TMCD2 - Transporteurs membranaires, chimiorésistance et drug-design

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Transporteurs Membranaires, Chimiorésistance et Drug Design (TMCD2)

From the

Université Aix-Marseille 2

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

February 2011

Research Unit

Name of the research unit : UMR-MD1

Requested label : EA (whole unit) / ERL INSERM (team 2) / UMR

N° in the case of renewal :

Name of the director: M. Jean-Marie PAGES

Members of the review committee

Committee chairman :

M. Germain TRUGNAN, Université Pierre et Marie Curie, Paris

Other committee members:

M. Benoit DEPREZ, Université Lille 2, Lille, INSERM CSS representative

M. Hendrik VAN VEEN, Cambridge University, Cambridge, United Kingdom

Ms. Cecile WANDERSMAN, Institut Pasteur, Paris, France

M. Jean Louis KOECK, Service de Santé des Armées

Observers

AERES scientific advisor :

M. Gérard CORTHIER

University, School and Research Organization representatives

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

Ms. Christine TUFFEREAU, INSERM

Report

1 • Introduction

- **Date and execution of the visit**

The site visit has been organized within one day on February 10, 2011. The scientific program included an overall presentation of the Unit by its Director followed by 2 scientific presentations of the projects by the proposed team leaders for the two new teams. An additional presentation has been made on specific teaching activities of the Unit's researchers. Meetings with PhD students, engineers, technicians and administrative staff, researchers with permanent positions were also organized.

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

This research unit results from the aggregation of a former EA2197 with chemists from University and bacteriologist and biochemist (2) from INSERM, University and SSA. This unit has been colabelized in 2008 by the University and the CRSSA. The present proposal concerns a labelization by University, CRSSA for the whole Unit and by INSERM for one of the two teams (team 2). The unit (1185 m2) is located on two sites on the "Campus Santé" (975 m2) and at the Army site (210 m2, HIA and IRBA). The unit wish to regroup all the civilian personels on a unique site.

The Unit is dedicated to the study of bacterial membrane physiology and the search for new antibacterial molecules and their targets (mainly proteins involved in antibiotic influx or efflux). The unit uses a large panel of approaches from chemistry to clinical bacteriology.

- **Management team**

The head of the Unit during the last period was M. Jean-Marie PAGÈS. It is proposed that M. Jean-Marie PAGÈS keeps the direction of the Unit during the next term and that two teams will be created: team 1 headed by Mme Anne Davin-REGLI and M. Eric VALADE, and team 2 headed by M. Jean-Michel BOLLA.

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	4
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) (including SSA)	6+2	6+3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade	7	8

2 • Overall appreciation on the research unit

- **Summary**

The unit develops an original research program, aimed at improving tools to overcome bacterial resistance both at a fundamental and clinically applied levels. This is a hot topic, important for public health and for basic knowledge. This relatively small unit has a very good level of publication with more than 90 papers published over the past period, most of them in the best specialized journals of the discipline (IF>4: Emerg. Infect. Dis., Clin. Infect. Dis., J. Infect. Dis., J. Antimicrob. Chemother., Antimicrob. Agents Chem., Expert Opin. Inv. Drug., …) but also in high impact generalist journals (Nat. Rev. Microbiol., J. Biol. Chem. Proteomics, PLoS One, Biochemistry). The unit develops strong collaborations with industry (2 contracts, 4 patents). The unit is rather attractive for PhD (8 PhD defended), for collaborations (several international and national collaborations, including a Marie Curie RTN and a COST action) and has obtained 3 ANR contracts (1 as PI, 2 as participant), funding from Ministry of Defense and from PACA Region. The Unit director is well recognized by the international community. The proposed new organization with two teams is strongly supported by the University, the "Service de Santé des Armées" (SSA) and national and local INSERM representatives. The committee considers that this is a very good proposal that has to be supported.

- **Strengths and opportunities**

- Very important and hot topics are adressed by the whole unit and the two teams;

- Thematic continuity between the two proposed teams is excellent;

- The scientific production is very good (90 publications, 4 patents, 8 PhD, 24 invitations to national and international meetings);

- Large topic coverage observed from fundamental microbiology to clinics and epidemiology;

- There is a very good collaboration with army and industry;

- There is an access to rare strain libraries and strong connections with reference centers;

- Strong support from Army, INSERM and University is noticed;

- National and international visibility is observed.

- **Weaknesses and threats**

- Range of techniques available in the unit is still limited : there is a need to develop DNA techniques and biochemistry;

- Research topics would need to be more precisely defined to adapt to the actual size of the unit;

- Some results will require a more in-deepth analysis and additional experiments to allow publications in higher impact factor generalist journals;

- Team leaders need to demonstrate more clearly their leader position;

- Scientific animation within the unit should be improved (clarify the role of the lab council, organize lab meetings on a regular basis, use english to help students and permanent researchers to more efficiently communicate inside and outside the unit).

- **Recommendations**

- Given the very good results obtained, the importance of the topics addressed, the quality and the dynamism of the unit members, the strong support of all the organisms in charge, this unit with its two teams will represent a very good opportunity to produce new knowledge on bacterial resistance mechanisms and on new active drugs and to transfer this knowledge to patients.

- There is a need to recruit more permanent researchers and engineers to reinforce the potential of research, namely in biochemistry.

- The production of the unit could be improved (in term of quality of impact factor) by defining more precisely the topics to be studied in-deepth, i.e. combining more methodological approaches.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	4
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)]	1
A4: Number of HDR granted during the past 4 years	1

- **Appreciation on the results**

Most of the results have been obtained until now by collaborations between members of the two teams that are foreseen for the next term, thus indicating a very good continuity between the different topics developed by this unit. The work concentrates on membrane transporters of Gram-negative bacteria, on their relations with antibiotic susceptibility and on the synthesis and the characterization of original molecules able to interfere with these transporters or the bacterial barrier. Major advances have been made during the past period such as: (1) the identification and characterization of several transporters in *Campylobacter* and *Enterobacter*. The genes have been cloned and deposited in data banks and the proteins have been characterized; (2) Regulators such as Mar and Ram, involved in multidrug resistance (MDR), have been characterized from clinical isolates, their role in the dynamic equilibrium of antibiotics inside bacteria (*Enterobacter aerogenes*) controlled by influx and efflux mechanisms has been studied; (3) some efflux pumps from *Bukholderia*, *Campylobacter*, *Enterobacter* and *Klebsiella* have been studied and their role in the MDR phenotype have been demonstrated; (4) new molecules have been discovered and some of them have been shown to partially restore susceptibility to antibiotics molecules.

More than 90 papers have been published during the past period. Most of them appeared in the best-specialized journals of the discipline (IF>4: Emerg. Infect. Dis., Clin. Infect. Dis., J. Infect. Dis., J. Antimicrob. Chemother., Antimicrob. Agents. Chem., Expert Opin. Inv. Drug.) but also in highier impact journals (Nat. Rev. Microbiol., J. Biol. Chem., Proteomics, PLoS One, Biochemistry). All PhD students have defended their thesis, all of them with at least 2 papers.

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

During the past period, members of the unit have been invited to present their results in 24 national and international meetings.

Among the 8 PhD students, 2 were recruited from abroad (Algeria, Germany). Four post-doc have worked in the unit, 2 of them from abroad (Germany and Portugal).

Three ANR contracts have been obtained (1 as PI, 2 as participants).

Two industrial collaborations are running, one with Bio-Mérieux, the other one with "L'Occitane" associated with one CIFRE contract (PhD).

The leader of team 2 obtained an INSERM "contrat d'interface" to develop research in collaboration with the University of Corte (Corsica).

Overall, the opinion of the committee is that the visibility and attractiveness of the unit is very good.

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

The unit has functioned until now as a single team with two main complementary research themes, with an excellent coordination between them. The proposal to split the unit into two teams appears logical both for scientific and structural reasons. One part (team 1) will continue to work on antibiotic resistance mechanisms from bench to bed, with a strong implication of the University hospital and the health army service (SSA). This research will benefit from the huge experience of its members on highly pathogenic species (collections) and will be perfectly positioned at the crossroad between microbiological research and clinics to improve MDR diagnosis and management. The second part (team2) will concentrate on the discovery of new molecules able to counteract the increasing MDR phenotype among pathogenic bacteria.

To ensure that such a new organization may efficiently function, it will be required to improve the internal communication by structuring more efficiently the lab council, by organizing the scientific life of the unit on a more regular basis. The committee is convinced that the unit director and the team's leaders have the capacity to manage this scientific animation improvement.

It is important to point out that most of the staff members are heavily involved in teaching activities, including permanent researchers, and that the teaching activities concern highly important topics that are very original (notably those linked to the bacteriological risks).

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

The project proposed by the unit and its two teams concerns highly important questions that will have profound implications on public health. The global increase of bacteriological infections and the increase of antibiotic resistances worldwide urgently require the development of new approaches aimed at specifically interfere with one of the strategies developed by bacteria to adapt to antibiotics. One of the interesting specificity of the unit TMCD2 rely on the fact that all the proposed research themes converges towards the characterization of influx or efflux mechanisms of antimicrobials, which represent putative targets of innovative therapeutics. Such a better knowledge of fundamental mechanisms of MDR is a strict prerequisite for the development of new drugs able to efficiently counteract bacterial adaptation to antibiotherapy. The unit has defined a logical and original approach to answer these essential and complex questions. The collaboration of field microbiologists with medics, pharmacists and chemists and the use of local and regional platforms provides a very good feasibility to the global project and to the

team's projects. However, given the size of the unit and the tools available, care should be taken to more precisely define the specific goals.

It is important to notice that funding have been obtained to ensure that most of the projects can be done. However, a critical point will be that organisms in charge, University, SSA and INSERM, provide an adequate support, especially in term of permanent positions for engineers and researchers.

The overall appreciation of the committee is that the project of the unit and of the two teams is very good.

4 • Appreciation team by team

- **Team 1: Bacterial membrane physiology,**
- **Team leaders: Ms. Anne DAVIN-REGLI and M. Eric VALADE**
- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	0,5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	8
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,5	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	5	4.5

- **Appreciation on the results**

The research of this Team is very good. One of the attractive and unique features of the team is the multidisciplinary character with contributions by chemists, biochemists, bacteriologists and clinicians. The team is also well supported by technical and administrative staff. In their research team 2 focuses on the role of in the resistance to antimicrobials. This aims fits with that of Team 2 (not evaluated here) in which emphasis is on the identification of new drug targets in microorganisms and of compounds that inhibit drug resistance.

Hydrophilic antibiotics often enter the cell envelope of Gram-negative organisms through porins in the outer membrane, whereas drug efflux in these organisms often relies to on tripartite RND pumps (such as AcrAB-TolC in E. coli) that are composed of a protein component in the cytoplasmic membrane (AcrB), outer membrane (TolC porin) and connector that spans the periplasm (AcrA). In line with this, Team 1 investigates (i) the structure and function of porin proteins (Omp50, CadF, Omp36, OmpF), and the relation between their expression and drug resistance in

clinical isolates, and (ii) the occurrence of tripartite RND drug efflux pumps in pathogens such as Campylobacter, Neisseria, and Enterobacter, their role in drug resistance, and factors that trigger their expression such as global regulons (e.g. Mar, Ram, Sox) and local regulators (e.g. acrR, micF, ramA, ramR genes), but also external factors (e.g. preservatives and other chemicals).

The output of Team 1 is very good with more than 80 papers over the past 4 years, many of which are shared with Team 2. The team 1 is involved in a wide variety of collaborations within France [civil and military hospitals, the Soleil synchrotron, the CampyAdapt Network (MICA-INRA Department), INSERM teams, CNRS, companies (Occitane en Provence, BioMérieux)] and internationally [COST Action BM0701].

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

The reputation of the PIs and researchers in Team 1 is very good. One of the PIs has an H-factor of 30, demonstrating that papers from the team are well cited. The team is well funded by CRSSA, 2 ANR, and 1 European RTN Marie Curie contract. With 4 PhD and Master students and 1 postdoc the team is clearly providing an attractive environment for young scientists.

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

In the coming years, Team 1 will continue with the resistance assays in intact cells, and some new topics using the existing experimental tools will also be introduced.

- **Conclusion:**

— Summary

Team 1 in the Pages Unit represents a very good group of scientists that carries out research on an important topic for public health, with very good publication record and impact.

— Strengths and opportunities

Although this field is competitive, the team manages to obtain excellent funding from diverse sources, and to maintain a wide variety of collaborations at the national and international level.

— Weaknesses and threats

A major risk of the planned extension of studies on RND pumps to other species is that it might lead to less original results. In these new organisms, RND pumps might function like those already characterized. However, there are novel functions associated with RND pumps, which could provide new directions in already successful lines of work.

As Team 1 is composed of medics/cell biologists whereas Team 2 consists of chemists, the unit is in need of biochemists that can provide the link between Team 1 and Team 2.

- **Team 2: New drugs and new targets**
- **Team leader: M. Jean Michel BOLLA**
- **Staff members**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1,5*
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1
N5: Number of 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)	1
N7: Number of staff members with a HDR or a similar grade	3.5

- **Appreciation on the results**

The project presented is the natural therapeutic translation of the expertise gained by his team and the data generated by team1. Based on (1) the verified assumption that efflux mechanisms are at the origin of a large number of microbial resistance to antibiotics, (2) their ability to produce recombinant, functional membrane transporters, (3) their small screening facility and library.

They will identify small molecules that boost the efficacy of antibiotics by modifying transport dynamic of antibiotics across bacterial membranes. They have already obtained interesting compounds in several chemical families. The small chemistry group that has joined the team and their external collaborators will have plenty of work optimizing these compounds.

Beside the existing chemical knowledge, the team will nevertheless need to acquire experience in medicinal chemistry, i.e. proper optimization of not only potency, but also safety and pharmacokinetic parameters. The latter parameters are of utmost importance in the field of antibiotics, especially when drug combinations are designed.

They will need to complete the development of molecular, target-based assays, in order to make sure that the compounds act on the chosen target and keep the mode of action all along the optimization process.

The appraisal by the visiting committee reveals a small enthusiastic team with a timely project in the important field of antibiotic research. The team has already been able to raise money for its project via ANR and a COST program. With the regained interest of the pharmaceutical industry for this field, public-private partnerships are possible in the future. The university has assured us of its support to the team with the planned renewal of the MCU position in case of retirement. The position could be filled with an experienced biochemist to accelerate and scale up protein production.

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

This team has been able to commit several national and international partners in collaborative projects. The university, the Conseil Régional, the Conseil Général, Mairie, French-Poland agreements for bilateral funding (PHC Polonium) and ANR have been providers of financial support for the team for several years. Given its growing visibility in the field and the relevance of the reseasch topic, it is reasonable to expect no difficulty to recruit the talented

researchers needed to realize the full potential of the project team. Team 2 is also partner of Cost Action BM0701.

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

The project has clearly defined goals, but desserves a more accurate planing, a more detailed description of milestones, to help project management in the future. Indeed, a flow of information will be generated and, given the limited amount of material and human resources, choices and will have to be done.

- **Conclusion :**

— Summary

Team 2 is well structured and has clearly defined therapeutic goals, which are aligned with important medical needs.

— Strengths and opportunities

Team members have complementary expertise.

— Weaknesses and threats

The team does not have a track record in drug discovery. Difficulty to develop combination therapies in general and especially in the field of antiinfective compounds.

This team must be given the necessary ressources to demonstrate that the screening platform and the strategy can deliver compounds with a therapeutic potential.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
TMCD2 - TRANSPORTEURS MEMBRANAIRES, CHIMIORÉSISTANCE ET DRUG-DESIGN	**A**	**A**	**A**	**A**	**A**
NEW MARKERS AND NEW TARGETS [PAGES-BOLLA]	A	A	Non noté	A	A
PHYSIOLOGY OF THE BACTERIAL MEMBRANE [PAGES-DAVIN-REGLI-VALADE]	A	A	Non noté	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 - **S2UR120001649 - TMCD2 - Transporteurs Membranaires, Chimiorésistance et Drug-Design - 0131843H** - de l'unité TMCD2 - Transporteurs Membranaires, Chimiorésistance et Drug-Design

Observations d'Aix-Marseille Université

1- General points and overall appreciation on the research unit

- p5, Weakness and threats / Recommendations:
  - following the approval of UMR with two teams, the lab council will have new responsibilities and charges in the unit life, recruitment of students, preparation of proposal, etc.
  - team's leaders and unit director actively contribute to the improvement of this new management of unit life.

2- Specific points regarding Team1

- p8, Appreciation on the scientific strategy: team 1 is conducting genetic and molecular investigations with DNA micro-array analysis with GIS on resistant pathogenic bacteria in order to assess the role of regulators, this is a new experimental approach.

3- Specific points regarding Team2

- p 9, Appreciation on the results.

The team members have produced 23 publications since 2006 focused on new compounds and inhibition of resistance mechanisms, and four patents on new molecules active on MDR bacteria. Moreover, the members have also a recognized expertise in antibiotic resistance mechanisms associated with the bacterial membrane

In addition, as mentioned in the report on team 1, the aims of team 2 fit well with those of team 1. Team 2 will use data generated by team 1 to characterize the efflux mechanisms and identify inhibitors. Team 1 will benefit of the results of team 2, particularly on inhibitors, in order to assess the resistance mechanisms and develop diagnosis tools. The inhibitors identified will be further used, at the bacterial and the biochemical level, for a better understanding of the transporters. *In silico* and biophysical studies are also in development to define molecular features of resistance inhibition.

Studies of structure-toxicity-relationships of several molecules are in progress.

The team leader has a well-recognized knowledge in membrane protein purification required for *in vitro* study on target-molecule interactions. A platform Akta Explorer 10 is available in UMR-MD1. The collaboration with UPR9036 (Marseille) allows to develop

Jardin du Pharo . 58 Boulevard Charles Livon . 13284 Marseille cedex 07 . France
Tél. : +33 (0)4 91 39 65 00 . Fax : +33 (0)4 91 31 31 36 . www.univmed.fr

Biacore analysis methods and to transfer the methodology to UMR-MD1 (a Biacore station will be available in SSA).
Team 2 is conducting physical and molecular studies with Synchrotron Soleil (Disco team) focused on the intra-bacterial antibiotic concentration in order to dissect the role of membrane permeability in drug diffusion.
- p10, Strategy and project: Team 2 develops studies on different families of molecules. Each family will be studied as the proposed tasks schedule:
  - activity *in cellulo*, *in vitro* interaction with purified targets - assessment of cell cytotoxicity, - structure-activity and structure-toxicity relationships will be included in medicinal chemistry–studies. Only the molecules of interest will be further *in vivo* studied on animals. This last part will be performed in a collaborative network.
-p10, conclusion-summary: If the goal is to obtain therapeutic candidates, the first contribution is to better understand the bacterial transporters involved in drug activity, the interaction between molecules and targets. The team will also develop diagnosis tools with team 1.
-p10, conclusion-strengths and opportunities: a strong interaction exists between team 2 and Valor-PACA and helps in developing knowledge transfer to industrials. A grant from Valor-PACA was recently obtained, and an agreement with the veterinary Virbac Company is under redaction. A contact with Cubist Pharmaceutical is ongoing.
-p10, conclusion-weaknesses and threats: As mentioned above, although the drug discovery is the ultimate goal of our project, the initial necessary steps of this project include, target-guided screening of molecules and studies of their mechanisms of action. Developing new therapeutic combinations will benefit from collaboration with Virbac.

4- Conclusion:
Since a long time the UMR-MD1 is developing a very efficient and productive network to acquire new expertises. This network will now be extended for studying the regulation of MDR phenotype, *e.g.* GIS, the interactions of molecules with targets, *e.g.* Synchrotron Soleil, and for developing *in vivo* models, *e.g.* Virbac.

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