Homéostatie cellulaire et cancer : reprogrammation des réponses biologiques et thérapies alternatives

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Cellular homeostasis and cancer

University Paris 5

Mars 2009

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Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	Pierre Glorieux

Mars 2009

Evaluation report

The research unit :

Name of the research unit : Cellular Homeostasis and cancer (ex Phenotypic plasticity of the tumor cell)

Requested label : UMR_S

N° in case of renewal : U685

Head of the research unit : Ms. Evelyne SEGAL-BENDIRDJIAN (former director : M. Michel LANOTTE)

University or school :

University Paris 5

Other institutions and research organization:

INSERM

Date of the visit :

November 28th 2008

Members of the visiting committee

Chairman of the commitee :

M. Claude SARDET, CNRS, Montpellier

Other committee members :

M. Nedime SERAKINCI, University of southern Denmark, Vejle, Denmark

M. Ugo TESTA, Superior Institute of the health ,Roma, Italy

M. Nicol KEITH, University of Glasgow, UK

M. Robert DANTE, INSERM, UMR 590 laboratory, Lyon

Ms. Geneviève PRATVIEL, CNRS, Toulouse

M. Jean-Marc MALINGE, INSERM, UPR 4301 laboratory, Orleans

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

Ms. Annette LARSEN, INSERM CSS representative

Observers

AERES scientific representative:

M. Charles DUMONTET

University or school representative:

M. Bruno VARET, University representative

Ms. Marie-Claude LABASTIE, University representative

M. Daniel JORE, University representative

M. Frédéric DARDEL, Institut IMTCE representative

M. Philippe DJIAN, IFR representative

Research organization representative:

Ms. Annick BERTAULT, INSERM Representative.

Evaluation report

1 • Short presentation of the research unit

- Number of lab members : 13 including:
  - 3 researchers
  - 1 post-docs
  - 5 engineers or technicians, i ncluding 3 IE and 2 AJT
  - 4 PhD, all with a fellowship
- Number of HDR : 2
- Number of students who have obtained their PhD during the past 4 years: 9
- Average lenght of a PhD during the past 4 years: 3.5 years
- Number of lab members with a PEDR ; 0
- Numbers of "publishing" lab members: 3 out of 3

2 • Preparation and execution of the visit

The present unit was composed of three teams. All the presentations and discussions were performed in English. Team 2 is moving to Lyon and has not been evaluated by the committee. As the leaders of team 1 are retiring, Team 1's remaining members choose to merge with team 3 to, collectively, present a new project. They will be joined by a CNRS group.

Oral presentations of the research program were made by three senior CNRS/INSERM and one junior (CDD Inserm) scientists participating to the new project. These presentations have described the highlights of the past three years achievements and outlined the ongoing and future research direction of the new unit. In addition, a poster session was organized during lunch time and allowed the review group to evaluate in depth the scientific results of each project.

The committee members met the students and post-doc, the technical staff and the representative of the Paris5 University, Inserm and IFRs.

All members of the review group were present from the beginning to the end of this visit and have all returned independently their argumented comments to the chairman.

The review took place at the proposed future site of implantation of the unit (St Père) and not at its present location (St Louis). The review group have visited the futur lab space (200m2 + 70m2 to share) provided by the University Paris Descartes /IFR95 (6° floor / Sts Pères) that should, upon rebuilding (spring 2009 ?), welcome this team.

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

The present unit is located at Centre Hayem/ Hopital St-Louis/Paris, and composed of three teams working on various cellular, molecular and pharmacological aspects of acute promyelocytic leukaemia (APL) with an overal aim to identify and manipulate signalling pathways associated with differentiation, apoptosis and senescence in cancer cells:

- Team 1: Integration of signaling pathways and biological responses
- Team 2: Regulation of the alternative splicing", a former Avenir team
- Team 3: Physiological and pharmacological regulation of the expression and activity of Telomerase

Collectively, this unit has greatly contributed to the development of research on acute promyelocytic leukaemia (APL). The unit members are well known in the field of hematology to have developed, since the 90's, the APL cell lines NB4 and its multiple variants, for transformation, signal transduction, differentiation, telomerase and drug-resistance studies, placing this unit in good position for national and international collaborations.

Team 2 has been reasonably successful and is now moving to Lyon (Centre Anticancéreux Leon-Berard) and was not evaluated.

Leaders of team 1 are retiring. Team 1's remaining members and Team 3 have decided to merge to present a new project directed by the leader of Team 3. In addition, Team 3 recently begun to build a highly motivated chemistry/biology-based research collaboration with a CNRS group (Paris Descartes / Sts Pères site) on telomerase inhibitors and their impacts on leukemia. This small CNRS research group is willing to join the new unit by the end of 2009 and is therefore considered as being part of the new project. This fit with one of the main objectives of the new project which is to reinforce the chemical genetics expertise of the team by bringing biology and chemistry together in a functional way. This objective also led the U685 to respond to a 2006 international call made by this IFR and by the center Universitaire des Sts Père/ Paris Descartes to attract additional research units at the newly renovated 6th of the Sts pères campus and to integrate the IFR95/ Institut interdisciplinaire des sciences du vivant des Sts Pères in 2008. Undoubtly, the technology platforms and interdisciplinary laboratories present on this campus offer a better context for a project aiming to combine chemical/toxicological/pharmacological and biological approaches. However, no doubts either, that this unit might loose part of its priviledged connection with clinicians by moving away from St-Louis hospital.

University and IFR representatives that met the review group, confirmed that the new project has been selected in a competitive way and was proposed to occupy 200/270 m2 of renovated lab space whose delivery is expected for spring 2009. The review group was invited to visit the futur lab-space. Although it was observed that renovation have not started yet (November 2008). University and INSERM representatives, as well as official documents sent to the review group, all confirm that this operation is already financed and will take place in 2009.

University and IFR representatives also mentioned to the review group that a short/mid term project of the University is to redesign Descartes IFR's frontiers, with notably, the creation of a novel institute devoted to Drugs, toxicology, chemistry, environment and medecine (IMTCE). The project will be invited to join this new entity that should provide the perfect interdisciplinary context seeked by team members.

Overall, the installation of this unit at the Medical faculty of St Pères appears as a positive move actively supported by the tutelle, which should reinforce already existing, but not yet fully organized, interactions between biology and chemistry on this campus.

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

Achievements:

Team 1 and Team 3 aimed to identify and manipulate signalling pathways associated with differentiation, apoptosis and senescence in cancer cells. They have focused on : i/ the signaling and transcriptional programs induced by retinoids and cAMP on acute promyelocytic leukaemia (APL), ii/ the role, regulation and signaling of telomerase and of telomere length maintenance in drug resistance, proliferation and survival of APL cells. These programs were and are still of broad interest in hematology/leukemia as they concern, ongoing or promissing pro-differentiation and anti-telomerase therapies, as well as the associated resistance to these novel therapeutical approaches.

Several advances were made in these fields by Team 1 and Team 3, notably through the development of the very valuable APL cell lines NB4 and its multiple variants that have greatly contributed to the international development of research on APL and telomerase studies placing this unit in good position for national and international collaborations. One can regret that the interesting observations made on these cells have not been more extensively confirmed in this lab on primary tumor cells and, eventually, extended to patients; a weakness that might reflect the lack of clinicians in the unit.

Team 3 has also begun to build a highly motivated chemistry/biology-based research team with a CNRS group (See project/ item2 below). This core group showed good evidence of interactions and collaborations with the wider scientific and to some extent the clinical community.

Collectively, publication record of Team 1 and Team 3 is in the average, and although the group, as a whole, lack publications in high impact journals, several of their past scientific contributions have good citation index and have been recognized as milestones. The review group encourages the new team to develop a more ambitious and aggressive aproach for publications and patents, and to improve the recognition of their very valuable expertise and of their work delivered through collaboration with remote investigators. Of note, several publications of good levels are either submitted or in preparation as confirmed throughout our evaluation (Talks, Posters).

Project :

The new Inserm unit project visions three main lines of research :

1/ Transcriptional and post-transcriptional regulations of the retinoids and AMPc-response, and of telomerase in APL. This is the following of ongoing research developped by the unit on APL. This includes, broad transcriptomics and proteomics studies to identify novel target genes, pathways and protein complexes involved in AMPc- and Retinoid-responses, as well as more focused studies on already identified but not yet fully characterized transcriptional targets of these pathways (telomerase, CD44, RINF…).

The telomerase work within this area is a historical strength. However the current proposal could be more ambitious and should not limit itself to filling gaps in current knowledge. This is not necessarily bad, but the applicants are encouraged to be bolder and more competitive as they do have strengths here, particularly if the chemistry approach (see item 2 below) is pursued more vigorously.

Although at early stage, the project on RINF1 (Retinoid Inducible Nuclear factor) in myelopoeisis, led by a young investigator with a CDD Inserm is looking very promising with a pertinent investment in animal models. A more significant focus on this project is recommended if this group is to make timely headway. It is anticipated that this work will help to give the group visibility in the arena of retinoid and cancer biology.

The work on CD44 is of value but is somewhat limited and, like RINF1 project, disconnected from the theme of telomerase which runs through much of this Unit project and as so, appears as a more natural focus of the future unit.

Concerning the transcriptomics and proteomics approaches proposed in this project, the review group have some concerns about the capacity of the future research unit to be at the international forefront in this area considering the large investment in manpower and expertises (bioinformatics, biochemistry) that requires the validation of the usual crude results generated by these approaches, the risk being that much work will be delivered through collaboration with remote investigators.

In general, there are too many sub-projects in this first area and although advances are being made in several fields this might become a weakness in that the headcount devoted to any one topic is necessarily too restricted to develop all these research projects in a competitive way.

2/ Drug development. Search for synergistic action between retinoids and novel telomerase/telomere inhibitors. Team members recently begun to build a highly motivated chemistry/biology-based research collaboration with a CNRS group on novel telomere inhibitors (derived from cis-platine) and their synergistic action with retinoids on leukemia as well as other cancers. The CNRS group will join the new unit by the end of 2009 at the newly renovated 6th floor of the St-Pére campus to further develop this ongoing project.

This area shows most promise and the collaboration between the two groups s is clearly taking shape. This work focuses on a chemical genetic approach to interrogating hTR/telomerase/telomere structure/function and is also developing tools to manipulate telomerase activity. This is a very timely and competitive area of research, well worth investing in. With active management, commitment to compete and the application of appropriate resources this new unit could become internationally competitive.

The only weaknesses that can be identified in this area is an over-reliance on platinum compounds to target telomeres whereas there are room to use this promising chemical genetics and cellular strategies to initiate a more ambitious program aiming to compare several other classes of DNA/telomere inhibitors in the same assay.

Of note, this project will easily find its place within the futur IMTCE /parisV institute that should provide the perfect interdisciplinary context (chemical/toxicological/pharmacological and biological expertise) and platforms to advance through to pre-clinical applications.

3./ Extension to other human pathologies. The group have used the APL cells for much of their work. They now want to broaden their horizon to other leukemia and tumors that can be targeted for differenciation and /or senescence could be of therapeutical interest. Notably, they have already initiated external and pertinent collaborations with clinicians to apply their current expertice (impact/role of cAMP, retinoids, CD44, telomerase and drug-resistance) to Chronic myeloid leukaemia (CML) cells and Neuroblastoma. This is a sensible and appropriate decision but, at present, the thoughts on how these materials will be used within the program are underdeveloped ; however, this should strengthen over time. That's also a matter for reflexion whether there would be here a good opportunity to attract clinicians in the unit to work on these programs. The major threats in this area is, again, it might be difficult to develop all these new interesting projects in a competitive way with a limited staff already involved in their ongoing projects.

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

There are no causes for concern in the direction and management of the personnel and resources. The former principal investigator of the Unit is to be congratulated.

The new principal investigator appears as an excellent coordinator who clearly has the support of team members at all levels. There is a high degree of solidarity and coherence between the different members of the group, researchers, ITAs and students, that have decided to stay together during this period of transition, which is a strong point of the project. The arrival of a new investigator from a CNRS unit, and her students, is a very positive step that should help to build a highly motivated and synergistic chemistry/biology-based group of people. Considering the large lab-space that is offered to the new unit at the Sts Pères site, the permanent technical staff involved in the project (5) versus the large number of ongoing sub-projects, it will be possible and essential to attract/appoint additional scientists (permanent and post-doc) and clinicians at the profile of the new unit.

The group has a reasonably good but average track record in attracting external funding (national). As for publications, the review group recommends to be more ambitious, i.e. to apply for larger, more prestigious and competitive grants, including through participation to international networks.

6 • Recommendations and advice

Strong points :

Valuable expertises, reagents and clinical connections on signaling pathways, drug-resistance and telomere maintenance in acute promyeolytic leukemia (APL). This is of therapeutical interest in hematology. These are historical strengths that have to be preserved. New projects in this field (RINF1) are promising;

The willingness to move work in a translational direction and the already initiated move to broaden their horizon to patient materials, other leukemia and neuroblastoma through collaboration with established clinicians, are sensible and appropriate decisions;

New projects with high potential of yielding promising results for anti-cancer drug therapy. These include a promising chemical genetics/biology-based project aiming to target telomeres, which appears particularly motivated and synergistic. Chemical genetics is an emerging field, worth investing in, which fits with the objectives of the futur IMTCE /Paris V institute. With active management, commitment to compete and the application of appropriate resources this project as the potential to become internationally competitive;

Installation of the unit at the Medical faculty of St Pères appears as a positive move, actively supported by the tutelle, which fits with the drug design-oriented objectives of the latter to bring on this campus biology and chemistry together in a functional way;

The new principal investigator appears as an excellent coordinator, who clearly has the support of team members at all levels.

Weak points :

From the written application and the presentations at the site visit, the program tends to appear as a list of interesting but self-standing mini-projects rather than an integrated program. This appears as a program in transition that needs to be more focused. This period of change should be taken as an opportunity to focus on group strengths and matching these to unmet needs in the field;

There are too many sub-projects. Although advances are being made in several fields, this is a weakness in that the headcount devoted to any one topic is necessarily too restricted to develop simultanously and rapidly all these research projects in a competitive way;

Although many external collaborations represent a positive factor in itself, it is not clear which laboratory is responsible for what, this is essential to uncertain that members of the group clearly appear as principal investigators for a given aspect;

No clinicians in the unit;

The recent publication record of the unit members could be better. However, this likely reflects the fact that these groups have initiated several promising new projects that will take time to reach fruition. Notably, the new configuration of the Unit with Biology/Chemistry together requires time to develop. This time is required to evaluate whether this is a functional and competitive grouping or not.

Recommendations :

Overall, this is an interesting and forward looking application, that might took time to reach fruition but which justifies funding. The review group recommends:

to identify priorities and reduce the number of projects. This will require active management and strong leadership from the new director;

to attract additional scientists and clinicians;

to develop a more ambitious and aggressive approach for publications, patents, grants and participation to international networks, improve the recognition of their very valuable expertise and of their work delivered through collaboration with remote investigators.

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

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 3 avril 2009

DRED 09/n° 134

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 de comité de visite concernant l'équipe d'accueil « **UMR-S Homéostasie cellulaire et Cancer : reprogrammation des réponses biologiques et thérapies alternatives** » rattachée à mon établissement.

L'Université a pris bonne note des points faibles décelés par le comité de visite et veillera, en partenariat avec l'INSERM, à ce que les recommandations faites soient suivies d'effet.

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

Le Président de l'Université

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INSTITUT NATIONAL de la SANTE et de la RECHERCHE MEDICALE

Unité 685 I.N.S.E.R.M.
"Plasticité phénotypique de la cellule tumorale"

.....

EVAL-0751721N-S2100015253-UR-RPRELIM_SEGAL. Réponses-Observations.

Paris March 24th, 2009

Dear Madam, Dear Sir,

On the behalf of all the members of the proposal, I wish to thank the members of the visiting committee for the evaluation of our past work and current research project as well as their comments and very constructive criticisms.

Regarding several specific comments or recommendations, we would like to provide additional information or comments.

2. Preparation and execution of the visit, page 4:
The review took place at the proposed future site of implantation of the unit (St Père) and not at its present location (St Louis). The review group have visited the future lab space (200m2 + 70m2 to share) provided by the University Paris Descartes/IFR95 (6è floor/Sts Pères) that should, upon rebuilding (spring 2009?), welcome this team.

We are pleased to let the committee know that the rebuilding of the lab actually was started beginning of March 2009. Therefore we expect to move all the lab and equipments early in June so that the team could settle in the new lab in July 2009.

3. Overall appreciation of the activity of the research unit, of its links with local, national and international partners, page 5:
Besides recognizing that "*the technology platforms and interdisciplinary laboratories present on [Sts Pères] campus offer a better context for a project aiming to combine hematological/toxicological/pharmacological and biological approaches"* the committee considered also that it will result in the "*lost of our privileged connection with clinicians by moving away from St-Louis hospital*".

The collaboration with St Louis Hospital clinicians is historical, strong and well established, and distance has never been in the past a difficulty for fruitful cooperations. Of note our lab benefits also from long-term collaborations with clinicians worldwide, namely with the Shanghai Rui-Jin Hospital (Prof. Z. Chen, QJ Chen, JH Tong, YL Wu) and the University School of Medicine in Bergen (Norway, Profs. SO Doskeland, B-T Gjiersten, G. Houge, Bruserud). These clinicians have been our constant and reliable partners over more than a decade. Importantly our project better benefits from a worldwide clinician network, than a privileged site connection, since rare interesting patients, rather than cohorts, are urgently searched. For these reasons other national collaborations have been recently developed in Créteil (S. Giraudier), Bordeaux (FX Mahon) and Toulouse (V. Demas). We do not feel that being at Saints-Pères Campus will be detrimental to any of these already established collaborations. In contrast as clearly appreciated by the committee, we believe that being on Saints-Pères campus at the close proximity of its technology platform and laboratories, offers a widely opened and competitive environment for chemistry and biochemistry studies, that we missed before. This will should benefit to our project, namely to develop therapeutic applications and targeted strategies through the study of transcriptional regulations. Furthermore, our integration in Paris Descartes University will foster local collaborations with the Departments of clinical hematology in Cochin (F. Dreyffus) and Necker (O. Hermine).

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

Project, page 6-7:

- *"The telomerase work within this area is a historical strength. However, the current proposal could be more ambitious and should not limit itself to filling gaps in current knowledge"*

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This sentence does not reflect our basic research activities. We feel that this remark is pejorative regarding the amount of work and data of recognized quality it refers to. What is here called "filling gaps" is, in our mind, solving problems or scientific questions that are embarrassing and thus left apart by many scientists. Questions that are “gaps” often prove of extreme difficulty. Thus embarking in “gaps”, generally, is not immediately rewarding. However, this is a fascinating aspect of research, and not the less productive on the long-term.
Possibly, we have not been enough convincing during our oral presentations; however we have many examples showing that our works at U-496, then U-685 have brought clear improvements in the knowledge and contributed to move several dogma.

1. It was a dogma that retinoids can regulate telomerase during differentiation. **We were the first to show that they can also do so independently of differentiation** opening a new opportunity for the therapeutic use of these already clinically relevant drugs (PNAS 2001, Oncogene 2003). Furthermore, we disagree with the statement written in the report ("*One can regret that the interesting observations made on these cells have not been more extensively confirmed in this lab on primary tumor cells*"), our results have been confirmed on patient cells (Leukemia 2006). Thanks to this telomerase downregulation by retinoids independently of maturation, cells resistant to retinoid-maturation are eradicated through induction of a telomerase-dependent death. It pointed at one unexpected antitumoral action of retinoids. This remains a fascinating aspect of our results and proposed concept.
2. **We were also among the first to assign to telomerase an anti-apoptotic** role (Oncogene 2004).
3. When over years, inconsistencies and conflicting conclusions about immunodetection of hTERT flourished in the literature, our laboratory decided to deal with this issue, with determination. **We finally showed that the most common used antibody to detect telomerase was in fact recognizing nucleolin**. It was not so easy to demonstrate but even more difficult to make it accepted. Indeed, these results called into question the conclusions of many already published results. Instead of working on telomerase numbers of scientists have investigated nucleolin. However, after the publication of our results (J Cell Sci, 2006) we received congratulations letters from recognized scientists in the field of telomerase. Here, our work carried out with tenacity has brought a large contribution for the scientific community in the field of telomerase detection.

Our current proposal on telomeres and telomerase is **to develop an interdisciplinary research program that we have been already initiated and wish to pursue more actively in the next years combining chemistry/biochemistry and biology expertises in an adequate environment**. Our project is structured into three highly interactive areas of activity (hTERT targeting, hTR targeting and Telomere targeting) in an integrated effort getting together complementary technical expertise to investigate the biology of telomerase and telomeres in order to develop combinatorial therapeutic strategies targeting in an innovative way each component of the telomerase/telomere complex.

- The discovery of RINF, a potential tumor suppressor and possibly a telomerase repressor, is not an unexpected fruit of our research program. This is indeed a Paris-born project, never discontinued during many years, that we extended to our historical partner labs (Bergen), with extensive bilateral exchanges of scientists post-docs seniors and PhDs (both ways), with recurrent supports of INSERM. **The first results we obtained are very promising and this project will be actively continued in the next years with appropriate collaborations.**

- When we propose here a research program in Proteomics, this is because we wish to ask precise questions, have already developed all the adequate biological tools to go further and benefit of valuable partners and platforms. The experts seem to doubt of the feasibility of the transcriptomic and proteomic approaches, because of our team is modest in size. "*Concerning the transcriptomics and proteomics approaches proposed in the project, the review group have some concerns about the capacity of the future research unit to be at the international forefront in this area considering the large investment in man power and expertise (bioinformatics, biochemistry)…*". Precisely, if technological platforms have been developed in all advanced and innovating research centres, it is to allow small research teams to develop ambitious programs. **This proteomic approach, complementary to the microarray approaches already performed, is part of a new collaborative project that has**

already begun with the Paris Descartes Proteomic Platform. This proteomic analysis should enable us to reveal candidate effectors and signaling pathways involved in cAMP/retinoid responses and their cooperation. Paris Descartes Proteomic platform has all the expertise (biochemistry, bioinformatic) necessary to develop this approach. The validation of the results obtained will be performed in our laboratory which has the expertise in these fields and appropriate cellular models. **We were pioneers in the study of cross-talk between cAMP and retinoid signalling,** when more than 10 years ago we were first to show that defective cAMP signalling was a cause of resistance to retinoid-maturation and one of the defective therapeutic action of retinoids in leukemia. During more than a decade, this was considered as "anecdotic" despite our publications in reputed journals. These papers, although they received hundreds of citations, were not in the main stream of thinking, but we pursued our research accumulating data. Furthermore, our lab (U-496) was the first to show that retinoid-refractory leukemia cells were differentiation responsive to rexinoid/cAMP cross-talk. Rewardingly, we now see major group leaders coming back to our early proposal referring to our publications in major journals. What was initially a gap, has turned in a central theme.

- The great benefit for us is that during a decade we developed the tools necessary to this research (promoter regulation, epigenetics and proteomic projects) and sub-projects detailed in our current proposal that will be carried on in the next years. Already, our team has received requests to benefit from those tools. Note that with constancy during more than a decade the international scientific community sent us material requests. We have no doubt that we are at the forefront and confident that we have ammunitions to keep this position. This is what we can best answer when the issue of our competitiveness is raised. Again, possibly we have not been enough convincing in our research proposal, but we thought that we had not to detail it.

Project, page 7:

The committee considers that there is "*an over-reliance on platinum compounds to target telomeres*". Our aim is: 1) to establish if platinum complexes are able to target telomeres in cells (by binding to them and by modifying their structure) and 2) to design a generation of new platinum complexes that will combine the recognition of quadruplexes structures, specific of telomeric DNA, using known ligand of quadruplex DNA, with the covalent binding of these molecules, using the cross-linking agent platinum agent. As suggested by the committee it is clear that the effects of these new compounds will be compared with other classes of DNA/telomere inhibitors.

6. Recommendations and advice

Weak points:

The committee noted that *"the recent publication record of the unit members could be better".*
As noticed by the committee, our projects have been viewed in the context of long-term investment. Each scientific question we wondered needs appropriate biological tools (probes and cell models) and we developed them methodically. Furthermore, regarding the studies on telomere/telomerase, it is well known that any telomerase dependent responses need time to develop (sometimes more than 3 months).
However our investments begin to be fruitful and we are pleased to inform the committee that since the visit of the Unit,

-Two submitted manuscripts (Pendino *et al.* Blood; Bombard *et al.* Org. Biomol. Chem.) have been accepted for publication in the top level journals of their disciplines,

- One invited review (Deville *et al.* BBA) in a special issue on telomerase assembling reviews articles by prominent international specialists, is now accepted for publication,

- One new original manuscript reporting on the hTERT promoter regulation has been submitted (Azouz *et al.)* ,

- A fifth manuscript is been finalised and submitted shortly (Nguyen *et al.):* it reports on functional defects of PKA regulatory isoforms and their shRNA silencing during retinoid.

This additional list intends to show that our research team is highly vivid and productive. We hope that the referees will consider our continued record of publications over the last decade of U-496 and U-685 (rather than the last year record). As noted in the proposal, U-685 was due to a mid-term renewal evaluation this year. For private reasons, a premature end of the professional activity of the director was decided, the team had to reorganise and some studies were postponed, other reoriented in the current proposal. This explains why several papers are late.

The committee remarks that "*although many external collaborations represent a positive factor in itself, it is not clear which laboratory is responsible for what*".
It is clear that some of our works are part of a long-term concerted scientific collaboration mainly between Bergen and Paris, between Shanghai and Paris and between Debrecen and Paris which recently resulted in exchanges of PhDs (2), Post-docs (4) and sabbatical years of seniors during the last 10 years and in publications in common. This network of collaborations (Paris, Bergen, Shanghai, Debrecen) is indeed lasting since 1989, all over the INSERM U-301, U-496 and U-685 from which most projects have stemmed. These collaborations are maintained in a reciprocal spirit of confidence and in the proposal that has been evaluated, the members of our group are undoubtedly the principal investigators.

Recommendations:

- The review group recommends to"*identify priorities and reduce the number of projects*".

As well recognized by the committee, our program is in a period of transition. The INSERM Unit 685 “Plasticity of the tumor cell”, director M. Lanotte, has been created on January 1, 2005 at Saint-Louis Hospital for a period of 4 years. The projects that have been initiated and performed during this first period are in the process to being productive in terms of publications. Some are fully mature and will close shortly, others are emerging. This may give the appearance of spread interest, which is not real. However, as recommended we indeed intend to carefully focus our projects what will occur naturally over the next two years depending on the results obtained.

- We fully agree with the committee in that we "*need to attract additional scientists and clinicians*".

It will be actually our priority for the next four years and we have already begun to attract scientists:

- **The group leaded by S. Bombard (CR1, CNRS) will join us.**

- We are also engaged in a strategy of recruitment by **supporting the application of F. Pendino (INSERM CDD) for a researcher position (CR1/CR2) at INSERM.** His recruitment will be invaluable to our project.

- In addition, **we have a new post-doc candidate and 3 new PhD candidates (including a clinician** who has already done his Master2 in our lab). Applications for their respective fellowships are in evaluation.

Furthermore, through a teaching program between Syria and France, we are setting up presently (a Tempus joined project application is under evaluation by the European Commission), we intend to participate in an exchange program of students and researchers between our countries.

- The review group encourages the new team "*to develop a more ambitious and aggressive approach for publications, patents, grants and participation to international networks, improve the recognition of their valuable expertise and their work delivered through collaboration with remote investigators*".

The term “aggressive” has not been of common use, so far, in Science. However, we understand what the review group meant. If it consists in submitting our paper to higher impact journals, note that if accepted the quality of the work is not changed. Possibly, the number of citations will be increased. We consider that we do not have to be blamed for our scientific production. Most of our papers are published in journals whose impact factors range between 5 and 11, with a mean value above 6. Most are well cited in the literature and importantly they have living citation periods over many years, which amongst all criteria is the most difficult to obtain.

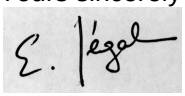
Regarding our participation to international networks, as mentioned in the written proposal, in the 10 past years, we organized in Paris three INSERM international workshops, two on "Cell Death and Apoptosis" and one recently on "Telomeres and Telomerase". These workshops combined a theorical part with lectures made by recognized specialists in these fields and a practical part organized in our laboratory. This will be pursued in the next years. These workshops helped to increase our international credit in these fields. These very constructive experiences will be renewed as soon as we have integrated Saints-Pères campus.

Regarding the grant applications, I wish to mention that we obtained grants from EMBO (fellowship for one PhD student in a codirectory program with Hungary), from Marie-Curie (post-doctoral fellowship and European reintegration grant for F. Pendino). As pointed out above we are

presently involved in a joint project with Syria. We agree with the committee in that presently our participation in international networks can be increased, in that, **the development of our on going proposal should offer us the opportunity of a better integration of our projects at the international level in the future.**

Hoping that these comments may help to clarify the strategy of our research project.

Yours sincerely



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