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

Department for the evaluation of research units

AERES report on unit:

Recherche de Molécules à visée Thérapeutique par approches in silico

MT*i*

Under the supervision of the following institutions and research bodies:

Université Paris 7- Denis Diderot

Institut national de la santé et de la recherche médicale

January 2013

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

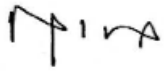
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.

NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report and its in-house teams received the following grades:

- Grading table of the unit: Recherche de Molécules à visée Thérapeutique par approches in silico

C1	C2	C3	C4	C5	C6
A	A+	A+	A+	A+	A

- Grading table of the team: Structure-based peptide design

C1	C2	C3	C4	C5	C6
A	A	A+	NN	A+	A

- Grading table of the team: Pharmacologic profiling

C1	C2	C3	C4	C5	C6
A	A+	A	NN	A+	A

- Grading table of the team: Virtual screening

C1	C2	C3	C4	C5	C6
A+	A	A+	NN	A+	A

Evaluation report

Unit name:	Recherche de Molécules à visée Thérapeutique par approches in silico
Unit acronym:	MTi
Label requested:	
Present no.:	UMR-S 973
Name of Director (2012-2013):	Mr Bruno VILLOUTREIX
Name of Project Leader (2014-2018):	Mr Bruno VILLOUTREIX

Expert committee members

Chair:	Mr Gilles LABESSE, CNRS, Montpellier
Experts:	Mr Alexandre BONVIN, Utrecht, Netherlands
	Mr Vincent DIVE, CEA, representative of INSERM CSS
	Mr Brian MARSDEN, Oxford, United Kingdom
	Mr Bernard OFFMANN, Université de Nantes, représentative of CNU

Scientific delegate representing the AERES:

Mr Jacques BARATTI

Representatives of the unit's supervising institutions and bodies:

Mr Richard LAGANIER, University of Paris Diderot

Ms Marie-Josèphe LEROY-ZAMIA, INSERM

1 • Introduction

History and geographical location of the unit

The unit MTi was created in 2009 as a Paris-Diderot/INSERM unit. It was composed of only one team including 8 researchers/professors and 6 other staff members with a permanent position. Since then, the unit has grown to 11 researchers/professors with permanent position (by Sept. 2012). It now includes 8 other permanent staff members. In between the unit was moved to a temporary place before reaching its definitive place last year within the new campus of the University Paris 7- Denis Diderot.

Management team

Mr Bruno VILLOUTREIX

AERES nomenclature

SVE-1 LS-1 and LS-2

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	4	4
N2: Permanent researchers from Institutions and similar positions	7	7	7
N3: Other permanent staff (without research duties)	8	9	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2	3	2
N6: Other contractual staff (without research duties)	3	3	
TOTAL N1 to N6	24	27	13

Percentage of producers	**93.3 %**

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	8	8

2 • Assessment of the unit

Strengths and opportunities

• Successful unit recently created, and showing a significant attractiveness locally, nationally and also internationally for both young and senior scientists.

• Leading laboratory in France and in particular at the INSERM, in an emerging and multidisciplinary field combining bioinformatics, statistics and chemoinformatics.

• Recognized expertise in the field leading to (and now reinforced by) the opening of European Master for 'in silico Drug Design'. Teaching is an essential commitment for the whole community and an excellent opportunity to establish connection with leading scientists in the area of research.

• Number and quality level of the publications by members of the unit is on average very good and including methodology papers in recognized journal in the field (N.A.R., Bioinformatics, PLoS Comput. Biol., Drug discovery Today, ...) and application papers often in collaborations with biologists (P.N.A.S., ...).

• Several good national and international collaborations as well as a convincing networking within the national communities of bioinformatics and chemoinformatics.

• There is a good potential to increase the collaborations at international level and participate to European projects.

• The unit benefits from a strong support from both the INSERM and the university Paris 7- Denis Diderot.

Weaknesses and threats

• Peptide modeling and protein-protein interface are two fields with high international competitions.

• The lack of papers published in journals with very high impact factors may limit international visibility and therefore involvement in international network or research programs (FP7, ...). The productivity of some teams might be improved.

Recommendations

• The committee fully supports the project and may recommend:

• strengthen connection/collaboration between teams (e.g.: for validation purpose, target analysis).

• keep improving teaching excellence locally and at the European level (master isDD).

• strengthen collaborations in bioinformatics at the international level possibly within the ELIXIR/OPENSCREEN/... infrastructures or through grant applications to FP7 projects.

• keep attracting additional scientists possibly with complementary skills in aim at strengthening experimental applications (teams 1 and 2).

• Extend the current SAB to an international level.

3 • Detailed assessments

Assessment of scientific quality and outputs

Over the last period, the MTi has reinforced its main lines of research:

- extending structural alphabet development toward efficient peptide conformation prediction;
- developing original approaches for ab initio ligand conformation and structure-based protein pocket predictions;
- continuing the development of state-of-the-art ADME-Tox predictions and starting to adapt this topic to Protein-Protein Interface.

On top of these topics, it is now adding, in due time, the emerging field of pharmaco-profiling thanks to new professor recruitment.

All this is bringing together a large panel of expertise in bioinformatics and chemoinformatics backed by an impressive amount of theoretical and technical skills in statistics.

All these complementary aspects are nicely connecting each other in the current project of the unit.

The maturation of these fields and the growth of the unit led to a relevant organization into three teams.

The publication level of the entire unit is very good in number (103 in the period 2007- 2012) and quality with both methodology papers, application papers and numerous book chapters (20) or invited reviews (18). Lab members are often first and/or corresponding authors of these publications.

In parallel, the involvement in the development and maintenance of two well-established platforms, RPBS and CDiThem, is also a strong and important commitment to the nation-wide scientific community.

Assessment of the unit's academic reputation and appeal

Since its recent creation (in 2009), the MTi has been growing successfully, showing a great attractiveness to both young and senior scientists. This gave the opportunity to become a national leader in its research field by combining complementary topics including bioinformatics, biostatistics and chemoinformatics in a rather unique manner in France.

Assessment of the unit's interaction with the social, economic and cultural environment

The unit has developed and maintained various software, freely available to the academic community through the IBISA platform RPBS.

Several original and up-to-date tools (e.g.: PEP-FOLD, FROG, FAF-DRUG, ...) achieved high access rate (~ 10000/year) world-wide.

The unit has developed a unique protocol, Mobyle, to disseminate rapidly a plethora of bioinformatics and chemoinformatics tools (Collaboration with Institute Pasteur, Paris).

The integration and the efficient networking through the MobyleNet platform, gathered most of the French laboratories in the field of bioinformatics and also chemoinformatics.

Seven patent applications (2007-2012) have been deposited and several contracts with the industries are ongoing or under investigations.

Assessment of the unit's organization and life

The three teams are scientifically sound and coherently dealing with the new arrivals (4 assistant professors, one professor, two researchers ...) that bring complementary expertise.

During the committee visit, an excellent atmosphere was evidenced as well as a strong trust in the unit leadership.

Regular lab meetings (once a month) are scheduled and opened to all members during the former period and now involve elected delegates due to the rise in the number of unit members.

Assessment of the unit's involvement in training through research

The unit shows an excellent commitment to teaching at various levels (L3 and M1 "Biology-informatics" and the European M2 "in silico Drug Design") and a similar trend regarding training of master (22 M1 and 15 M2 from 2007 to 2012), doctoral students (6 defended and 5 on-going) and also several post-doctoral fellows (6).

All the PhD students publish in good journals in the field and also attend a national/international meeting during the time course of the thesis.

Teaching and training benefit from the various tools developed and made accessible by the unit through the platform RPBS.

Assessment of the five-year plan and strategy

Based on the results from the previous period and the new recruitment in the unit, a new project has been established through a long and thorough process of self-evaluation. Within the global context of in silico drug design, three main axes have been delineated:

- Structure-Based Peptide Design;
- Computational Pharmaco-Profiling;
- Virtual Screening and design of protein-protein interface inhibitors.

The new lines of research push forward the limits and scope of the current methodologies developed in the Unit. The three main focuses will provide an original framework of efficient methods for tackling the problem of developing drugs targeting protein-protein interactions. This represents a risky and highly competitive area of research. The experiences and the skills gathered at the unit suggest that is a timely move.

In parallel, to this methodology development, several applications studies are planned through collaborations and this would provide challenging and interesting validations.

4 • Team-by-team analysis

Team 1 : Structure-based peptide design

Name of team leader: Mr Pierre TUFFERY

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	1	1
N3: Other permanent staff (without research duties)	3	2	2
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	
N6: Other contractual staff (without research duties)	2	1	
TOTAL N1 to N6	9	6	4

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

In the previous four years the members of this proposed team have demonstrated clear successes in developing and making available competitive methods for predicting the structure of relatively large peptides (PEP-FOLD) and also protein pocket detection (Fpocket) and ligand conformation (Frog-2). The external adoption of PEP-FOLD has been significant, with the implementation on the RPBS web platform becoming the most used method with over 11,000 hits in 2012.

A number of papers associated with these methods have been published in journals with relatively high impact factors (9 in Nucl. Acid Res., I.F. ~ 8). The PEP-FOLD method stands out as the key development having been shown to be able to compete with complementary methods from other groups, some of which are fortunate to possess significantly more resources than that available to this team, historically.

The MobyleNet web platform represents an unusually well-integrated and federated set of chemoinformatics, bioinformatic and computational chemistry tools which show significant numbers of hits both nationally and internationally. Additionally, a number of publications, of varying impact (2 PNAS, 1 Hepatology, 1 Genome Biol.), have resulted from this platform.

In general the number of publications authored by members of this group is reasonably good (39), for a methods-development team.

Assessment of the team's academic reputation and appeal

The well-used Paris-wide RPBS web platform have ensured that the work of this proposed team is well-known and well used at an international level.

In parallel, the team manage the development of the national MobyleNet connecting several important French web-based platforms. Team 1 leads the RPBS effort and motivated the implementation of MobyleNet.

The proposed group have been successful in becoming part of the national Bip:Bip bioinformatic project.

There have been a relatively low number of invited external talks given over the previous four years which is surprising given the apparent utility of the PEP-FOLD method, for example.

Assessment of the team's interaction with the social, economic and cultural environment

The free and unrestricted release of all methods and software either as standalone downloads (open-source) or via the RPBS/MobyleNet web platform has meant that the work of this proposed team has had a direct and immediate availability to others in the field both nationally and internationally.

PEP-FOLD has in the past been licensed to at least one company and discussions are underway with a number of other biotech companies with regard to licensing of MTi's software and datasets.

The head of Team 1 is a member of a number of national committees related to bioinformatics and also heading the axis 'Structural Bioinformatics' at the French Infrastructure for Bioinformatics.

Assessment of the team's involvement in training through research

The level of teaching by members of the proposed group is good, with involvement with the organisation and teaching of the MTi-designed in silico drug design masters course as well as teaching in other local courses at various levels.

Assessment of the five-year plan and strategy

The proposed plan involves the focusing of effort upon two complementary themes:

- . peptide folding and design;
- . further development of the MobyleNet platform.

These two directions make sense given the previous success with PEP-FOLD and also the federated bioinformatics web platform.

It is intended to continue developing PEP-FOLD to explore the possibility of predicting protein:peptide interactions by folding peptides close to the cognate protein surface. In parallel, effort will be placed on identifying 'hotspots' between peptide & protein, and then designing de-novo fragments which are then linked together either via PEP-FOLD, fragment mining from the PDB or via stable, well-defined, peptide sections. The ability to identify the hotspots is well-established and the idea of creating linkers is not entirely novel, although in the context of 'large' (up to 50 residue) peptides this is clearly challenging. The fast mining of existing fragments from protein structures is something this team have enough experience with to ensure that the method they are developing shall be competitive within the field.

Deducing possible interactors for targets identified by team 3 should provide a useful parallel set of 'hints' to prioritise. The proposed work, whilst not entirely novel, is timely and appropriate for the scientific questions posed and has a good chance of success.

The group intend to extend the functionality of MobyleNet to include more complex, multi-scale workflows. Furthermore, there is work planned on 'semantic' approaches to enable MobyleNet to be more accessible to non-structural biologists/bioinformaticians. These are two complementary and important developments for this platform in order to continue to extend its use broadly.

Conclusion

- Strengths and opportunities:

A very professional approach to software and web platform development should ensure a high quality of the developed products.

Assuming sufficient IT resources can be provided, it should be possible to develop MobyleNet to become a clear leader in providing ad hoc structural bioinformatics to the community both nationally, and internationally.

- Weaknesses and threats:

There is quite some competition in the field of protein : peptide interaction modelling

It will be important that web-based tools and workflows are clearly discoverable by non-specialists both via search engines and social media.

- Recommendations:

The team will have to increase their visibility and the visibility of the developed methods to make an impact at the international level.

To demonstrate method efficiencies, it will be important to branch out and attempt demonstration on various targets, so that the method can be shown to be generic and not biased towards one particular target/family/classification.

Team 2 : Pharmacologic profiling

Name of team leader: Ms Anne-Claude CAMPROUX & Mr Olivier TABOUREAU

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	5	5
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2	
N6: Other contractual staff (without research duties)		1	
TOTAL N1 to N6	6	10	7

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

Overall Team 2 members made significant contributions in their respective fields of expertise *i.e* chemoinformatics, structural bioinformatics and data analysis. They developed original computational approaches integrating statistical, geometrical and network biology considerations towards profiling of ligands, targets and ligand-target interactions.

The recent and original contributions in the area of druggability of targets and developing field of multi-scale pharmacology is to be highlighted as it is expected to impact substantially research in pharmacology.

The six permanent scientists of this newly formed team co-authored 53 original articles in the 2007-2012 period, all of which were published in average or relatively high impact journals (Nucl. Acid Res.; PLoS Comput. Biol.). Half of this production was done by new MTi members before they joined this lab showing good attractiveness of this unit.

Assessment of the team's academic reputation and appeal

The team members have many ties collaborations with several external teams or collaborators, most of which are experimental-, clinical- or pharma-based which is of outstanding value to team 2.

Team 2 successfully attracted funding from national agencies (ANR Piribio, Bip-Bip) and team 2 is involved or heading several EU-based consortia (OpenPHACTS, eTOX, …) and the Danish-based INDICES consortium.

Members of Team 2 belong to editorial boards of specialized journals, have been solicited on conference boards and have been recruited as scientific experts at national and international levels (ANR, FP7).

Assessment of the team's interaction with the social, economic and cultural environment

Team 2 members through their interactions with members of team 1 and Team 3 have been involved in developing several software and methodology made available through Web-based servers.

As part of its contribution towards translational medicine, team 2 is now involved in the development of the database ChemProt. This huge database was developed towards integrating relationships between drugs, targets and diseases using clinical data and translational technologies and has been made available publicly. This has potential for high clinical and social outreach.

Assessment of the team's involvement in training through research

MTi members from team 2 have outstandingly played a leading role in nurturing training in bio-informatics at the University Paris7- Denis Diderot (at license L3 and master M1 level).

Team 2 members led the creation and are now coordinating a unique European MSc degree in Drug Design.

In addition, a substantial number of students were provided training through research internship by MTi members from team 2.

Team 2 members are also actively involved in Doctoral Schools from higher education institutions in Paris.

Assessment of the five-year plan and strategy

Team 2 will be focusing on the development of new computational approaches towards pharmacological profiling through three complementary directions:

- ligand space profiling and target space profiling;
- pharmacological network profiling.

Their main objective is to develop innovative platforms and new methods by considering network and systems biology towards knowledge enrichment about mechanism of diseases, drug safety and activity.

These original resources and methods will allow prediction of drug side effects and potential off-target. They will be integrated in a "systems pharmacology" approach with the aim to develop "hybrid" models to improve pharmacological profiling of drugs with special emphasis on drug safety. Collaboration with team 3 on mechanistic ADME-Tox prediction is foreseen.

The proposed work relies on the adequate combination of complementary scientific expertise. The question of druggability and ligand profiling is a very competitive area.

Conclusion

- Strengths and opportunities:

Team 2 involvement into EU projects (eTOX, OpenPHACTS) and heading of the development of one of the largest databases in chemical biology, will provide the unit with a leading position at the international level.

Combination with structural analysis for ligand and active site profiling shall bring additional advantage in the emerging but already highly competitive field of integrated pharmacology/chemical biology.

- Weaknesses and threats:

The plans are very ambitious compared to available human resources.

The cooperation between scientists in team 2 is low

- Recommendations:

Additional dedicated technical personnels would be critically needed to keep team 2 moving forward in a timely fashion.

Strong interactions between team 2 scientists should be encouraged (with aim of joint publications) as it is expected to positively consolidate the team as a whole.

Team 3 : Virtual screening

Name of team leader: Ms Maria MITEVA

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions	3	3	3
N3: Other permanent staff (without research duties)		3	3
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	2	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	7	8	6

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	3

Detailed assessments

Assessment of scientific quality and outputs

This is a strong team with as research focus virtual screening and rational design of protein-protein interaction modulators with balanced ADME-Tox properties. The team comprises the unit director, who is clearly the most senior and recognized scientist in the unit.

The team has a number of national and international collaborations (although no direct involvement in EU projects at this time). They are involved in the Cdithem bioinformatics platform (IBISA label) to which they have contributed a rather unique resource about protein-protein interaction inhibitors.

The research output of the team over the last five years is very good. All team members are actively publishing (67 as a whole) and their work is well cited, indicating a good international impact. They have also published several key reviews that are being (and will most likely be) highly cited (3 in Drug Discovery Today; 1 Curr. Opin. Struct. Biol.). This is a highly visible team at the international level, publishing excellent quality research, both on methodology and application. Their expertise is well recognized as indicated by numerous oral contributions at conferences, editorial memberships of various journals and referee activities.

Assessment of the team's academic reputation and appeal

The team has quite a number of collaborations, both at the national and international level, in most case bi-lateral ones.

They have been successful in national funding and got support from industry as well. Although, their strong national network is not reflected in participation in large EU projects, they do have however connections to various EU projects/networks (e.g. eTOX).

The team members are also active as reviewer for well-known journals in the field and for funding agencies, including various EU programmes. All this is indicative of a good visibility and reputation of the team.

Young and senior members of the team have a well-established international reputation and visibility, with significant contributions to the field, as reflected in citation analysis.

Assessment of the team's interaction with the social, economic and cultural environment

Team 3 members deposited several patents, and manage several collaborations and support from the industry.

Team 3 has developed, published and made available to the whole community several original softwares dedicated to ligand docking (MS-Dock) or ADME-Tox predictions (FAF-Drug). Similarly, their original database will be essential for the emerging field of protein-protein interface inhibition.

The research topics concentrate around human health and as such have are socially highly relevant.

The targets they choose to concentrate on for the coming years are all highly relevant and associated with various important diseases.

Assessment of the team's involvement in training through research

All team members are deeply involved in teaching including the European master for in silico drug design, and in the doctoral school on drugs which is an inter university school.

The head of the unit is board member of this doctoral school and will take co-directorship in the future.

The team has further trained several PhD students and post-docs over the last years.

Assessment of the five-year plan and strategy

Team 3 has defined a plan and strategy for the coming five years with a strong focus on identifying and optimizing (potency, ADME-Tox) modulators of protein-protein interaction (PPI). Three main themes have been defined:

- Chemical space for modulating PPI;
- Hit Optimization & 3D Mechanistic ADME-Tox prediction;
- Applications to selected PPI targets.

Team 3 project works in a highly relevant and timely area of research in which the team has an excellent expertise, placing them in an excellent position to successfully carry out the proposed research.

Team 3 has already built a unique database of PPI modulators, iPPI-DB in order to initiate a global categorization of PPIs and to determine some class of PPI targets for which a clear and homogenous chemical subspace can be established.

This project also involved a more methodological part on software development for the docking of flexible peptides, and identification of binding pockets, building on the in-house MS-DOCK approach. This is potentially a part where the competition will be high and the team will have to demonstrate their performance to make an impact internationally. This part has direct links to team 1, the two teams working in synergy.

In addition, dedicated protocols will be developed for multi-parameter optimization for potency and ADME-Tox properties.

This project will benefit from the available results of the experimental screening of a 40,000 compound library on 4 selected PPI targets (screening performed at the Institut Pasteur de Lille/Inserm U761 in the context of the funded ANR Piribio project (coordinated by the director of the unit).

Conclusion

- Strengths and opportunities:

This is a timely project with promising preliminary results likely to enhance significantly the international visibility and impact of the team.

In general, the already existing expertise and the access to experimental data should give this project a head start for some aspects of the project. Maintaining and further developing collaborations with experimentalists will be crucial to ensure success since the team is dependent on experimental input and work from other parties. The collaborations in place are already very good which gives a good confidence that the team will meet the defined objectives in the coming period.

- Weaknesses and threats:

Lack of participation in EU networks and projects.

- Recommendations:

Increase participation to non-national networks (EU,…)

5 • Conduct of the visit

Visit date:

Start: January 18, 2013

End: January 18, 2013

Visit site:

Institution: Université Paris Descartes, INSERM U973

Address: 39 rue Helene Brion, 75013 Paris

Conduct or programme of visit:

08:00 Welcome to the committee (15 min)

1. Centering of the committee

8:15 Preliminary meeting of the committee (closed hearing) (30 min)

Attending: Committee members, AERES scientific delegate

2. Scientific part

8:45 Presentation of AERES evaluation and of committee members

(Jacques BARATTI and Gilles LABESSE)

8:55 Presentation of the unit project: Bruno VILLOUTREIX (30 min + 30 min discussion)

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

9:55 Scientific Presentation Team 1 - Pierre TUFFERY (20 min + 20 min discussion)

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

10:35 Scientific Presentation Team 2 – Anne Claude CAMPROUX & Olivier TABOUREAU (20 min + 20 min discussion)

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

11:15 Break (15 min)

11:30 Scientific Presentation Team 3 - Maria MITEVA (20 min + 20 min discussion)

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

3. Meeting with representatives of Institutions

12:10 (30 min discussion with committee members)

Attending : Committee members, AERES scientific delegate, representatives of University Paris Descartes (Marc BENEDETTI) and of INSERM (Marie-Josèphe LEROY-ZAMIA and L LOMME)

12:40 Lunch - buffet / discussion (90 min)

4. Meeting with researchers, technicians, doctoral students and post doctoral fellows

14:00 in parallel the committee splits into three groups.

Meeting with researchers

Meeting with technicians

Meeting doctoral students and post doctoral fellows

Attending: Committee members, AERES scientific delegate, without the leaders, representative of institution, without the direction of the unit and without team leader

5. Meeting with the unit Director

14:30 (30 min discussion with the committee)

6. Debriefing of the committee

15:00 Deliberation of the committee (closed hearing) (150 min)

Attending : Committee members, AERES scientific delegate

17:30 Thanks and leave of the committee

17:45 End

6 • Statistics by field: SVE on 10/06/2013

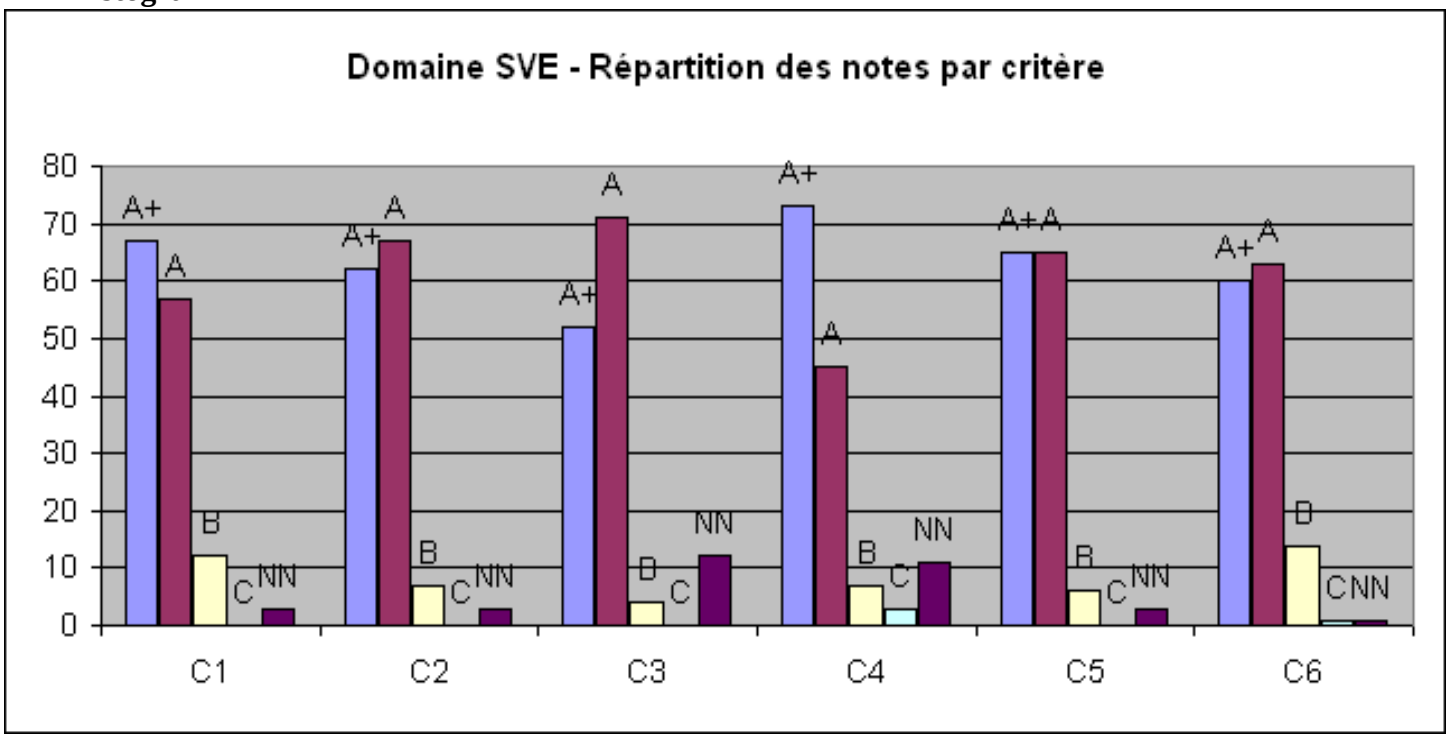
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

Le Président

P/VB/RL/NC/YM – 2013 - 076
Paris, le 15 avril 2013

M. Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

S2PUR140006436 - Recherche de Molécules à visée Thérapeutique par approches in silico, MTi - 0751723R

Monsieur le Directeur,

Je vous remercie, ainsi que les membres du comité de visite, pour l'envoi du rapport d'évaluation concernant le « MTi», rapport qui souligne l'excellence de la qualité de la recherche qui est produite, attestée par le haut niveau qualitatif et quantitatif des publications tant au niveau national qu'international.

Je me réjouis également des commentaires très élogieux qui sont portés sur l'appui solide tant de l'INSERM que de l'Université Paris 7-Denis Diderot à cette équipe.

Enfin, comme le comité le mentionne, l'équipe doit renforcer les collaborations en bioinformatique au niveau international, dans les infrastructures existantes ou par le biais de demandes de subvention à projets du 7e PC. L'établissement en tiendra compte, à la hauteur de ses moyens, notamment en termes de soutien au montage de projets européens.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de toute ma considération.

Vincent Berger

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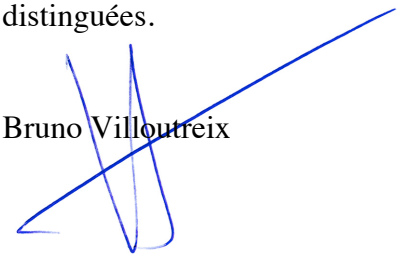
Le 10 Avril 2013

Monsieur le Président,

Veuillez trouver ci-après nos réponses à l'évaluation de notre UMR_S 973, Recherche de Molécules à visée Thérapeutique par approches *in silico* (MTi) par l'AERES.

Je vous prie de recevoir, Monsieur le Président, l'expression de mes salutations distinguées.



Bruno Villoutreix

Dear Colleagues,
Please find enclosed our comments about the AERES evaluation of our research unit.

Ref number for the report:
S2PUR140006436 - Recherche de Molécules à visée Thérapeutique par approches in silico, MTi - 0751723R

Director UMR-S 973: BO. Villoutreix

Overview of the research unit

First we would like to thank the AERES committee for providing very positive and constructive feedbacks about our research unit. Our group is indeed rather unique in France, as mentioned in the report, as it combines skills in the areas of chemoinformatics, bioinformatics and biostatistics. One of our goals is to develop new *in silico* approaches and protocols to assist the rational design of therapeutic molecules and to apply these tools and expertise in several therapeutic areas. As stated in the report, our group is well recognized in the field, is very active in terms of publications, grant applications, teaching, and is attractive to young and senior scientists and has numerous national and international collaborations. We were up to now organized in one single team but the committee is very supportive of our proposal for the next contract to work in 3 teams, each focusing on a well defined topic (team 1: structure-based peptide design, team 2: computational profiling and team 3: *in silico* screening of protein-protein interactions under ADMET constraints) but with a common goal (methodological developments in the area of *in silico* drug design with applications on selected therapeutic areas). The committee acknowledges the two platforms associated to our laboratory and the fact that they provide support to the scientific community. The continuous support from Inserm and Paris Diderot is also highlighted in the report and we would like to take this opportunity to here thank both, our institute (and corresponding ITMOs) and the university.

Points to improve in the unit

- The committee notes important international competitions in the field of protein-protein interaction and peptide modeling. We agree with this observation and it is also clear that the competition is fierce in the area of profiling. In fact the topics that we address are timely and critical and therefore, competition will be strong. However, we are already well established in these areas of research, we have the skills, the right collaborations, the financial supports to carry out our projects and each team has convincing publications on the addressed topics. As such, we believe that we will be able to face competition. The new organization of the laboratory in 3 teams should also have positive impacts.
- The committee mentions the lack of publications in very high impact factor journals. This is correct, as for the time being most of our papers have impact factors between 5 and 11. First, we all know that the best journals in the field of computational biology and chemistry tend to have impact factors in this range, as the community is smaller. Yet we also think that the new organization of the lab in 3 teams will help us to improve this point, as projects will be more focus. Further, the publications of some data is being postponed, as we want to accumulate sufficient *in silico* and experimental data prior to submitting papers in very high impact journals. At present, with the data at hand, we believe this should be possible for two unpublished projects since we have discovered compounds that are acting in relevant animal models.

Recommendations for the unit

- The committee suggests strengthening collaborations between the teams. If we look at our previous work (up to 2007), we note 14 publications that involve many scientists of the unit. We

also have projects involving all members of the lab and as such, internal collaborations are favored in our group.

- The committee also mentions to keep improving our teaching and we are indeed paying attention to this point. To succeed here, we have international scientists involved in our trainings from all over Europe as well as industrial partners from pharmaceutical companies.
- The committee suggests becoming more involved in FP7 or other European projects. In fact, one recently appointed professor in our lab is involved in 2 FP7 projects and we have submitted an application in the area of drug discovery in January 2013, the work passed the first review and we are now awaiting the final decision.
- The committee talks about keeping attracting additional scientists to the laboratory, especially in teams 1 and 2. In fact, a candidate who would like to join team 1 sent one Avenir application and we are very likely to get a new assistant professor position to join team 2 in September 2014. One foreign young scientist is also applying to Inserm to join team 3. We are thus actively working on this specific point.
- The committee suggests that we should extend our current scientific advisory board and invite international scientists. This is in fact ongoing and is indeed easy as we have many international contacts with leading scientists in the field.

Answers from team 1 (head: Dr. P. tuffery)

General

We first would like to thank the AERES committee for its assessment, highlighting that we are a team of developers, sharing our efforts between the RPBS platform (and the technological developments associated with it) and more fundamental efforts on peptide protein interactions and peptide design. As stated in the report, the RPBS platform is largely used in France and abroad, and some actions that we have initiated such as the MobyleNet project have resulted in the federation of web-based platforms in France. Our developments of methods have in the past tackled various areas of interest for the UMR-S 973, including pocket detection, ligand 2D/3D conformation generation, and also peptide de novo modeling, an important contribution for the team for the future project.

Points to improve and recommendations

The committee mentions a number of publications reasonable for developers: the number reported by the committee is 39 but is different from the one reported in our report and now validated by INSERM and the number should be indeed 44. Several of our publications have been published in the high impact factor journals of the field.

The committee relates few participation/invitations in international events. We agree that our participation in international meetings should be improved. Yet we would like to point out that, for instance, PEP-FOLD has been the subject of oral presentations in international meetings each of the past three years including the European Peptide Society meeting, at the end of 2012.

The competition in the field of protein-peptide interactions is high. In addition to the answers made above at the level of the Unit, we would like to point out that our project is Structure-based peptide design, i.e. not only protein-peptide interactions, and we intend to focus on structural aspects for which we have demonstrated skills validated by many publications.

The committee points out the need to increase the team visibility to get an impact at the international level. We are actively working to improve our visibility. Our participation to international meetings and the several contacts made should result in some new international collaborations. In addition, RPBS is also involved in the ongoing French application to ELIXIR.

The committee suggests us to work on attracting additional scientists possibly with complementary skills with the aim of facilitating experimental applications. We fully agree to increase our interactions with experimental teams. Contacts have been taken with NMR, X-ray and SPR expert teams in Montpellier, Nancy and Lyon, and one young scientist with an experimental background has been applying to the Avenir program.
The committee suggests demonstrating the method developments on various targets to avoid a bias towards specific application. The *in silico* methods that we develop are general and validated on protein/peptide data-sets that encompass much more than one particular target/family. It is for instance a point mandatory for de novo peptide structure predictions that have been validated over all folds experimentally available.

Answers from team 2 (head: Profs. AC. Camproux & O. Taboureau)

General

We acknowledge the reviewers for their discussions during the presentation of the newly formed team 2 during the visit of our unit and for their comments about the team in the written report.
We appreciate that the reviewers were enthusiast about the leading role of team 2 in training in bioinformatics and *in silico* drug design and we will continue to provide relevant, and of quality, course in this area.
We thank them about their positive assessment regarding the scientific quality and outputs in the area of druggability of targets, ligand profiling and multi-scale pharmacology.

Points to improve and recommendations

We recognize that pharmacology profiling is a very competitive area and the plan might appear ambitious compared to the available human resources present in the team. We would like to emphasize that we agree with the reviewers and to achieve our objective we will have to pursue our involvement into national and EU projects, in international and industrial collaborations with the leaders in our area of research in order to attract new grants and new scientists in our team. For example since the visit of the reviewers, we have a new engineer (IE for technical helps for three years from the "investissements d'Avenir" grant) that starts to work on chemogenomics and we are top-ranked by the university to hire a new assistant professor in 2014.
We aim to pursue our collaborations with external teams, experimental-, clinical- or pharma-based, highlighted as outstanding value by the AERES committee.

We understand that the reviewers think that the cooperation between scientists in team 2 seems low, but we would like to remind the committee that the team 2 got partially started in September 2012 with the arrival of a new professor and of an assistant professor. However, we would like to note that we have already started strong intra team interactions resulting, for instance, in publications in preparation based on a PhD co-direction involving different themes of team 2. Finally, grant applications are on going with the involvement of the 2 professors inside the team 2. We hope that this clarifies the situation inside team 2.

NB

We also noted some minor typos in the AERES table workforce. The number of permanent professors and similar positions as of June 2012 mentioned in the table is 4 but should be 3, the number of other EPST researchers noted is 2 but should be 1, the number of theses defended should be 2 (and not 3), the number of postdoctoral students having spent at least 12 months in the unit is 3 (and not 2) and the number of supervisors with an HDR should be 2 (and not 3). The numbers for the future project are correct.

Answers from team 3 (head: Dr. M. Miteva)

General

We would like to thank the AERES committee for the strong appreciation of the high quality of the past work and the timely research project. The acknowledged visibility of the team at the national and international level is highly appreciated. During the last few years we have been developing and successfully applied *in silico* screening protocols with the goal of identifying new potent hits for cancer, cardiovascular and rare diseases. We continue to work in the same therapeutic areas but we will now focus on modulating protein-protein interactions with drug-like molecules under ADMET constraints in order to develop high quality optimized hits. We strongly believe that we have the required experience, right skills, funding (both public and from private companies) and collaborations to fulfill successfully the objectives of our ambitious project.

Points to improve and recommendations

The committee notes that we are not currently involved in EU networks and projects. In fact, we have submitted a EU FP7 Innovation proposal in the area of drug discovery in January 2013, the work passed the first review stage and we are now awaiting the final decision. We intend to continue our efforts in this direction.

We would also like to underline our strong international collaborations with recognized scientists, for instance:
-cardiovascular diseases, the coagulation and complement cascades with Dr. Nicolaes, Netherlands; Prof. Dalback and Prof. Bloom, Sweden (PI from the silico side: the unit director).
-rare diseases with Prof. Alexov and Prof. Schwartz, USA; Dr. Ikeguchi, Japan (PI from the silico side: the team leader)
-ADMET predictions with Pr. Pajeva, Bulgaria; Prof. Wiese, Germany; Prof. Baell, Australia (PIs: the team leader and the unit director).

Indeed, these fruitful interactions resulted in a total of 22 joint publications with our collaborator scientists since 2007.
(Segers et al. PNAS 2007; Dahlback c est un J Biol Chem 2008; Lagorce et al. Bioinformatics 2011; Blom et al., J Immunol. 2008; Zhe et al. J Am Med Inform Assoc 2013; Martiny et al. in "Predictive ADMET: Integrated approaches in Drug Discovery and Development", J. Wiley & Sons, Inc. 2013; etc).

NB

We would like to note that the correct number of HDR supervisors expected in 01/01/2014 is 3 (2 is mentioned in the Table).

Also, it is written in the AERES report that Cdithem is a bioinformatics platform, in fact it is larger and is a Consortium for Drug Discovery & Chemical Biology dedicated to protein-protein interaction modulation employing several complementary methodologies: medicinal chemistry, cellular bioassays and protein chemistry and in silico predictions (the latter are ensured by members of the MTi team 3).