



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

Section des Unités de recherche

Report from the visiting committee

Research unit :

Recherche de Molécules à visée

Thérapeutique par approches in silico

University Denis Diderot



March 2008



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de recherche

*Le Directeur*

Jean-Jacques Aubert

March 2008



# Report from the visiting committee

## The research unit :

Name of the research unit : Recherche de Molécules à visée Thérapeutique par approches in silico

Requested label : UNIT-M INSERM

N° in case of renewal :

Head of the research unit : M. Bruno VILLOUTREIX

## University or school :

Université Denis Diderot - Paris 7

## Other institutions and research organization:

INSERM

## Date(s) of the visit :

March, 5<sup>th</sup> of 2008

# Members of the visiting committee



## Chairman of the committee :

Mr Michel KOCHOYAN, Montpellier

## Other committee members :

Mrs Marianne ROOMAN, Brussels, Belgium

Mr Juan FERNANDEZ RECIO, Barcelona, Spain

Mr Michael NILGES, Paris

## CNU, CoNRS, CSS INSERM, (représentant INRA, INRIA, IRD...) representatives :

Mr M. NILGES, Illkirch, INSERM CSS representative

No CNU representative was available at the date of the visit

# Observers

## AERES scientific representative:

Mr Pierre CHARDIN

## University or school representative:

Mr Philippe REGNIER, University Denis Diderot - Paris 7

## Research organization representative (s) :

Mrs Catherine LABBÉ-JULLIER, INSERM

# Report from the visiting committee



## 1 • Short presentation of the research unit

The unit includes :

- 7 scientists with permanent positions (4 researchers from INSERM, 1 Professor and 2 assistant professors from UP7)
- 6 administrative and technicians
- 5 PhD students
- 3 post-docs

Previously all of the members of unit, but one, were part of INSERM Units 726 and 648.

Among the 7 researchers with permanent position, 4 have a HDR and all (7 out of 7) are publishing according to AERES criteria.

Since January 2004, 6 students have obtained their PhD.

The members of the unit have produced 78 publications in peer-reviewed journals during the 2002-2007 period, among which some in high-level general-audience journals (PNAS), and the majority in the best specialized journals in the topics (J.B.C., J. Mol. Biol., Nucleic Acids Res., Biophys. J., Bioinformatics, J. Med. Chem....). 17 % of these publications are in the top 10 of their respective fields, and an additional 15% in the top 20.

This application is for a "unit-M" contract with INSERM and the Paris 7 University. This means the recognition and support by both partners as a laboratory primarily devoted to the development of methodological approaches for the improvement of human health.

## 2 • Preparation and execution of the visit

The scientific committee listened to an overall presentation by the head of the unit. Several issues were addressed including the scientific strategy, the human, technical and financial resources, the integration into the institutional and industrial environment, and the management. Then 5 short formal presentations of the main scientific themes that will be developed during the contract were given by scientists participating in the project. The morning session ended by a brief summary of the involvement of the unit members in teaching activities. During the afternoon, a poster session gave the committee the opportunity to discuss in greater detail with the scientists. The technical staff (6 persons) followed by the undergraduates and post doc researchers were then interviewed privately by the committee. The scientific council has deliberated in plenary session for 1 and half hour at the end of the day, in the presence of the INSERM representative.

## 3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

During the past period (2002-2007), the members of the unit, belonging to 3 different labs of the "Paris, left bank area" , have been mainly involved in 3 different lines of research :

- The development of structural alphabets to describe protein structure and the use of these alphabets for ab initio protein folding.
- In silico ligand screening both at the level of tool development and applications.



- Genome analyses and development of methods for comparative genomics.

The teams now joining to form the new unit have produced scientific achievements of very high quality with an even distribution of the papers, in terms of amount and quality, along the 3 original teams.

The scientists wishing to join the unit come from various fields of bioinformatics. They possess an impressive amount of theoretical and technical skills, ranging from molecular modeling and ab initio protein folding to in silico drug screening, chemoinformatics and genome analysis. They want to join forces in view of developing an integrated lab of “in silico” drug discovery with the aim of speeding up the drug discovery process and of lowering its cost, in addition to provide computer tools and databases publicly available to the scientific community.

Both aspects, the development of new tools for the screening and, in strong partnership with experimental labs, the discovery of lead compounds against innovative targets, will be pursued during the contract.

The project is ambitious and in a field occupied by very few academic labs nationwide, although a strong need for such expertise obviously exists, as testified by the numerous collaborations developed by the members of the unit.

#### 4 • Specific appreciation team by team and/or project by project

For the forthcoming period, the projects are focused on the development and use of computer-assisted methods for the design of new drugs, and on in silico ligand screening. Two main lines of research are proposed :

- The improvement of existing tools and the development of new tools for in silico screening, and in particular (a) The improvement of the modeling techniques applied to potential protein targets of unknown structure, and more precisely to the often poorly defined loop regions in these structures, using the structural alphabet approaches and (b) The development of faster and more efficient protein-ligand docking methods based on a better systematic characterization of the binding pockets, the use of alternative modeled structures to take into account the target flexibility, and the rationalization of the choice of the most appropriate scoring function. In the medium/long term, the development of free energy calculations upon ligand binding will also be considered : (a) the development of ADME/Tox filters and 3D libraries of ligands, and (b) The use of genome analyses to identify potential new targets.
- The application to new targets: Projects focused on specific targets will be performed in collaboration with experimenter teams. Some have already started, either in the context of national consortia (i.e. CEDITEM, Oxford Structural Genomics), or with individual teams. Among the projects with the CEDITEM consortium, the one aiming at targeting protein-protein interfaces is certainly the most challenging and interesting.

#### 5 • Appreciation of resources and of the life of the research unit

The project will be carried on by scientists and technical staff with a strong will to collaborate and work synergistically towards a well-defined and challenging goal. The strategic choices have been made consensually by all the participants, and the team leader has full support from them. Furthermore, the team leader is internationally recognized at in the field of chemoinformatics and in silico drug design.

The team is strongly supported by the Paris 7 University, which has allocated 350 m<sup>2</sup> in its newly built campus on the Bercy site.

Several members of the future lab are strongly involved in teaching at the university and are starting a new European master in partnership with other Universities in Spain and Sweden. Lastly, the new team will host the Paris Bioinformatics Platform that provides access to computing facilities and tools developed by the lab to the academic community.



## 6 • Recommendations and advice

### – Strong points :

- A strong desire of all the participants to create a lab together and to reinforce and extend their collaborations, as well as a strong support of the Paris 7 University.
- The wide and complementary technical and methodological expertise of the members of the new team in protein modeling, in silico screening, and in the development of new tools (docking/scoring functions...).
- The several collaborations with external experimentalists for research on specific targets of biomedical interest.
- The active participation of several undergraduates and post docs to the project.
- The involvement in teaching both at Paris 7 and in the European master in Bioinformatics.
- A very weak involvement of other academic labs at the national level in this field, which is of great interest in view of speeding up and decreasing the costs in the drug discovery process.

### – What needs to be improved :

- The added value of participating to the project is not obvious for the scientists of the team involved in the "genomics" project, but this does not seem to be a concern for any of the participants.
- The analysis of docking in terms of absolute binding free energy would benefit from the development of novel energy potentials not currently addressed by the research project.

### – Recommendations :

The committee fully supports the project and recommends :

- The involvement in developing ADME/tox, a 3D repertoire of ligands, is very technical and should be given lower priority than the other projects that are much more ambitious.
- A wider opening to foreign collaborators (Master students, post-docs) is recommended. The European master that they are organizing can be an excellent opportunity for that.
- Members of the unit are encouraged to strengthen oral communication of their most interesting results in international events.

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Paris, le 22 Mai 2008

**Volet général annexé au rapport d'évaluation rendu public**

**Answers to the Aeres questions and recommendations for the MTi project  
(Inserm-Paris 7 - Diderot)  
Head: Dr. Bruno O. Villoutreix**

We first would like to thank the committee for analyzing our application and for their full support.

**The committee suggests improvements on the following topics:**

a) *“The added value of participating to the project is not obvious for the scientists of the team involved in the “genomics” project.*

We believe that it is important to master *in silico* know-how, concepts and methods, from *in silico* target validation/characterization to *in silico* screening and hit-to-lead optimization. For instance and for some projects like infectious diseases or cancer, comparative genomics can shed light on relevant targets that could then directly be analyzed via different structural bioinformatics methods mastered in the lab. and go through *in silico* screening experiments (in collaboration with our partners biologists, clinicians, chemists). In addition and to illustrate our point with a simple example, it is beneficial to compare binding sites within the same genome or across genomes to, for instance, put priority on a target, define relevant zones for specificity and selectivity, for defining sequence-structure-function relationships. Therefore, some ongoing “genomics” projects and related methodological developments will be carried out within the frame of a drug discovery/chemical biology endeavor. Integration and mining of structure-function data, both, from the side of the chemical compounds and from the target side, are definitively important at this time, new methods are needed and the group has an established track record along this line that is important to preserve (*Bajorath, J. Curr Opin Chem Biol. 2008 Mar 12; Gregori-Puigjane & Mestres, Curr Opin Chem Biol. 2008 May 2; Harris & Stevens, DDT, 11 : 880-888, 2006; Stockwell, Nature 432 : 846-854, 2004*). We will thus combine *in silico* “genomics” approaches with virtual screening and related chemoinformatics strategies as we believe that tomorrow’s cutting edge projects will require all these different skills to be present in the same laboratory to be treated successfully.

*b) The analysis of docking in terms of absolute binding free energy would benefit from the development of novel energy potentials not currently addressed by the research project.*

We indeed plan to work on developing new scoring functions and work along relative free energy computations but not absolute binding free energy in its conventional definition per se (Huang *et al.*, *Phys Chem Chem Phys*, 2006, 8, 5166). Definitely some terms could be added or have to be re-visited, solvation energy for instance needs attention and so does the “so-called” ligand strained energy (Rajamani & Good, *Curr Opin Drug Discovery & Development* 10:308-315, 2007). On the other hand, we do not think that it is appropriate for our group at this time to develop a new “forcefield”. Yet, we will put a strong emphasis on defining new ways and, if possible better ways, to rank molecules in the context of a large *in silico* screening experiment, or via relative free energy calculations, when the number of compounds is tractable through such type of computation.

**The committee recommends:**

*a) The involvement in developing ADME/Tox, a 3D repertoire of ligands, is very technical and should be given lower priority than the other projects that are much more ambitious.*

We agree with this recommendation. We have one ongoing project on ADME/Tox that will soon end and we will not re-develop yet another compound database. Such work will be carried out by our partner, the RPBS (Ressource Parisienne en Bioinformatique Structurale) platform, if judged appropriate by the scientific committee in charge of the project.

*b) A wider opening to foreign collaborators (post-docs, Master students) is recommended. The EU master that they are organizing can be an excellent opportunity for that.*

We agree with this comment but it should be borne in mind that while during the AERES visit we had no foreign post-docs or visiting professors in the laboratory, we used to have visiting scientists in the group. For instance, in 2006-2007, Tania Pencheva (Associate Professor in Sofia) was visiting us from the Bulgarian Academy of Science through a grant from the Paris City Hall. Along this line, Dr. WH. Lee from the Scripps Clinic and Research Institute (La Jolla, USA) spent about 2 years in the group (2004-2005) and is now senior scientist at the Structural Genomics Consortium in Oxford, UK. However, we again fully agree with the committee that foreign scientific visitors are extremely important for a laboratory as they bring different ideas, different concepts and experiences. Definitely, we will work on finding funding to invite foreign scientists and the new EU master that we are setting up will also contribute to diversifying our recruitment efforts in this direction.

*c) Members of the unit are encouraged to strengthen oral communication of their most interesting results in international events.*

We mentioned in our application about 55 invited presentations (national and international) these last 5 years. As such, we consider that we do take part to many congresses in France and abroad. Several exciting results in the lab., such as novel

inhibitors modulating protein-protein interactions, are being patented and, unfortunately, can not be discussed during a meeting this year nor next year. However, we will present new methods, theoretical approaches and applications in some major congresses when appropriate.



Bruno Villoutreix