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Génétique moléculaire évolutive et médicale

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Génétique moléculaire évolutive et médicale.
of the University Paris 5



March 2009



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et de l'enseignement supérieur

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of the University Paris 5



Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

mars 2009



Evaluation report)

The research unit :

Name of the research unit : Molecular Evolutionary and Medical Genetics

Requested label : UMR_S INSERM

N° in case of renewal : U571

Head of the research unit : M. Ivan MATIC (former director: M. Miroslav RADMAN)

University or school :

Université Paris 5

Other institutions and research organization:

INSERM

Date of the visit :

February 4th, 2009

Members of the visiting committee



Chairman of the committee :

M. Didier MAZEL, University of Paris 7

Other committee members :

M. Angus BUCKLING, University of Oxford, UK

M. Giora SIMCHEN, The Hebrew University of Jerusalem, Israel

M. David LEACH, University of Edinburgh, UK

Ms. Nora GOOSEN, University of Leiden, The Netherlands

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

Ms. Nathalie DOSTATNI, CSS INSERM representative

Observers



AERES scientific representative:

M. Philippe BOUVET,

University or school representative:

M. Bruno VARET, University of Paris 5

Research organization representative :

Ms. Chantal LASSERRE, INSERM

1 • Short presentation of the research unit

Total number of lab members: 35 Including:

- Researchers with teaching duties : 1
- Full time researchers : 3
- Postdoctoral fellows : 14
- Engineers, technicians and administrative assistants : 10 (9,5 ETP)
- PhD students : 7, all with a fellowship
- Number of HDR : 3
- Number of students who have obtained their PhD during the past 4 years : 11
- Average length of a PhD during the past 4 years : 4 years
- Number of « publishing » lab members : 4 out of 4

2 • Preparation and execution of the visit

Program of the visit

Morning :

- Door-closed meeting : AERES representative
- Short visit of the laboratory
- General Presentation by the future director of the Unit
- team 1 : Evolutionary strategies
- team 2 : Molecular biology of resilience and survival
- team 3 : Evolutionary systems biology

Afternoon :

- Posters
- Researcher committee meeting
- ITA committee meeting
- Students and Postdoctoral Fellows committee meeting
- Experts with the director of the Unit
- Door-closed meeting : AERES representative, University and INSERM representatives
- Door-closed meeting : AERES representative

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

The Committee was very impressed by the quality and originality of the research performed in this unit and considers it among the top 10% of international research. In continuation of their past activity, the team leaders have made several outstanding contributions and breakthrough in the fields of bacterial cell cycle and chromosome repair during this 4 years period. This unanimous conclusion is supported by an analysis of the publication record of the different teams, which is uniformly excellent, as well as by the international prominence of the three team leaders within the Unit.



In addition, the Unit has a proven record in attracting funding at the highest level and in training excellent students and postdocs from international origins. Scientific excellence, as well as a common interest in molecular evolution and single cell technology, brings together those 3 teams into a very effective and interactive unit.

The Committee was very pleased with the level of integration and collaboration within the Unit, mentioned by all unit members (from students to PIs), which is reflected in several publications authored by more than one team and in the intricacy of several projects. The Committee also emphasized that, if unusual for France, the “à l’anglo-saxone” organization of this unit (only 4 staff scientists for 21 students and postdocs, 7 technicians) was an extremely successful example in their case. The committee was also impressed by the number of national and international collaborative projects tied by the PIs of the unit. They also appreciated the effort made in terms of technological developments, especially in microscopy and accompanying image treatment softwares. Finally, the Committee appreciated the positive and science-driven management by the Head of the Unit and the team leaders, who maintain an excellent and nurturing environment.

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

Team 1: DNA repair, stress responses and aging.

This team is composed of 1 Researcher, 1 Research Engineer, 5 post-doc and 2 graduate students.

28 publications, among which 2 Science (1 with teams 2 & 3, 1 with team 2), 1 EMBO J, 2 PNAS USA, 1 PLoS Pathogens, 1 PLoS Genetics, several Molecular Microbiology, J Bacteriology.... reports

This team has continued to contribute massively to our understanding of DNA repair and evolvability over the last 5 years. It has shown an almost unique ability to integrate sophisticated molecular microbiological techniques with cutting-edge evolutionary thinking and is arguably one of the few top groups in this field in the world. Mismatch repair plays an important role in all kingdoms of life to prevent accumulation of mutations resulting from replication errors. Under stressful conditions, however, it is advantageous to increase mutation rate. This team has nicely shown that in aging colonies of *Escherichia coli* this can be achieved by down regulating the mismatch repair genes and up regulating the *dinB* gene. They have identified *RpoS* as an important factor in this modulation of expression. They have published several key papers in this area. In collaboration with Team 3, they also developed an *E. coli* - *C. elegans* model system to investigate host-parasite evolutionary ecology from two very novel angles, and have shown that rates of nematode aging varies with exposure to bacteria that differ in virulence . Another key area is understanding the maintenance of apparently maladaptive *E.coli* virulence factors, which allow colonisation of host tissues in relation to the inflammatory responses. Understanding why virulence factors are maintained is clearly of great applied importance. These projects are very promising firstly because they will largely benefit from the excellent expertise of the team in the genetics of *E. coli* adaptive variation and secondly, because they are strengthened by collaborations with specialists in immune response to bacterial infections both in the vertebrate and invertebrate systems outside the unit. This work will certainly have important impacts on the understanding of the emergence of pathogens from resistance to the host immune system and/or from fights with other microorganisms. The Committee is in no doubt that the team will continue to be an important player in these fields.

DNA REPAIR, STRESS RESPONSES AND AGING

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+



Team 2 : Biology of Robustness

This team is composed of 1 Professor, 1 Researcher (50%), 1 Research Engineer, 3 post doc, 1 graduate student

16 publications, among which 4 Science (2 with team 1, 1 in collaboration), 1 Nature, 1 Cell, 1 PNAS USA, 1 PLoS Genetics, several Molecular Microbiology, J Bacteriology.... reports

This team explores the mechanistic basis for living cells robustness on specific bacterial and eukaryotic models. The research on the robustness of species like *Deinococcus radiodurans* to desiccation and radiation is extremely interesting. Until now the work has mainly focused on the resistance of the DNA to irradiation which has led to the identification of a very efficient mechanism to reassemble completely scattered chromosomes into intact copies.

They have published several key papers on this process. They have extended these studies to the resistance of proteins to the massive oxidative damage caused by irradiation and desiccation. They have nicely shown that somehow protein in *D. radiodurans* are protected from oxidation and their main goal is to identify the substance(s) responsible for this protection. The approaches that are chosen are novel and very challenging. The team is now extending their research on robustness by including eukaryotic species like rotifers and tardigrada which have the extraordinary capacity to revive after extreme desiccation. To identify the molecular mechanism of the protection of these organisms several lines of research will be set up. Some of these are more or less straightforward (i.e. quantification of ROS and oxidation), others are much more challenging (i.e. identification of 'protectors') but very original.

BIOLOGY OF ROBUSTNESS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+

Team 3 : Evolutionary systems biology.

This team is composed of 1 full time Researcher, 1 half-time Researcher, 6 post doc, 4 graduate students

28 publications, among which 1 Science (with Team 1 & 2), 2 PLoS Biology, 2 PNAS USA, 1 PLoS Pathogens, 1 PLoS Genetics, several Molecular Microbiology, Microbes and infections.... reports

This team is interested in understanding the cause of the phenotypic differences between single, isogenic cells in a constant, homogenous environment. They are at the forefront of international research in the field and made several seminal works over the last 4 years period, through the development of novel image acquisition and analysis tools in microscopy approaches to follow on single bacterial cell fate, over 1000 generations. They have started to study aging in bacteria and for the first time been able to demonstrate aging and death of the model bacterium *E. coli*. The group has developed a strong and original research in the definition of aging in bacteria that they found correlated to the accumulation of protein aggregates in old cells. These important discoveries made use of powerful imaging system built up in the lab to tackle these questions at the level of individual cells. The team proposes to continue on this line to study the processes involved using genetics and to develop new tools based on nano-imaging and micro-fluidics technology to link aging in bacteria with changes in the cell morphology, in the elasticity of cell membranes and search for new cellular structures specific of aging. As protein aggregates have been implicated in neurodegenerative disease in humans, the research in the team although fundamental could provide important idea in the treatment of such diseases. The team has recruited collaborators with various expertises and has several collaborations outside the unit in microfluidics and nanofabrication as well as with statisticians and theoretical biologists.



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A+	A+	A+	A+	A+

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

The Committee was impressed by the excellent scientific and human relationships within the Unit, which occur despite the spatial division of the Unit over the 2nd and 6 th floors. Scientific interactions are positively encouraged by means of weekly journal clubs and lab meetings. The spatial organisation of lab in a single large room favours the mixing of the people from the different teams, and reinforce the close scientific links between the three groups. This organization has been exceptionally productive and innovative. It is obviously internationally very attractive, as student and postdocs are of various origins (France, Europe, USA, China...). It is also a very interdisciplinary environment, with molecular biologists, bioinformaticians and mathematicians working side by side. Two of the four staff scientists of the unit are particularly involved in an interdisciplinary doctoral school, that they created 4 years ago, and which has already achieved considerable national and international success. The lack of a very hierarchical structure is also very much appreciated by the technicians and engineers of the Unit. Funding of the unit is mainly based on grants from various programs which complement the main recurrent funding given by the Inserm. The only concerns raised by the committee was the small number of staff scientists and the consequent precariousness of the teams, especially in light of the retirement of one of the team leaders, which should occur at at the end of the next 4 years period of the Unit.

6 • Recommendations and advice

• Strengths :

U571 operates as a highly-effective consortium and represents a model for similar Units in France and abroad. Its strengths include a diverse but well-integrated portfolio of cutting-edge research, the use of both bacterial and eukaryotic models allowing for cross-species validation and the establishment of innovative technological development in microscopy and image treatment as a common resource within the Unit. In addition, the Committee feels that the Unit derives much strength from its atmosphere of collegiality and scientific aspiration, which binds different teams together and acts to inspire and motivate the entire staff.

• Weaknesses:

The Committee considers that the future location in two different sites would weaken the interactions between the 3 teams, and if this separation is unavoidable at present, efforts should be made by the Paris 5 university to regroup them rapidly to limit the separation to a minimal transitory period. A second weakness is the small number of staff scientists, which is a threat for the continuity of their expertise. This will soon be the case with the retirement of one of the 3 team leaders, which will occur during the next 4 years period. Another weakness pointed by the technical staff and the microscopy users (students and postdocs) is the lack of a real microscopy engineer. The committee was also concerned by the extremely low funding by the University (despite hosting which has not been evaluated).

• Recommendations :

The Committee fully endorses the current management of the Unit. The Committee also recommends that, if at all possible, the Paris 5 university considers consolidating the entire Unit into a single site. The university should prepare the future by opening a professor position to replace the team leader who will soon retire, and secure the rather small stable scientific staff of this unit. The committee also recommends the recruitment of a technician/engineer specifically trained in microscopy, and able to insure the maintenance of the 3 stations and the training of the users. Finally, the Committee encourages the Paris 5 university to give more support to this exceptional unit.



Génétique moléculaire évolutive et médicale

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+

Le Président
Axel KAHN

Paris, le 27 mars 2009

DRED 09/n° 101

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité **UMR-S 571** «**Génétique moléculaire évolutive et médicale rattachée à mon établissement**».

L'Université, consciente de la qualité remarquable de l'UMR-S a dégagé d'importants locaux au sixième étage du site Cochin pour permettre à cette unité de redéployer une partie de ses activités déplacées par la fermeture pour quelques années des bâtiments universitaires du site Necker, et contribue à ses aménagements.

L'Université a bien reçu le message concernant la succession universitaire de l'actuel directeur. Ceci sera envisagé en tenant compte des contraintes inhérentes au système hospitalo-universitaire français actuel.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université



Axel Kahn

**DIVISION DE LA RECHERCHE
ET DES ECOLES DOCTORALES**

Paris, le 31 mars 2009

UMR-S 571 Laboratoire de génétique moléculaire évolutive et médicale

Retour sur le rapport du comité AERES – Observations de portée générale

Pas d'observations.