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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

Department for the  
evaluation of research

AERES report on unit:

Robustness and Evolvability of Life

Under the supervision of  
the following institutions  
and research bodies:

Université Paris Descartes

Institut National de la Santé et de la Recherche  
Médicale





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**



## 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: **Robustness and Evolvability of Life**

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

- Grading table of the team: **Avoidance and Repair of Biological Damage**

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

- Grading table of the team: **Systems Engineering and Evolutionary Dynamics**

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



## Evaluation report

Unit name :	Robustness and Evolvability of Life
Unit acronym:	
Label requested :	
Present N°:	INSERM U1001
Name of the director (2012-2013) :	Mr Ivan MATIC
(2014-2018) :	Mr Ivan MATIC

## Expert committee members

Chair :	Mr.Dominique SCHNEIDER, Université Joseph Fourier (representative of CNU)
Experts :	Mr Michael LASSIG, University of Cologne, Germany  Mr Bernard de MASSY, CNRS, France (representative of INSERM CSS)  Mr Csaba PAL, Biological Research Centre of the Hungarian Academy of Sciences, Hungary  Mr Gaël YVERT, CNRS, Ecole Normale Supérieure de Lyon

### Scientific delegate representing the AERES :

Mr Jacques BARATTI

### Representatives of the unit's supervising institutions and bodies:

Ms Marie-Josèphe LEROY-ZAMIA, INSERM

Ms Catherine LABBE-JULLIE, University Paris Descartes



## 1 • Introduction

### History and geographical location of the unit

Historically this group was created in the late 1980-ies at the CNRS Jacques MONOD Institute (Mutagenesis Unit) in Paris. In 1998, the group moved to Inserm (Necker Medical School), founding the E9916, then U571 that was localized on two different floors (second and sixth). The unit U1001 was created in January 2010 as a successor of the U571 laboratory. They recently all moved at the same geographical location at the Medical School of University Paris Descartes. The most important modification of the laboratory organization in the next funding period will be the fusion between two teams after the administrative (but not scientific) retirement of the most senior researcher at the end of 2013. Starting from January 1<sup>st</sup> 2014, the unit will be composed of two teams: "Avoidance and Repair of Biological Damage" and "Systems Engineering and Evolutionary Dynamics". The unit is located at the Medical School at Paris Descartes.

### Management team

Director of the unit: Mr Ivan MATIC.

Head of team 1: Mr Ivan MATIC.

Head of team 2: Mr François TADDÉI.

### AERES nomenclature

SVE1\_LS1, SVE1\_LS2, SVE1\_LS6, SVE2\_LS8, SVE2\_LS9.

### Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
<b>N1:</b> Permanent professors and similar positions	1	1	1
<b>N2:</b> Permanent researchers from Institutions and similar positions	13	13	13
<b>N3:</b> Other permanent staff (without research duties)			
<b>N4:</b> Other professors (Emeritus Professor, on-contract Professor, etc.)			
<b>N5:</b> Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	9	9	9
<b>N6:</b> Other contractual staff (without research duties)			
<b>TOTAL N1 to N6</b>	<b>23</b>	<b>23</b>	<b>23</b>
<b>N6:</b> Other contractual staff (without research duties)	100,00 %		



<b>Unit workforce</b>	<b>Number as at 30/06/2012</b>	<b>Number as at 01/01/2014</b>
Doctoral students	6	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit*		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	4	



## 2 • Assessment of the unit

### Strengths and opportunities

All members of the Committee were impressed by the quality and innovative aspect of the research that is developed in this unit. The research is grounded in key biological questions, and aimed at testing exciting and timely hypotheses. The unit level ranks highly likely within the top 10% at the international level.

During the last period, the two teams developed four special strengths: i) they provided outstanding contributions and breakthrough in the fields of bacterial mutagenesis and ageing, as evidenced by their publication record which is constantly excellent; ii) the attractiveness of the PIs (both to get outstanding people in the lab and funds); iii) the training of excellent students and postdocs from all over the world; iv) the development of invaluable technological tools, including time-lapse microscopy and accompanying image treatment software, microfluidics and single-cell technology. Moreover, a solid level of integration and collaboration exists between the two teams. This was evidenced through the discussion with all the lab members (from students to PIs) and by several publications co-authored by members of the two teams. Indeed, the research projects are complementary, one team being driven by molecular mechanisms and investigating them not in a reductionist way but in exploring the implications in terms of population and evolution, and the other team being driven by the dynamics of phenotypic variability at the single-cell level and developing experimental strategies based on models. Both teams use transversal approaches from biology to mathematics.

The Committee was also impressed by the nice “flat” horizontal organization of the unit, everything being discussed in a collegial way between the small number of permanent PIs (4 staff scientists). The organization is also based on an impressive number of national and international collaborations and on an extremely efficient scientific management.

### Weaknesses and threats

The committee has identified very few and quantitatively small weaknesses. We note a certain disconnection between some research lines of the team 2 (on cooperation and ageing) and the “Towards citizen and playful science” plans. While the main research program and the teaching efforts are each highly positive, the research efforts should be concentrated on the main lines that can be maintained at top level, in order to avoid a too large diversification. The committee also found the link with evolutionary theory loose in some projects (*e.g.* the effect of sex on cooperation), which may limit the impact of the work in the field of evolutionary biology and which could be addressed by increased collaborations with theorists.

A second weakness is the small number of staff scientists, which is even more important after the retirement of the senior permanent researcher, which will happen in about one year. On a practical note, the group’s working space is small, which was a complaint heard from several lab members and may also compromise the attraction of students for the planned projects.

The research unit in its current state has no unit council with representatives of lab members. Although it works well without it for the moment, such a council would not require much work for them to organize, and it is important when problems arise.

### Recommendations

The University Paris Descartes has provided a nice space allowing the two teams to work now at the same geographical location. They will continue to develop their strategy of sharing expertise with a unique setup where the two lab spaces are fused into one single large laboratory. Their scientific productivity now leads them to develop new research projects and to increase their highly successful investment in attracting and training students. This will undoubtedly result in the emergence of new research groups that may arise internally or from newly recruited researchers. Moreover, recruiting staff scientists will be important, first to consolidate the projects - particularly those relying on novel specialized tools - and also to cope with the retirement of the senior permanent researcher. On a more practical level, the research unit should develop a dedicated web site, with up-to-date information on ongoing projects, publications and activities of senior scientists, Ph.D. students alike.





### 3 • Detailed assessments

#### Assessment of scientific quality and outputs

The activity of the research unit during the last four-year period was characterized by a very strong track record in microbial evolutionary genetics, including analyses at the population and single-cell levels. Breakthrough discoveries have been made in bacterial mutagenesis, cell biology and ageing, relevant to all biological systems. These studies have been possible owing to the development of innovative technological tools that are made available to the scientific community through many fruitful collaborations with national and international laboratories.

The outstanding activity of the research unit is evidenced by its scientific output, with a total of more than 40 peer-reviewed publications, 9 book chapters and 4 patents. The production is indeed excellent, involves collaboration when needed and the results are almost exclusively communicated in top-ranked journals (*Nature Comm.*, *Science*, *Cell*, *Proc. Natl. Acad. Sci. USA*, *PLoS Genet.*, *Mol. Sys. Biol.*, *Current Biol.*, *Nucleic Acids Res.*, *DNA Repair*). All topics that have been developed in the research unit have been successful in terms of output. Moreover, important efforts are made to popularize science with two publications for popular science, many communications with media (numerous public interviews, newspaper, radio, TV), and a large EC-funded project "Towards citizen and playful science".

#### Assessment of the unit's academic reputation and appeal

The outstanding achievements of the research unit both at the levels of their excellent publications and of their state-of-the-art equipment result in an excellent ability to attract students, postdocs and collaborations at the national and international grounds. The two teams either coordinate or participate actively in international networks supported by competitive funding (Human Frontiers, FP7 from EC, national and transnational ANR, Labex). As the projects have applications in environmental and medical sciences, the PIs also developed a strong ability to get funds from private companies and from industry. This research unit represents therefore a very attractive scientific environment, well positioned at the international level. This outstanding scientific environment proposed by the two PIs was mentioned during the discussions that the members of the Committee had with all the members of the research unit (technical staff, students, post-docs and permanent staff).

The success of the research unit is also obvious when looking into the careers of previous lab members, with for example one former PhD student being now established elsewhere with an ERC grant. Moreover, education is at the heart of the activities of the research unit, one team leading an innovative project of education with very substantial funding.

More generally, members of the research unit participate in various scientific committees, one member is the founder of the Mediterranean Institute for Life Sciences, and one team leader is associated editor at *PLoS Genetics*, expert in many review panels and funding agencies worldwide, and co-organizer of international meetings (Stress meeting) and of the French 3R meeting.



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

The research unit has a broad interest and allocates much effort into the communication of science (concepts, knowledge, and technology) towards the public. Several members of the unit have regular and diverse communication activities: interviews and work-related articles in national and international newspapers, on television and radio; public debates and lectures; science festivals.

Education is another facet of the activities of the research unit. Besides the fact that members of the unit take part in the High Council on Education and other administrative bodies of the university, two main innovative educational programs are developed, one over the last decade and one very recently. The research unit established over the last decade groups of students who participated in the iGEM competition, challenging the creativity of undergraduate students to design interesting synthetic biological circuits. The involvement of the research unit in this contest was highly successful with many medals including mostly gold medals over the years. More recently, one team of the unit developed an innovative project based on the crowdsourcing of data and on the analysis of information networks leading to discoveries. The project is based on the contributions of citizens, and the overall program is funded and connected to various social partners (ethical, social and organizational issues) and to industry.

The research projects of the two teams have potential applications at the short term in public health (mechanisms of ageing and of microbial adaptation to antibiotics). These “applied” aspects of the research provide opportunities for obtaining additional research funding, and help disseminate the results of their studies to a broad public. A staff scientist is co-founder of a company which aims at innovating in the field of biofuels by taking advantage of bacterial metabolism. In addition, collaborations have been developed with private companies. These applied aspects of the research resulted in two articles for general audience, four patents, and numerous public interviews.

Altogether, the investment and innovation of this unit, both in outstanding basic research and in promoting economical development, is very unique in France.

### Assessment of the unit's organisation and life

The last period was characterized by different geographical locations of the teams constituting the unit (at the second and sixth floors at Necker Medical School in Paris). The coming period is characterized by the co-localization of the two teams at 420 m<sup>2</sup> at the Medical School of the university Paris Descartes, and the unit will greatly benefit from this improved situation.

All members of the Committee were truly impressed by the outstanding scientific environment and excellent social relationships within the research unit. Both scientific and social interactions benefit from sharing laboratory and office spaces by the people of both teams and common group meetings on a weekly base.

This organization benefits both teams through strong collaborative projects, while each team preserves its own specific, but still complementary, projects. The overall unit is structured horizontally without a formal hierarchy, which was very positively appreciated by all members of the Committee. This organization provides the opportunity to share all equipment and even, when administratively possible, the synergistic use of research funding. Therefore, the decisions about scientific and political strategies of the unit are taken collegially among the senior scientists. The unit is equipped with most state-of-the-art technological tools in the field that are fully available to all people of the two teams.

The period starting at 2014 will however be characterized by the retirement of the most senior of the permanent researchers and the members of the Committee emphasized that this situation should also be the opportunity to reconsider the recruitment of permanent staff, in order to complement the existing strengths of the teams. Moreover, one of the permanent researchers plays a key role in his team's (team 2) scientific output and will undoubtedly be able to lead an autonomous group in a near future. Together with the recruitment of a successor to the most senior permanent researcher, the research unit will have significant opportunities to complement its research program.



### Assessment of the unit's involvement in training through research

Members of the research unit are involved in teaching in several graduate and postgraduate programs. The research unit benefits from a Ph.D. program called "Frontières du Vivant" that was developed by the PI of one of the two teams. This is an interdisciplinary program recruiting students with multidisciplinary research projects. Besides this specific Ph.D. program, the research unit also welcomes students from more conventional Ph.D. programs. Therefore, the research unit has developed a unique situation in France, whereupon the members can attract not only good students, by providing them with additional opportunities for Ph.D. fellowships, but also graduate students from other disciplines like physics or computer science. Additionally, the iGEM contest, and the success rate of the unit's participation, also provide an unprecedented way to attract students and importantly, at an early education stage.

The research unit also motivates most young members to teach, and this is an important way for them to mature as scientists and mentors. All students mentioned that they work in a very positive and motivating scientific environment. The students are globally very motivated and committed to their research. They also have opportunities to travel to national and international conferences. This situation results in students with good publication records and promising career opportunities. One former student of the research unit has established his own group elsewhere with an ERC fellowship.

### Assessment of the five-year plan and strategy

The next period will be characterized by the structuration of the research unit in two teams, after the retirement of the senior permanent researcher who was leading a third team during the previous period. The latter team will be included into one of the two other teams.

The project of team 1 will explore five main directions during the next five-year period (origin of spontaneous mutations, effect of sub-inhibitory concentrations of antibiotics on mutation rates, genome-wide visualization of mutations, generation and maintenance of diversity, and ageing). Some of these projects rely on completely novel hypotheses that build on recently published data (involvement of protein carbonylation in ageing), on novel technological developments (direct visualization of mutations without relying on their fitness effects), and on "old" questions but addressed in an innovative and original way. The originality and research strategy of these projects are very interesting and convincing. Moreover, this fundamental research has a great potential to contribute toward human health.

The project of team 2 will be developed along two research themes (ageing and cooperation), a teaching program and a novel approach of 'citizen science'. The research projects are exciting, ambitious and of fundamental importance, and use state-of-the-art tools. The risks are limited since preliminary results have been gathered revealing both their feasibility and high probability of success. The ambition to develop highly innovative technological tools will be pursued as well as the interdisciplinarity of the approaches. The committee foresees an interesting development within this team, as one permanent researcher has a strong line of research that is complementary to that of the PI. This permanent researcher should be in a position to establish an independent team in the future.

As for the entire research unit, the members of the Committee were really impressed by the quality and originality of the proposed projects. Moreover, they are really well-structured and show very clearly that the two teams are fully complementary, sharing common themes (single-cell experiments, ageing) but preserving their own focus based on their well-established expertise. Their original and successful horizontal organization, based on sharing lab space, funding when administratively possible, brainstorming and scientific ideas, paves the way for the success of their strategy and project, with in addition ample opportunities to expand (emergence of new groups, recruitment of permanent staff including a senior position, attraction of new people).



## 4 • Team-by-team analysis

**Team 1 :** Avoidance and Repair of Biological Damage

Name of team leader: Mr Ivan MATIC

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
<b>N1:</b> Permanent professors and similar positions	1	1	1
<b>N2:</b> Permanent EPST or EPIC researchers and similar positions	7	7	7
<b>N3:</b> Other permanent staff (without research duties)			
<b>N4:</b> Other professors (PREM, ECC, etc.)			
<b>N5:</b> Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	5	5
<b>N6:</b> Other contractual staff (without research duties)			
<b>TOTAL N1 to N6</b>	<b>12</b>	<b>13</b>	<b>13</b>

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	



- Detailed assessments

#### Assessment of scientific quality and outputs

This team has produced several landmark papers on the evolution of bacterial mutation rates, horizontal gene transfer and microbial ageing. It is one of the leading research units on microbial evolution. The publication activity in the past five years has remained outstanding with 20 publications (10 with the PI as last author). The five best papers of the 2007-2013 period were published in top-ranked journals including *PNAS* (2007), *Biogerontology* (2010), *Current Biol* (2010), *NAR* (2011, 2012). Most notably, they have two other papers that have just been accepted (in *DNA repair* and *Nature Communications*). The team also produced two book chapters and two publications for popular science. The team also managed to generate two patents. The research of the team is very original, and resulted in several major theoretical and methodological breakthroughs. Most notably, the team has recently developed a method that allows visualization of *de novo* mutations in real time. This is a major breakthrough with many potential applications. The production of the team is therefore excellent, involves some collaboration when needed and the results are communicated in excellent international scientific journals.

#### Assessment of the unit's academic reputation and appeal

The team leader is a world-renowned expert in the field of microbial genetics and evolution. He is an associate editor at *PLoS Genetics*, reviewer in many international scientific journals and expert in many review panels and funding agencies worldwide. The team leader has co-organized an international meeting on Stress (2007) and is co-organizer of the French 3R meeting. As recognition of these achievements and activities, the team is currently supported by various funding programs, including from the prestigious Labex "Who am I", from ANR, from a private company and from European funding agencies (FP7). The team has also several excellent international and domestic collaborating partners.

Based on these outstanding achievements, the team is able to attract very good students and post-docs at both the national and international levels.

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

Overall, the team's research has many potential important implications for the healthcare sector. Among others, they study molecular underpinnings of ageing, antibiotic resistance and disease mutations. The team has ongoing efforts to find potential industrial applications of their findings. In a collaborative effort, the principal investigator not only initiated patents, but also launched a company. Moreover, the team has made substantial efforts to reach a broad and general audience and popularize the ongoing projects (exemplified by two popular science papers, 2009 and 2010). Moreover, the team collaborates with prestigious private companies.

#### Assessment of the unit's organisation and life

non applicable.

#### Assessment of the unit's involvement in training through research

The team is involved in several graduate and postgraduate programs. Thanks to vibrant lab life and the extensive collaborative network, the team is a very attractive workplace for foreign senior scientists and PhD students alike. Current and past students have excellent publication records, and many of them have become prominent scientists of their field. Most notably, one former student has recently received the highly competitive ERC Starting Grant. Moreover, given the multidisciplinary nature of the lab and its extensive collaborative network, PhD students have excellent opportunities to learn a wide range of experimental and theoretical techniques together as scientific concepts.



## Assessment of the five-year plan and strategy

Overall, the projects are both ambitious and challenging but technically feasible owing to the results that they gathered during the last period and the expertise of the team. Moreover, in joint efforts with the other team, they developed all the technological tools that are needed for the projects. The proposed projects can potentially raise a broad interest from the scientific community. The following five main directions will be explored.

The first subproject aims to understand the origin and molecular control mechanisms of mutations. So far, most approaches investigated mutation rates at the population level, and little is known about the inter-individual stochastic variation due to changes in cellular physiology or epigenetic regulation. The team will aim at detecting mutations, cellular physiological state, and gene expression level of individual cells in real time. The approach will take advantage of state-of-the-art technologies previously developed by the team. Based on fluorescent detection of mismatch repair proteins, it allows identification of subpopulations with increased MMR activity and the corresponding phenotypic states. Using this setup, the team plans to study pathogenic *E. coli* strains in their host environmental settings. Both the strategy and novelty aspects of this project are outstanding and convincing.

The second subproject will investigate why and how antibiotic stress elevates mutation rate. The team previously showed that a sub-inhibitory antibiotic dosage induces mutagenesis through changed regulation of a general stress response pathway and mismatch repair proteins. This important finding provides a mean to adapt to novel environments, including antibiotic stress. The project will explore the implications of these findings through characterization of mutation rates, phenotypic heterogeneity, physiological responses and genetic polymorphisms of the stress response in natural *E. coli* isolates. This project not only explores fundamentally important biological questions, but also has clear medical implications.

The third subproject explores the ecological mechanisms underlying the generation and maintenance of microbial diversity through space and time. The team will study the rise, maintenance, costs and predictability of phenotypic diversity within *E. coli* colonies. Identified variants will be characterized by whole genome sequencing to identify the underlying molecular traits. This subproject is well-structured and innovative.

The fourth subproject investigates the molecular mechanisms of ageing. The team has previously shown that ageing is associated with protein damage (carbonylation) and increased mutation rates. The team and collaborative partners suggested that protein carbonylation is the chemical event that may trigger cellular ageing, and the underlying protein polymorphism may account for a substantial variability in ageing susceptibility. Among others, this fascinating hypothesis will be tested for applications in humans with the aim to develop a novel approach to improve human health. They will investigate the interplay of oxidative damage, human ageing and quantification of the corresponding molecular variation across individuals. This fundamental research has a great potential and may improve human health.

In the fifth sub-project, the team aims to visualize mutations on a genome wide scale, independently of the effect of mutations. This is very exciting and ambitious.



## Conclusion

- Strengths and opportunities:

The team has a very good publication record, raises excellent research questions, and developed unique experimental tools. The projects are well-thought and innovative. As shown by recent years, one of the key aspects, the ability to attract motivated and talented students and researchers, has been successful. The members are proud of being part of an excellent team.

The team has a remarkable expertise and knowledge in the study of genetic diversity, its mechanism and evolution. The approaches taken are very original and unique, with ambitious strategies. The projects proposed will extend this, as they are innovative and well planned, taking advantage of combined expertise of the unit and interdisciplinary approaches. The various lines of research, although challenging different questions, fit quite well together and are well organized around the central theme of the team. This is important such as not to diverge into too many directions. This is thus expected to consolidate the specificity and originality of this team, in particular in the context of the international competition and of large scale projects than can be developed now to investigate the genetics of any organism in any environment.

- Weaknesses and threats:

The members of the Committee were really impressed by the outstanding quality of the projects, and the fact that they are extremely well-thought and organized. Therefore, the weaknesses are really low but two points can be raised. The first is related to the fact that the realization of these ambitious projects will depend on the availability of several skilled senior scientists and technicians. To ensure the success of these projects, although we experience times of shortage of appropriate funding, an additional permanent position in this team would be ideal. The second point is related to the fact that most ongoing projects have clear links to central issues in evolutionary biology. Some of these possibilities and links to evolutionary theory have remained unexplored.

- Recommendations:

In terms of organization, recruiting a staff scientist would certainly be important to consolidate the projects from the team, in particular since the PI of the team is also the director of the research unit. In terms of scientific projects, the overall aims and strategy are convincing. Without the risk of overloading the project with extra goals, the team might wish to relate the investigated mechanisms to evolutionary theory.



**Team 2 :** Systems Engineering and Evolutionary Dynamics

**Name of team leader:** Mr François TADDEI

**Workforce**

<b>Team workforce</b>	<b>Number as at 30/06/2012</b>	<b>Number as at 01/01/2014</b>	<b>2014-2018 Number of project producers</b>
<b>N1:</b> Permanent professors and similar positions			
<b>N2:</b> Permanent EPST or EPIC researchers and similar positions	6	6	6
<b>N3:</b> Other permanent staff (without research duties)			
<b>N4:</b> Other professors (PREM, ECC, etc.)			
<b>N5:</b> Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	4	4
<b>N6:</b> Other contractual staff (without research duties)			
<b>TOTAL N1 to N6</b>	11	10	10

<b>Team workforce</b>	<b>Number as at 30/06/2012</b>	<b>Number as at 01/01/2014</b>
Doctoral students	6	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	





- Detailed assessments

#### Assessment of scientific quality and outputs

This group has a strong track record in microbial evolutionary genetics at the highest international level. The questions addressed are very important and are relevant to all biological systems. The team's achievements have led to breakthrough discoveries on key factors determining bacterial mutagenesis and ageing, and the development of innovative technological tools that will be invaluable to the scientific community. The committee has been particularly impressed by the development of microfluidic systems able to dynamically monitor intracolonial phenotypic variability and ageing/mortality at single-cell resolution while keeping track of their phylogenetic history. Observations made by the team with these tools have forced the community to revisit accepted fundamental biological concepts. These discoveries include: 1) bacteria presumed to undergo symmetrical cell divisions were shown to partition damaged molecular material asymmetrically, with important consequences for ageing, 2) individual cells respond differently to specific environmental changes, with important implications on phenotypic control, evolutionary mechanisms and antibiotic resistance, and 3) the intracellular enzymatic activities can be enhanced or relocated using synthetic molecular scaffolds.

The scientific output of the team is outstanding, with a total of 20 peer-reviewed publications almost exclusively in top-ranked journals (*Science*, *Proc. Natl. Acad. Sci. USA*, *PLoS Genet.*, *Mol. Sys. Biol.*) and 7 book chapters.

#### Assessment of the unit's academic reputation and appeal

The team has shown a great ability to attract students, postdocs and collaborations worldwide. A particularly attractive feature of the group is its state-of-the-art equipment (microfluidics, robotic liquid handling, custom software for image analysis, FACS). The group has a remarkable capacity to launch and lead collaborative projects, locally, nationally and internationally. This is apparent from the large number of collaborations, and the participation and leading role in international networks supported by competitive funding (Human Frontiers, E.U., national and transnational ANR, Labex). In addition, the group obtained additional significant funding (EURYI, AXA, partnership with industry). The comfortable financial support obtained for research projects by the group makes it a very attractive environment and indicates an undeniable international competitive ability. One former PhD student has now established his own group elsewhere holding an ERC grant. The group is leading an innovative project of next-generation educational program for which it obtained very large financial support (IDEFI, 6.5 million euros).

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

The group has constantly communicated scientific concepts, knowledge, and technology towards the broader public. In addition to the teaching and research activities performed in the laboratory, the group is involved (and leads) an original project aimed at developing new research methodologies that benefit from the contribution of all citizens. The approach is based on the crowdsourcing of data and on the analysis of information networks leading to discoveries. The team leader has substantially invested in this program, which connects the team with various social partners (ethical, social and organizational issues) and the industry.

The group communicates very actively to the public, as shown by appearances in the media (interviews and work-related articles in national and international newspapers, on television and radio), public debates and lectures, science festivals, and the publication of several articles on teaching methodologies and scientific interdisciplinarity. Team members also take part in the High Council on Education, and other administrative bodies of the university and government.

Students of the group have been very successful participants in the iGEM contest, which challenges the creativity of undergraduate students to design interesting synthetic biological circuits. Several projects from students of the group were awarded iGEM 'medals' over the years.



The group performs fundamental research that is oriented along two major topics of public health: the molecular roots of aging and the mechanisms of microbial adaptation to antibiotics. This context offers opportunities for the dissemination of results and concepts towards the medical community. At the same time, these “applied” aspects of the research provide opportunities for obtaining research funding from outside the main fundamental-science funding sources.

### Assessment of the unit's organisation and life

Non applicable

### Assessment of the unit's involvement in training through research

The group has established a recent Ph.D. program called “Frontières du Vivant” which is unique in its interdisciplinary nature. It recruits students that “are most likely not eligible” to other Ph.D. programs, because of their particular background and/or because of the multidisciplinary nature of their research project. The group also welcomes students from more conventional Ph.D. programs. This provides for a secure situation for attracting good students, because it increases the funding possibility for Ph.D. fellowships and it enlarges the perimeter of possible applicants by including graduates from physics, computer science or other disciplines. The active participation in iGEM is also an opportunity to meet and attract students at an early stage of education.

The committee also approves the cascading mentorship taking place in the group: undergraduates have mentors among PhD. students, who themselves have postdoc mentors who are mentored by PIs. Most of the young staff is involved in teaching, which is an excellent way to mature as a scientist and mentor, as well as to identify and attract promising students at an early stage. The students are globally very motivated and committed to their research. They express that they develop in an excellent scientific environment and have ample possibilities to travel to national and international conferences.

### Assessment of the five-year plan and strategy

The plan and strategy of this group for the upcoming 5 years is oriented along two research projects (ageing and cooperation), a teaching program and the development of novel approaches in ‘citizen science’. The committee evaluates the research projects as exciting and ambitious: the questions addressed are of fundamental importance, the group will attack them from novel and original angles, by combining state-of-the-art tools with intelligent questions. Preliminary results show that this research will be feasible and most likely be very fruitful. The group will continue to pursue its ambition to develop and apply highly innovative technological tools. It will benefit from previously developed tools and recent equipment in which it has invested. The interdisciplinarity of its staff will allow to exploit and combine models and data, and to automatize experiments in a productive manner. The committee also noticed the important role of a permanent researcher in the group, who co-supervises most projects, and has a strong line of research that is complementary to that of the PI. The committee therefore foresees the establishment of another independent group in the future.



## Conclusion

- Strengths and opportunities:

The scientific reputation of the group is excellent, as evidenced by a series of high-impact papers that have contributed to changing the field of microbial evolutionary genetics, the continuous attraction of good students and an excellent visibility due to many outreach activities. At the same time, the group's viability is strong, based on complementary expertise in microbiology, genetics, engineering and modeling, a high success rate in obtaining funding, and the involvement in powerful technological developments. Numerous fertile collaborations are taking place internationally, and team members are willingly involved in various teaching programs. The plans for the next five years are very innovative. They build on the existing expertise and interests within the group, and extend these in different promising directions, with sufficient overlap with the other team of the research unit, to allow for fruitful interactions.

- Weaknesses and threats:

The committee has identified only few and relatively small weaknesses. One potential threat is the disconnection between the research lines (on cooperation and ageing) and the "Towards citizen and playful science" plans, particularly since substantial time and energy are spent on the latter projects. It is not fully clear to the committee how these divergent lines of activity will benefit from one another. The committee also found the link with evolutionary theory a bit loose in some projects (e.g. the effect of sex on cooperation), and thinks that the impact of the work in the field of evolutionary biology may be improved by strengthening this link. On a more practical note, the group's working space is small, which may compromise the attraction of students for the planned projects.

- Recommendations:

The committee recommends that the group will maintain its focus on the lines of research they have started and have elaborated in their plans. An attempt to link this research with their activities on discovery games and crowdsourcing may maximize cross-fertilisation of concepts, methods and data. Some care will be necessary to avoid the potential pitfalls of dispersing research topics and managing overwhelming data. To strengthen the link with evolutionary theory, the group may consider new collaborations with theorists in this field. Also, an increased exposure of the group's work at international conferences on evolution is desirable. The cascading mentorship system is very positive but it shall not alleviate the implication of senior supervisors in the details of the research projects. Finally, the prominent role of a permanent researcher of the team may justify the establishment of an additional independent research group in the unit in the future.



## 5 • Conduct of the visit

### Visit date:

**Start:** Thursday, 31st, January, 2013, at 8am

**End:** Thursday, 31st, January, 2013, at 5:30pm

**Visit site(s):** Medical School, Center for Research and Interdisciplinarity

**Institution:** University ParisDescartes

**Address:** 24 rue du Faubourg Saint-Jacques 75014 Paris

**Specific premises visited:** Laboratory space of the unit, equipment platforms (microfluidics, robot,...)

### Conduct or program of visit:

#### Morning:

- Door-closed meeting: AERES representative
- General Presentation by the director of the Unit
- Team 1: Two scientific presentations
- Door-closed meeting : AERES representative, University and Inserm representatives
- Team 2: Two scientific presentations

#### Afternoon :

- Posters and short visit of the laboratory and platforms
- Researcher committee meeting
- ITA committee meeting
- Students and Postdoctoral Fellows committee meeting
- Experts with the director of the Unit
- Door-closed meeting: AERES representative.

### Specific points to be mentioned:

A poster session was organized during lunch allowing a discussion between the members of the Committee and the unit members.



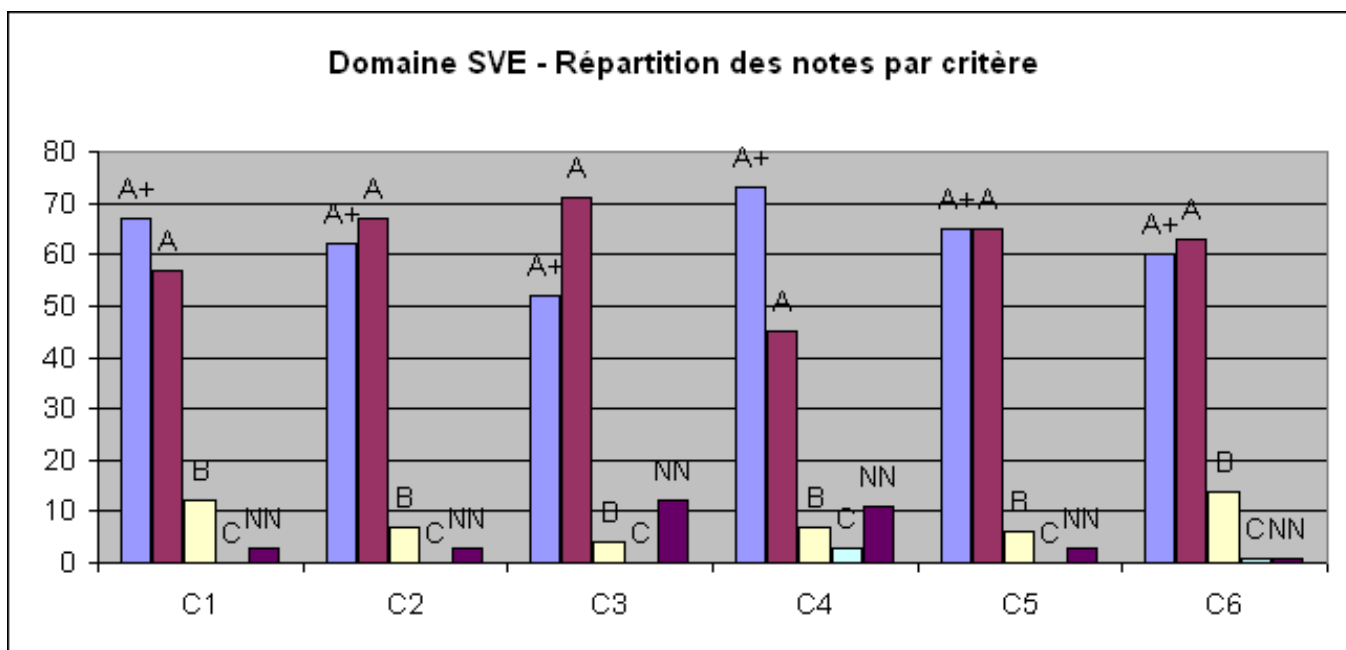
## 6 • Statistics by field: SVE au 10/06/2013

### Notes

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

### Pourcentages

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%





## 7 • Supervising bodies' general comments

Vice Président du Conseil Scientifique

Paris le 11.04.2013

Vos ref : S2PUR140006269 –  
Génétique Moléculaire Evolutive et  
Médicale - 0751721N

Monsieur Pierre GLAUDES  
Directeur de la section des unités de recherche  
Agence d'Évaluation de la Recherche et de  
l'Enseignement Supérieur  
20, rue Vivienne  
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Génétique Moléculaire Evolutive et Médicale »

Vous trouverez ci-joint les réponses du Directeur de l'unité, Ivan MATIC, auxquelles le Président et moi-même n'avons aucune remarque particulière à rajouter.

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

Le Vice Président du Conseil Scientifique



Stefano Marullo, DM, DesSci

# Inserm



Institut national  
de la santé et de la recherche médicale



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75002 Paris  
France

Subject: Comments on the AERES evaluation report [S2PUR140006269 - GENETIQUE MOLECULAIRE EVOLUTIVE ET MEDICALE - 0751721N](#)

Dear Madam, Sir,

In its report, the AERES committee noted that they were impressed by the quality and innovative aspects of our research. Committee considers our scientific output outstanding and ranks our laboratory within the top 10% of our speciality at the international level. Finally, committee considers the organisation of our laboratory as extremely efficient.

The committee has identified very few and quantitatively small weaknesses, which we would like to comment upon:

i) The committee has noted *“a certain disconnection between some research lines of the team 2 (on cooperation and ageing) and the “Towards citizen and playful science” plans. While the main research program and the teaching efforts are each highly positive, the research efforts should be concentrated on the main lines that can be maintained at top level, in order to avoid a too large diversification.”*

Over the past 10 years, team 2 record has proven its capacity to diversify while maintaining a competitive international level. This stems from their capacity to wield together their research activity and teaching through research innovative pedagogy at the interface with biomedical sciences. The citizen science nascent interest in the group (fully supported by an FP7 multinational grant piloted by the team) is based on bridging ever more the research/teaching divide thanks to innovative digital tools that aim at reproducing the successes of Fold-it, EteRNA or Phylo after having initiated a collaboration with the pioneers that initiated such projects in the US. Further, they aim at proof of principle results within the coming years that could be applied to biomedical and patient-driven research, in collaboration with Dr. Stephen Friend (“The Visionary”. *Science 2012*) who has chosen to spend a sabbatical period with us to develop such innovative approaches in Europe.



The innovative teaching activities of this team, headed by its two permanent researchers, were also very well evaluated by AERES, (A+, 2013) and have been very complementary with their research activities. Indeed, their teaching allows them to train students of the highest quality that are capable to develop original projects in collaboration with leading international experts in our lab as well as contributing to interdisciplinary research in Paris and beyond. One of the former students has recently been awarded by the ERC, and all succeeded in their post-doc abroad. Such productive way of functioning will be further developed in the future through citizen science projects supported by Europe and modeling of genetic exchanges supported by the ANR thanks to ongoing collaboration with researchers at Harvard, Edinburgh, UCL, Imperial College and CERN.

ii) Absence of the laboratory council.

Given the small size of our laboratory, we hold weekly meetings where all members discuss the organization of laboratory. The problems are quickly identified and solutions found by the entire staff. So, all members of our laboratory are de facto in the laboratory council. However, to comply with the regulation in force, we will establish a laboratory council with representatives of different categories of staff.

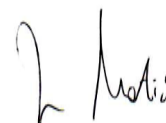
iii) Small number of permanent staff scientists.

We plan to recruit permanent staff scientists in the near future to solve this problem, which becomes acute with the retirement of Professor Miroslav Radman. However, as noted by the Committee, the space in our laboratory is limited (currently, there are no available benches or desks), which prevents us to envisage a real expansion and justifies the strategy of collaboration and spin-offs described above. Such laboratory organisation has so far been very successful in terms of publications, attractiveness, training, partnerships and scientific results.

To solve above mentioned problems, the Committee recommends to recruit permanent researchers and to facilitate emergence of new teams, which we intend to do in the near future with the help of our partners. However, for this we need significant support of our host institutions.

In Paris, 11 April 2013

Best regards



Ivan Matic

Laboratory director