies). No details are available concerning the identities or numbers of staff involved in each axis or team. The assessment below concerns the projects presented as well as the results for each axis since the reconstruction of the unit means that some of the themes previously pursued are no longer relevant and have been replaced by new ones.

Axis 1: Therapeutics. The research for new therapeutic agents has been carried out using two main strategies, ethnopharmacological and target-based. The ethnopharmacological strategy has been most pursued in a variety of

contexts, principally to discover antimalarials but also anti-fungal or anti-cancer agents, or more generally to characterize anti-oxidants. Both approaches have yielded lead compounds that can be taken forward. Moreover, a novel chemiluminescence-based method for assessing parasite viability has been developed. The impact of the results obtained is so far limited, mainly due to the publication of essentially descriptive articles and, thus far, a lack of development of characterized molecules as potential drugs. The potential impact is much higher.

Axis 2: Physiopathology. The focus on pulmonary complications of malaria is original and promising. Initial results have been published (Malaria J, 2011) that met with some resistance from reviewers, apparently since they run counter to the existing paradigm. This axis has a strong clinical component that will be pursued in collaboration with the Monkole Hospital in Kinshasa. However, the relevance proposed murine model combined with in vivo imaging requires better definition.

Axis 3: Transmission. The transmission axis is characterized by a holistic approach concerning the vector, the parasite and the human host and concerns both malaria and visceral leishmaniasis. Studies on the genetics of Anopheles vectors (of both malaria and Wuchereria bancrofti) have led to publications on distribution maps and molecular phylogenetic studies of species complexes. Ecological analysis of the distribution of visceral leishmaniasis identified infection foci in different environments. The development of a mobile field laboratory allowing the analysis of clinical blood samples and Anopheles specimens directly in endemic areas is highly original and more importantly provides a practical solution that should give wide-ranging benefits.

The number of publications produced by the unit is good. For the period 2006-10, 136 peer-reviewed publications were produced by the groups constituting the UMR-MD3 at the time. A further 64 were published by the Parasitology and Mycology laboratory of the AP-HM and 7 by the Reanimation Service of the Laveran Army Hospital, groups now joining the unit. It should be noted that the data for 2010 are incomplete. However, a significant number of these publications concern themes not presented in the current project.

A number of publications have appeared in medium to high impact journals (PNAS, PLOS Pathogens, J Immunol, J Virol, Genes Immun, Cancer Res, Allergy). However, of these, the publications in PNAS and PLOS Pathogens as well as two publications in J Immunol are due to the Toulouse group that has had to leave the UMR. Moreover, two publications in J Virol and the articles in Genes Immun, Allergy and Cancer Res concern themes that are not part of the present project. A member of the AP-HM group is a coauthor on a paper published in J Clin Invest, but which does not concern a theme presented in the project. Another member of the AP-HM group is a co-author of a paper that has just appeared in New Engl J Med, but again concerning a theme not presented in the project. Finally, an IRD researcher has participated in a study on global mapping of Anopheles vectors published in 2010 in PLOS Med. Although some of these publications are not relevant to the project presented, they do indicate the excellent international visibility of the researchers concerned.

Further articles have been published in journals that are considered to be among the best within a given domain such as Int J Parasitol and PLOS Neg Trop Dis (the highest rated parasitology research journals; 2 in each) or Antimicrob Agents Chemother (3 articles).

The vast majority of articles were published in journals specific to the domain. It should, however, be emphasized that this is not unusual for a laboratory specializing in research on parasites (as opposed, for example, to those working on immunity to parasites or on human genetics in relation to parasites).

Four patents have been submitted through Protisvalor (Université de la Méditerranée).

A total of 12 PhD students have graduated since 2010 and a further 15 are in progress as of March 15, 2011.

Partnerships with organisations in malaria endemic areas in South-East Asia (Vietnam, Thailand, Cambodia), Africa (particularly RDC) are strong and well established. Research partnerships with groups in Canada (Chicoutimi University), Italy (Universita degli studi di Milano) and Switzerland (EPFL, Lausanne) are established but no details were given concerning common publications generated. Moreover, partnerships are established with 3 french groups concerning the development of quinazoline antimalarials. Industrial partnerships with four companies are established and have generated significant funding for common projects (Kalliste, InnoMad). In addition one of the co-directors is a co-founder of a biotech start-up.

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

An award was made by the Athens National Academy of Sciences to a staff member. One national (oncology) congress and one international (PAGE) congress were organized by the unit. A total of 7 invitations to international conferences and symposia are itemized, but the list is incomplete for the teams newly joining the unit.

The recruitment of PhD students at a local level (15 current PhD students) is satisfactory. Post-docs, apart from 4 contractual researchers remunerated by the IMTSSA are absent, as are high-level scientists recruited from abroad.

The unit currently participates in 3 ANR-funded projects and 3 internationally funded programs. The latter include funding from the WHO/TDR, MAE and USDEP (EC). The unit is also funded by 2 collaborative research contracts labelized by the Lyon competivity pole and 7 other contracts and collaborations with industry are in progress. The UMR-MD3 is particularly strong in this area.

The unit does not take part in any funded international networks. International collaborations are mainly restricted to local structures in endemic areas although two collaborations with universities in Canada and Italy are listed. These latter have not been supported as yet by any publications.

The translation of research results is a growing strength of the unit with 4 patents being filed and, for example, the development of the mobile field laboratory. The director of the unit is also director of an associate laboratory at the National Malaria Reference Centre.

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

The organization of the research unit would greatly benefit from clarification. Although the respective roles of the Executive committee and the Laboratory council are clear, the division of the unit into research groups, while indicated, is not explained. No indication is given as to the heads of each team or the personnel involved. It seems imperative that this organization should be rapidly established. This would in no way adversely affect the communication between researchers or between the researchers and the Executive committee.

The quality and authority of the management requires reinforcement. The inadequacy of the written project, although probably in part due to the ongoing reorganization when it was prepared, indicates a lack of authority and vision.

The regularity of the Executive committee and Laboratory Council meetings, coupled with the use of the interactive web site for the exchange of information and data should ensure adequate communication between the various sites occupied by the unit.

Two scientific meetings per year are proposed to present and discuss the research. This seems inadequate given the numbers of researchers and students. In particular additional opportunities for interaction between the students should be given (regular presentations, journal club).

Most of the tenured staff are involved in University teaching programmes (medicine, pharmacy and sciences) at different levels. Four M2 teaching programmes and one DU are supported by teaching staff from the unit. The teams of the UMR are host laboratories for students from 3 doctoral schools (one in Montpellier, two in Marseille).

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

The objectives fixed for each research axis correspond to at least a 4 year project. The proposed research programmes concerning the development of therapeutics, investigating the pulmonary involvement of malaria and the transmission axis, although having clear intermediate objectives, are all long-term projects that will be viable beyond the next mandate.

No clear policy exists for the allocation of common ressources. Individual researchers are responsible for managing their own contracts, under the control of the Executive committee.

Several projects are cutting-edge with respect to the field. This is notably true of the development of novel antimalarials via ethnopharmacology, the pulmonary complications of malaria and characterization of Anopheles species complexes. The visibility and success of the UMR depends on the focus given to these projects.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
INFECTIONS PARASITAIRES : TRANSMISSION, PHYSIOPATHOLOGIE ET THÉRAPEUTIQUES	B	B	B	B	B

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 - **S2UR120001657 - Infections Parasitaires : Transmission, Physiopathologie et Thérapeutiques - 0131843H** - de l'unité Infections Parasitaires : Transmission, Physiopathologie et Thérapeutiques

Observations d'Aix-Marseille Université

Precisions

It must be noticed that the UMR-MD3 is one of three units supported by the Ministry of Defence, having strong requirements to these Units to: (i) meet the expectations of the university (high-level research, international cooperation...), (ii) improve military health services (expertise, preventive medicine and innovative therapeutic approaches in endemic areas...) and (iii) favour innovation through the development of intellectual property and strong interactions with small and medium enterprises as well as with and the pharmaceutical industry. Individuals and research programs of UMR-MD3 unit fulfil these three conditions, and in addition they are strongly determined and committed to develop successful programs that constitute the base of our proposition: Parasites Transmission, Physiopathology and Therapy.

Answers

1. Written document: the document written 8 months before the evaluation was out-dated by the ongoing reconstruction of the unit. We expected that the oral presentation would allow us to clarify how this reconstruction will be accomplished. Unfortunately, the timing of the evaluation visit was too short (two units were visited the same day) to directly and easily respond to most of the questions raised within a framework that would have deserved to be longer and more interactive with the evaluation committee.

2. Management: due to the Unit size increase, the management has evolved towards a triangular leadership shared by the Unit Director and 2 Deputy-Directors with more responsibility given to the latter ones, based upon to their own scientific expertise, their experience in managing teams and conducting national or international research programs.

3. Unit organization and allocation of basic recurrent funds: The flow-chart presented below illustrates our human resources organization in relation to research axes. Along with this organization and in addition to obtaining external (national or international) funds, a basic recurrent funding will be shared and allocated to each main research priority axis (Therapeutic, Physiopathology and Transmission) in the aim to ensure their basic lab expenses (some equipment, fluids, etc), support some aspects of the research as well as the unit management.

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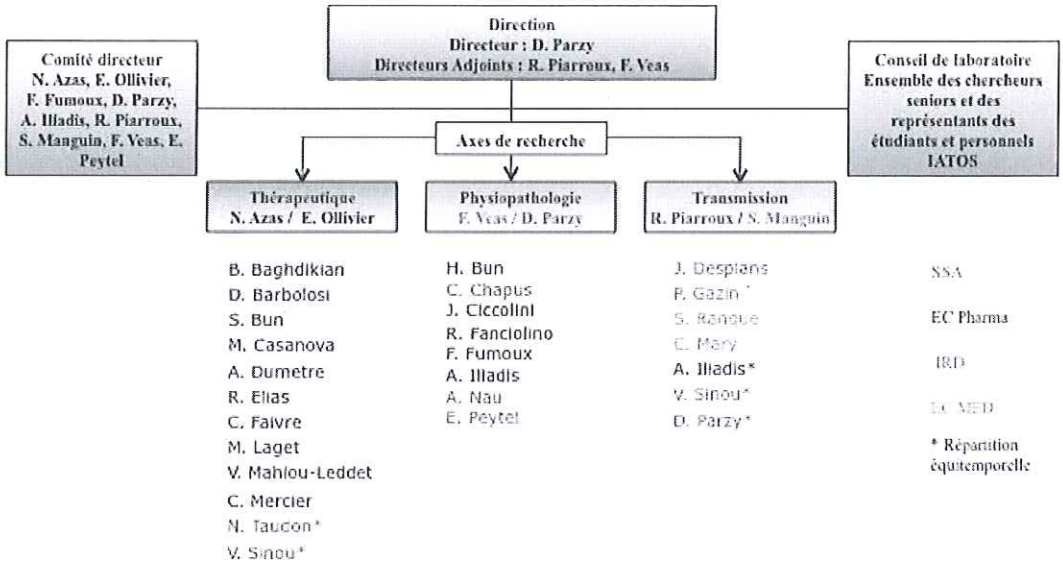

4. Geographic localization and improvement of unit cohesion: the communication among all the elements of the Unit will be maintained, as a high priority, to reinforce and promote cohesion despite the different geographical locations of teams. This approach led to the development, at the end of 2010, of a collaborative platform (private online workspace), as well as a Web site accessible to all the UMR members having the more recent communication techniques (Visio-conference, e-mail, call-conferences). In particular, the philosophy of the tool "News" is complementary and similar to suggestion made by the committee on a "Journal Club" as it consists of individuals and/or groups that analyze and comment scientific articles and other scientific related news. In addition, despite the presence of four sites, two of which are located within the same campus La Timone, the frequency of e-mail and call-conferences strongly contribute maintaining unit cohesion. Researchers from Marseille and Montpellier sites work on common UMR-MD3 technical platforms that enhance scientific interactions. Within the different thematic axes, the project coordinators discuss regularly with their teams and a tight follow-up is done on planning, results and analyses of their research. In line with the review committee recommendations, an "executive committee meeting" every three months has already been implemented, coupled with laboratory council meetings. At the IRBA, a deep thinking is underway to prepare the transfer of some scientists on the Bretigny/Orge's site, without destabilizing the structure. The HIA Laveran researchers remain at Marseille and some IRBA researches will probably join them. The implementation of several communication tools (cited above) is an important element of this major matter.

5. Research topics: The unit reorganization was the opportunity to strongly focus on its three major axes and consequently abandon some research topics particularly those where we did not feel competitive enough. For instance, in the thematic axis "physiopathology focus will be put essentially on the pulmonary pathophysiology of malaria cases by using different complementary approaches (available within the UMR-MD3 technical platform), including transcriptome, proteome, as well as in vivo real time imaging of rodent models in order to discover new therapeutic targets. Convergent data will reciprocally validate each other. In addition, the validation of molecular parameters obtained with these approaches will be compared with situations found in human cases in order to consider them for future developments of new therapeutic strategies for these kind of critical physiopathological situations.

Concerning the antisense strategy (Thematic axis: Therapeutic), the systematic inhibition of *Leishmania* genes in order to identify new therapeutic targets has been dropped. Indeed, this strategy is currently developed as a tool for inhibiting gene expression, notably for the study of apoptosis. The current focused strategy is to study the phenotype of gene expression *via* the use of non-inducible expression vectors, (but also that would be more rapid) of antisense oligonucleotides that will be used to transfect target cells using different techniques, notable liposomes. In this field, we have recently submitted an ANR (2011) project in collaboration with three additional UMRs having expertise in drug delivery systems and parasitology.

The ethno-pharmacological approach has generated the isolation of several bioactive natural compounds. Two of them can be considered as promising compounds. Based on these two very interesting natural compounds against *Plasmodium*, we have generated two projects: (i) the first project is currently funded by DGA on the mechanism of action is in progress with a Ph.D. thesis; (ii) the second project is in preparation in collaboration with a chemist team, to propose a method for total synthesis of this second natural compound for an easy access and pharmacomodulation studies.

In addition, a traditional improved drug (MTA, Médicament traditionnel amélioré) against malaria has been formulated from a plant growing in Mali and Burkina Faso and a first clinical study has already been launched (CORUS project).

6. Collaborations and international visibility: As pointed out by the AERES experts, the target-led strategy is backed up by strong collaborations with French laboratories. Nevertheless, during the AERES visit several international collaborations with leader teams on kinases and/or *Plasmodium* metabolism: C. Doerig (EPFL, Switzerland), C. Sibley Hopkins (Univ. Washington, Seattle, USA), M. Phillips (Univ. Texas, Dallas, USA) have been presented. Moreover, the unit currently collaborates with the French CERNM laboratory for an extensive screening of its chemical library. In this way, several MTAs for identifying new potential inhibitors of essential kinases have been established. On the same topics, research partnerships with groups in Canada have already generated common publications[1, 2] . During the past three years, the unit has privileged strong interactions with researchers from development regions, particularly including Africa (Kinshasa, DRC) and Asia (Hanoi, Ho Chi Minh, Vietnam and Bangkok, Thailand). It is noteworthy that, since 3 years, French teams have been able to work several months in endemic areas with local scientists. In addition to bilateral collaborations, researchers have already been involved in European projects recently completed which has been qualified as "a success story" such as the EC–STREP (FP6 2006-2010) Ultra-sensitive Detection of emerging Pathogens (USDEP) that involved 5 SME and 4 academic institutions, including the Catholic University Chile and IRD, as well as the project on "Hantavirus physiopathology" from the "Jeune équipe associée à l'IRD (JEAI)" and CONICYT (Chile), both projects created and conducted by F. Veas, having generated several publications. S. Manguin is involved in various international projects as partner or coordinator (Wellcome Trust Collaborative project (2009-11) "Global Malaria Mapping Project", MAE (2009-10) "Bacterial biodiversity in the midguts of mosquito vectors and transmission of parasites in Thailand". The Franco-Thai collaboration has generated 14 international publications.

Conclusion

The main objectives of the UMR-MD3's executive committee converge with most of the suggestions and comments of the evaluation committee.

This Unit has made deep thinking on its reorganization to optimize its synergy, cohesion and visibility. These important issues, along with the incorporation of new teams, took place only few weeks before the evaluation of the 2012-2015 UMR project. A new comprehensive organization (flow-chart) of our research and management as required by the evaluation committee has been defined.

This unit has established solid scientific bases that are being reinforced through already running or future funded programs (national and/or international calls) to respond to its objectives..

1- Cytotoxic steroidal saponins from the flowers of *allium leucanthum,* Mskhiladze L, Legault J, Lavoie S, Mshvildadze V, Kuchukhidze J, Elias R, Pichette A. Molecules. 2008 Nov 26;13(12):2925-34.

2- Antiplasmodial, anti-inflammatory and cytotoxic activities of various plant extracts from the Mascarene Archipelago. Jonville MC, Kodja H, Strasberg D, Pichette A, Ollivier E, Frédérich M, Angenot L, Legault. Journal of Ethnopharmacology, 2010; doi:10.1016/j.jep.2010.06.013

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

Pierre CHIAPPETTA