# Homéostasie cellulaire et cancer : reprogrammation des réponses biologiques et thérapies alternatives

Rapport Hcéres

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

Department for the evaluation of research units

# AERES report on unit:

## Cellular homeostasis and cancer

## Under the supervision of the following institutions and research bodies:

Université Paris Descartes

Institut National de la Santé Et de la Recherche Médicale

January 2013

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

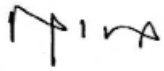
Research Units Department

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 received the following grades:

- Grading table of the unit: Cellular homeostasis and cancer

| C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|
| B | B | B | A+ | A | A |

# Evaluation report

| | |
|---|---|
| Unit name: | Cellular homeostasis and cancer |
| Unit acronym: | |
| Label requested: | UMR_S |
| Present no.: | 1007 |
| Name of Director (2012-2013): | Ms Evelyne SEGAL-BENDIRDJIAN |
| Name of Project Leader (2014-2018): | Ms Evelyne SEGAL-BENDIRDJIAN |

# Expert committee members

| | |
|---|---|
| Chair: | Ms Anabelle DECOTTIGNIES, University of Louvain, Belgium |
| Experts: | Mr Jean-Jacques FOURNIÉ, University of Toulouse (representative of CSS INSERM) |
| | Ms Xuefen LE BOURHIS, University of Lille (representative of CNU) |
| | Mr David SHORE, University of Geneva, Switzerland |

## Scientific delegate representing the AERES:

Mr Jean ROSENBAUM

## Representative(s) of the unit's supervising institutions and bodies:

Mr Nicolas JEANJEAN, INSERM

Mr Stefano MARULLO, Université Paris Descartes

# 1 • Introduction

## History and geographical location of the unit

The INSERM unit 1007 "Cellular homeostasis and cancer" was created in January 2010 when the director's team moved from Saint-Louis Hospital to Paris Descartes University (Centre des Saints-Pères) as a "mono-équipe". The director has expertise in the field of regulation of telomerase expression and other aspects of cellular signaling and differentiation. When unit 1007 was created, it included another research group, already based at Paris Descartes, with chemical and biochemical expertise in the field of telomeres and telomerase. Therefore unit 1007 initially comprised one DR2 and two CR1 altogether.Then, in 2009, a former PhD student advised by the director was recruited as CR2 in the unit. This new CR2 recently left the team but he is expected to stay in close relationship with unit 1007 through scientific collaborations.Similarly, one of the two CR1 left recently.The current team of unit 1007 further comprises two IE2 full-time engineers, including one promoted IE1 in 2011, one IEHC and two AJT (promoted TN in 2012). One of the two AJT is working as a secretary for the unit, the other one is in charge of maintenance and is also doing some benchwork.Scientists over the 2007-2012 period included one post-doc and nine PhD students, with five PhD theses still running.The unit also hosted 12 Master students between 2007 and 2012.

The main project of the unit was then to identify new putative anti-tumour strategies based on either activation or inhibition of pathways targeting cell differentiation, with a focus on telomeres and telomerase.The unit is currently located on the 6$^{th}$ floor of the building and is expected to stay there during the coming years.If the current proposal to include two additional research groups is accepted, the newcomers will be located on the 6$^{th}$ floor as well to ensure closer connections between the research groups.This is fully supported by the Dean of the Faculty of Medicine in Paris Descartes.

## Management team

Unit 1007 is under the supervision of Ms Evelyne SEGAl-BENDIRDJIAN.

## AERES nomenclature:

SVE1_LS1, SVE1_LS2 and SVE1_LS7

## 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 (0.65) | 3 |
| **N2**: Permanent researchers from Institutions and similar positions | 4 | 5 (4.5) | 5 |
| **N3**: Other permanent staff (without research duties) | 4 | 5 | |
| **N4**: Other professors (Emeritus Professor, on-contract Professor, etc.) | | | |
| **N5**: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.) | 1 | 2 | 2 |
| **N6**: Other contractual staff (without research duties) | | | |
| **TOTAL N1 to N6** | 9 | 15 (12.15) | 10 |

| | |
|---|---|
| Percentage of producers | ***100 %*** |

| Unit workforce | Number as at 30/06/2012 | Number as at 01/01/2014 |
|---|---|---|
| Doctoral students | 5 | |
| Theses defended | 5 | |
| Postdoctoral students having spent at least 12 months in the unit* | 2 | |
| Number of Research Supervisor Qualifications (HDR) taken | 0 | |
| Qualified research supervisors (with an HDR) or similar positions | 2 | 7 |

# 2 • Assessment of the unit

## Strengths and opportunities

- coherence of the research themes,
- complementary expertises coming from the different research groups willing to join unit 1007,
- opportunity to invest all unit's efforts in a single and well-defined area,
- great potential for research valorization,
- good training of students and staff,
- access to a tumor biobank thanks to direct interactions with clinicians,
- potential to directly apply the research results to clinical trials thanks to collaborations with clinicians,
- potential to attract Master and PhD students of good quality thanks to the recent recruitment of a MCU P5.

## Weaknesses and threats

- limited scientific production,
- low international visibility,
- increasingly competitive research field (two papers with a direct connection to the field were published in *Science* in January 2013).

## Recommendations

- increase scientific production,
- strengthen the expected positive interactions between the four research groups of the unit to fully benefit from everybody's expertise,
- do the best to remain successful in this extremely competitive research field and, when possible, establish external collaborations with well-established research groups to remain competitive,
- focus on research themes for which the research groups have the highest experience and try to optimize the use of the existing resources in the unit (model cell lines, …),
- if the new unit is created with the four research groups, it is strongly recommended to establish precise written rules for internal organization of the unit's life and resources sharing (equipment, engineers, money, etc.).

# 3 • Detailed assessments

## Assessment of scientific quality and outputs

The scientific production of the director's team itself has been rather limited over the 2007-2012 period. The director was corresponding author of two papers published in *Mol. Cancer Ther*. (IF of 5.2) and one in *Leukemia* (IF of 9.6), co-author of one paper published by a CR1 from the Unit in PLoS ONE (IF of 4.1) and three reviews were published. In addition, a paper has been published in *Blood* (IF of 9.9) in collaboration with another research group which signed the paper. We also note that, although the Director was not among the authors, a CR1 from the unit published one paper in *Leukemia* (IF of 9.6). The second group of the current unit, supervised by another CR1, published two papers in *J. Biol. Inorg. Chem*. (IF of 3.3) one as corresponding author and two as co-corresponding author, three papers as a co-corresponding author (one in Org. Biomol. Chem IF 3.6, one in J.Inorg Biochem IF 3.4,one in Nucleic Acids Symp Ser (Oxf) and two in collaboration: one in RNA (IF of 5.0)and one in *in Angew*. Chem.Int (IF of 13.4). The two groups willing to join the unit have a reasonable scientific production, with an average, for the period covering 2007-2012, of four papers/group published in journals with impact factors between 3.4 and 8.7. Hence, when put together, the total amount of scientific publications is satisfying.

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

The unit has been able to recruit a total of four M1 students, eight M2, nine PhD students (five PhD theses are still running) and one post-doc. Some of these students were recruited from abroad. Importantly, a former PhD student from the Director's team has been recently recruited as CR2 in the unit and a MCU is joining the unit. Although there are many Master and PhD students, the number of post-doc is rather limited. The group is also lacking international visibility in the telomere field.

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

The research project proposed by the unit is expected to yield results of high valorization potential. One of the two research groups willing to join the unit has close interactions with clinicians and clinical trials. This is certainly a very good point. Thanks to this direct connection with clinicians, the unit is also expected to have access to a well-documented biobank of tumor samples, a priceless advantage.

## Assessment of the unit's organisation and life

Management of the lab appears to be well organized with dedicated people for routine lab tasks including security, handling of radioactive products, orders.... Unit 1007 would like to increase in size and include two new research groups, one under the supervision of a DR2, and one currently supervised by a CR1. If the new structure is created with these two new groups it is expected that lab management would be properly ensured, putting all existing workforces together, with limited drawbacks. Rules regarding lab management should however be clearly formulated and written out to avoid problems and misunderstandings in the unit.

If the two new research groups indeed join the unit, there should be enough lab space and offices on the same floor of the building for everybody. The Dean of the Faculty of Medicine appeared to completely agree on this and to be ready to reorganize lab space very quickly to achieve this aim. There appears to be a real desire emanating from the various groups to work together and be physically close in order to optimize collaborations and fruitful interactions.

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

Over the past few years, the unit hosted a high number of Master and PhD students. PhD students appear to benefit from a very good training in the lab and the follow-up is good as well. In addition, opportunities to attend scientific meetings are regularly offered to PhD students, whether in France or abroad. Engineers get the chance to attend courses to help keep them up-to-date with new technologies. All people from the unit appeared to be very happy about this. Finally, the fact that a MCU (involved in Master 1 training) recently joined the group is very promising.

## Assessment of the five-year plan and strategy

The research project of the proposal is interesting and potentially of very high significance in the fields of cancer and aging. The idea to combine various competencies is very good. In particular, the fact that one of the research groups willing to join the unit has direct connections with clinicians and clinical trials would be highly beneficial to the unit. The Committee had the feeling that the four groups were very happy with the idea of working together and sharing their competencies to make their project work. The project has been well designed by the groups and appears to integrate the competences of all. A particular strength of the proposal is that the understanding of hTERT regulation, a major aim of the proposal, is likely to have very important clinical implications, yet it has received surprisingly little attention in either the cancer or telomere research communities until now. This situation may change rapidly, though, and it is unclear whether the unit may be strong enough to face growing competition. In particular, two papers directly connected to the project were recently published in *Science*. It is strongly advised to try to establish real synergies between the groups to get a substantial added value from the network in order to be sufficiently competitive. At the same time, they should carefully evaluate their relative strengths and weaknesses and seek outside collaborators when required.

# 4 • Conduct of the visit

Visit date:

Start: 30 January 2013, 8h30

End: 30 January 2013, 16h30

Visit site: Unit UMR-S1007

Institution: Université Paris-Descartes

Address: 45, Rue des Saints-Pères, 75006 Paris

Conduct or programme of visit:

8h30: welcoming of the Committee by the unit

9h-9h30: presentation of the AERES to the Committee by the AERES Delegate (Committee only)

9h30-9h45: presentation of the evaluation Committee to the unit and brief presentation of the AERES by the Delegate

9h45-11h15: general presentation of the unit and of the project

11h30-12h30: meetings with 1) the engineers only; 2) the PhD students and post-docs only; 3) the scientists with permanent positions only (without the Director)

12h30-13h30: lunch

13h30-14h: meeting with the authorities: the INSERM delegate, the University Paris-Descartes delegate and the Dean of the Faculty of Medicine

14h-14h15: meeting with the Director of the unit

14h15-16h30: discussions with the Committee, conclusions and preliminary report (Committee only)

16h30: end of the visit

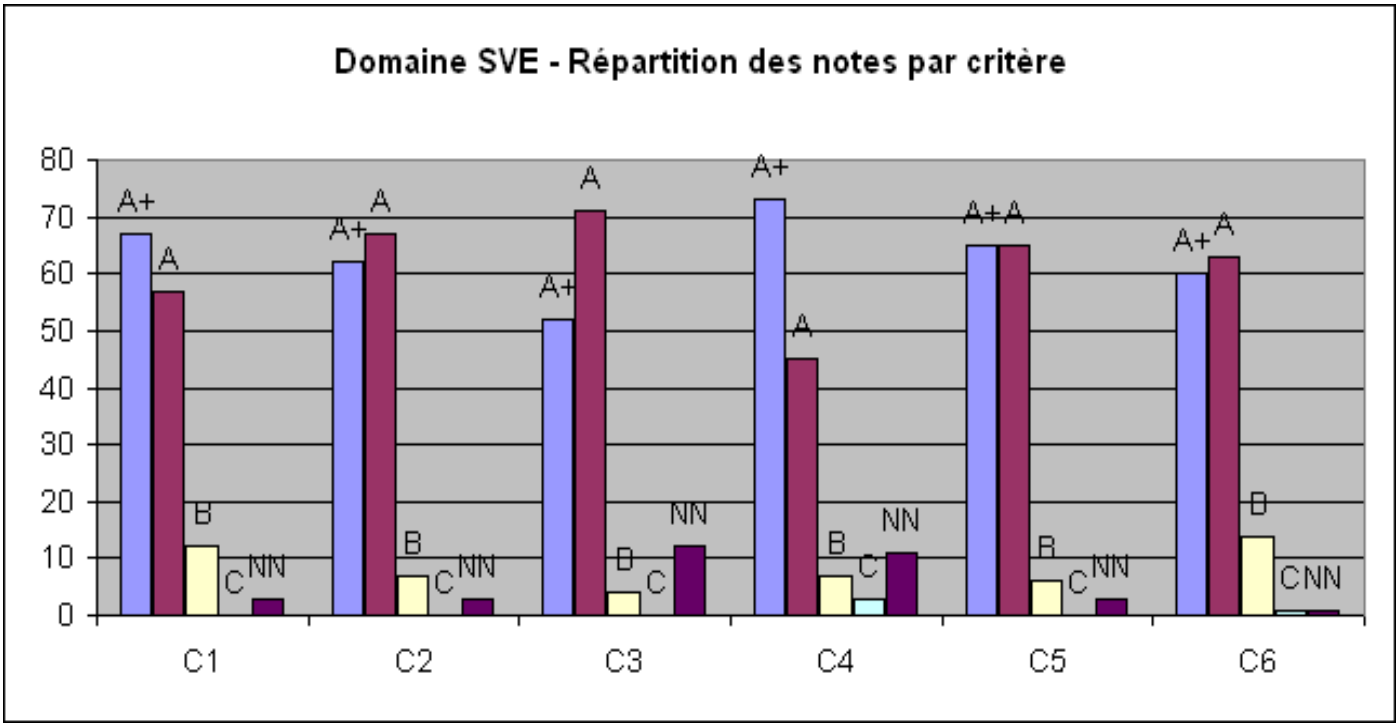
# 5 • Statistics by field: SVE on 10/06/2013

**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% |



## 6 • Supervising bodies' general comments

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 19.04.2013

Vos ref : S2PUR140006250 – Homéostasie Cellulaire et Cancer : reprogrammation des réponses biologiques et thérapies alternatives - 0751721N

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation 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 « Homéostasie Cellulaire et Cancer »

Vous trouverez ci-joint les réponses du Directeur de l'unité, Evelyne SEGAL-BENDIRDJIAN, 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

Université Paris Descartes, Vice-présidence du conseil scientifique, 12 rue de l'école de médecine, 75170 PARIS cedex 06
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INSTITUT NATIONAL de la SANTE et de la RECHERCHE MEDICALE

**Unité 1007 I.N.S.E.R.M.**
**"Homéostasie Cellulaire et Cancer"**

Paris, April 19th, 2013

**Response to the AERES visiting committee report**

Please find enclosed our answer to the evaluation report performed by the AERES committee. We would like to thank the reviewers and all the members of the AERES visiting committee for the positive feedback and the relevant comments they gave us to improve our projects.

In addition to the elements highlighted in the evaluation report we wish to provide additional clarification:

***Point 1: Assessment of scientific quality and outputs: A limited scientific production****: "The scientific production of the director's team itself has been rather limited over the 2007-2012 period".*

The production of the director's team over the 2007-2012 period may seem limited compared to the previous period. This can be partly explained by several factors which have spread our efforts and slowed down the progress of our work:

1. The structuring of a new unit for its creation in 2010, and the management of the laboratory renovation during the 2 years prior to our moving to Saints-Pères Center mobilized a great deal of our collective efforts.

2. Different applications to obtain the proper authorizations to work in the respect of safety rules and regulations applied to a research laboratory had to be done or redone due to our recent installation in the Saint-Pères Center (authorization for the manipulation of genetically modified organisms; the agreement for using radioactivity; training to animal experimentation). Even though this was indispensable, it was time and energy consuming.

3. Our laboratory had to move twice during this period. A first time in 2010 from Saint-Louis Hospital to Saints-Pères Center and a second one, 18 months after our installation at Saints-Pères in order to allow the university to carry out fire safety work, followed by a re-installation 2 months later.

We therefore believe that, <u>the committee should take into consideration not only the five papers published by the members of our team that were omitted in the original report</u> (see paragraph "erreurs factuelles") but also the <u>three papers recently published since January 1st 2013</u> (see below) that could had been published in 2012 if we had the possibility to dedicate our time and energy to science instead of moving.

***1.*** Mélanie Chtchigrovsky, M., Eloy, L; Jullien, H., **Saker, L., Ségal-Bendirdjian, E.,** Poupon, J., **Bombard, S***. Cresteil, T.,* Retailleau, P. and Marinetti, A.*. Antitumor *trans*-N-Heterocyclic Carbene-Amine-Pt(II) Complexes : Synthesis of Dinuclear Species and Exploratory Investigations of DNA Binding and Cytotoxicity Mechanisms. ***J. Med. Chem****. 2013 Mar 14;56(5):2074-86.* (*co-corresponding author) ***(IF of 5.3)***

***2.*** G Gausdal, A Wergeland, J Skavland, **E Nguyen, F Pendino,** L Herfindal, R Kleppe, N Rouhee, E McCormack, U Havemann, F Schwede, Ø Bruserud, B-T Gjertsen, M Lanotte, **E Ségal-Bendirdjian,** S Ove Døskeland. Cyclic AMP can promote APL progression, and protect myeloid leukemia cells against anthracycline induced apoptosis. ***Cell Death and Disease****.* 2013 Feb 28;4:e516. ***(IF of 5.3)***

***3.*** **E. Nguyen**, G. Gausdal, **F Pendino**, M Lanotte, S Døskeland, **E Ségal-Bendirdjian**. Activation of both Protein Kinase A (PKA) type I and PKA type II isozymes is required for retinoid-induced maturation of acute promyelocytic leukemia cells. ***Mol Pharmacol.*** 2013 Mar 1. [Epub ahead of print] ***(IF of 4.8).***

In addition two funding requests have been positively evaluated:

1. A scientific collaborative grant Paris Sorbonne Cité (Bimodal-G4) : PI S. Bombard, 134 000 euros (operating costs + post-doc salary).

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Université Paris Descartes 45 rue des Saints-Pères 75006 Paris. France.
Tél: 33 1 42 86 22 46 Fax: 33 1 42 86 21 62
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2. Valorization project for the development of new telomerase inhibitors by the SATTIdfInnov : 100 000 euros (operating costs + post-doc salary).

***Point 2: Assessment of the Unit's academic reputation and appeal.*** *"The number of post-doc is rather limited".* Even though at the time of the visit the number of post-docs was limited, if we consider the post-docs present in the two groups joining the unit, 6 post-docs have been hosted during the 2007-2012 period. Five of them obtained a permanent position, one is still in the lab. Furthermore, we have anticipated this recommendation of the committee and the current situation is likely to change as positions for the recruitment of post-doc have been included in four grant applications. Two have been already positively evaluated (see above) allowing us the immediate recruitment of a new post-doc. Three applications are still in evaluation (2 applications for ANR grant and one for Fondation de France).

***Point 3: Assessment of the five-year plan and strategy. Increasingly competitive research field****: "A particular strength of the proposal is that the understanding of hTERT regulation, a major aim of the proposal, is likely to have very important clinical implications, yet it has received surprisingly little attention in either the cancer or telomere research communities until now. This situation may change rapidly, though, and it is unclear whether the unit may be strong enough to face growing competition. In particular, two papers directly connected to the project were recently published in Science."*

As pointed out by the visiting Committee, one of our projects aimed at the understanding of the mechanisms regulating hTERT may lead to important clinical implications. This interest of this area of research is further highlighted by two papers published in *Science,* a week before our oral presentation, showing data complementary to ours and that are indicative of the actual relevance of this regulation in the development of melanoma.

We realize that this project will certainly become even more competitive after the publication of these papers but we have developed skills and experiences on telomere/telomerase over many years that make us confident on our capacity to successfully carry out original research in this subject. Our group is well known in the area of hTERT regulation and respected by the scientific international community. Our project is well focused on specific cancers, regulatory mechanisms and therapeutic approaches. As outlined by the committee, this project will benefit from the combination of the specific skills of each group constituting our new Unit (in chemistry, in biochemistry, in biology and clinic). The harmonization and collaboration between the four seniors' groups will allow us to develop a personal and original approach based on the optimization of the original tools that we managed to develop over the past years in order to cope with the pressing international competition in this field.

It should also be noted that this research on hTERT regulation is part of a larger project that includes other fundamental aspects pursued by the groups constituting the future unit such as G-quadruplex targeting, neurotensin signaling in cancer, nuclear organization and antiviral defense where the technologies and collaborations already developed by the senior scientists of the Unit (with chemists and clinicians) put us in a favorable position to meet the challenge of world-wide competition.

***Point 3: "Written rules for internal organization".*** *"It is strongly recommended to establish precise written rules for internal organization of the unit's life and resources sharing (equipment, engineers, money, etc.)."*
As recommended by the Committee, we are preparing a document describing in details the general organization of the Unit life in terms of animations, health and safety, deontological rules and resource sharing (recurrent funding and specific grants allocated for each specific group or project). A unit Council including all the members of the Unit will be set up. This forum will foster the exchange of information about the general organization and administration of the Unit's life.

In conclusion, we thank again the AERES committee for their advices and their remarks that will help us to the implementation of our project.

Sincerely yours

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