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

Section des Unités de recherche

AERES report on the research unit

Genetics, Reproduction and Development

From the

Université d'Auvergne

Université Blaise Pascal

INSERM

CNRS

March 2011

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

March 2011

Research Unit

Name of the research unit: Genetics, Reproduction and Development

Requested label: UMR CNRS, UMR-S INSERM

N° in the case of renewal

Name of the director: Ms. Chantal VAURY

Members of the review committee

Committee chairman

Mr. Pierre COUBLE, Center for Molecular and Cellular Genetics, Lyon. France

Other committee members

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Report

1 • Introduction

- Date and execution of the visit

The visit in Clermont Ferrand of the Evaluation Committee was organized in two days, the 3rd and 4th of March 2011. It started with the audition of the Director and the Associate Director who have managed the laboratory during the present 4-year period. It was followed by the evaluation of the 13 individual teams which proceeded with the presentation of the research achievements and projects by the team leader, in the presence of the team staff, and a short exchange with the sole team leader. A discussion was held with the representatives of the two Universities (Blaise Pascal and Auvergne) and those of the CNRS and INSERM. After separate meetings with the researchers (whole Committee), the technical staff (a sub-Committee) and thesis students and post-docs (another sub-Committee), the Evaluation Committee had a final closed-doors meeting to draw the main conclusions.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The GReD laboratory (Génétique Reproduction et Développement) has been founded in 2008 under the authority of the Université Blaise Pascal and the Université d'Auvergne, and the joint support of the CNRS and INSERM. It represents a major research unit in Biosciences in Clermont-Ferrand and gathers 149 personnels. The laboratory is located on two distinct sites, the Science University Campus "Les Cézeaux", for one, and the site of Saint-Jacques of the Medical Faculty for the other, each separated by a 2.5 km distance. A project to construct a new building in downtown Clermont-Ferrand which is planned for 2014 in the frame of the National Plan Campus, will allow to congregate all the GReD teams at the same location.

The research activities of the GReD focus on genomic dynamics and epigenetics, reproduction and development and on endocrinology, signalling and cancer. GReD teams approach a variety of biological situations and model systems, animal and plant, and work at unraveling basic mechanisms as well as at exploiting fundamental knowledge towards medical approaches and valorization.

- Management team

The management, administration and external representation of the GReD are assumed by a Director and an Associate Director. They are assisted by an administrator and a staff of 8 personnels (secretaries, fund managers, maintenance personnel). An Executive Board with the two directors and the group leaders makes decisions on all aspects of the scientific politic, the management and the administration. A Laboratory Council (Conseil de Laboratoire) brings together the direction and a body of representatives of all the GReD personnels.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	44	42
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	18	16
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	20	Estimated for 2010 : *20*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	28,6	27
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	10,85	
N6: Number of Ph.D. students (Form 2.8 of the application file)	27	
N7: Number of staff members with a HDR or a similar grade	36	37

In italc : estimation for 2012

2 • Overall appreciation on the research unit

- Summary

The GReD research project encompasses diverse scientific topics, all aiming at deciphering the molecular and cellular mechanisms that contribute to genome integrity, accurate gene expression, cell and tissues differentiation, as well as organismal development. The diversified research unit incorporates a large body of shared concepts and techniques rooted in a foundation of established and integrative biological approaches.

The collective project utilizes an original and rather unique set of plant and animal models, all with high intrinsic research potential and tractability, so as to answer an array of questions of general interest. The interactive diverse environment is clearly an asset to GReD, as it is apparent from the numerous inter-team co-published works. The GReD has also striven to develop well-equipped platforms that are utilized by GReD as well as other Clermont-Ferrand laboratories.

Throughout the last 4 years, the overall size of the GReD laboratory has remained nearly constant. Though, in light of the contract renewal, several restructuring changes were made: three former GReD groups have ceased activity, while two other teams have been reorganized and one new external group, composed of clinicians, has been invited to join. GReD hosts a set of excellent teams, two of which are newly established groups, headed by promissing young investigators.

Overall, GReD has an amassed potential due to its convincing research projects paired with its very good scientific production. Nevertheless, it is felt that several groups should progress in the next five-year period to be more competitive at the international level. Besides a strong emphasis on basic research programs, the laboratory has worked to incorporate more applied approaches in medical sciences by recruiting groups of clinicians from local hospitals, but their integration with the other GReD teams must progress. Conversely, scientists from the GReD have successfully integrated translational researches in their projects.

- Strengths and opportunities

The GReD is a well-organized and robust research unit. It provides a rich environment, the atmosphere is lively and the whole staff is getting involved. Collectively, GRed has organized a very active scientific animation with weekly seminars opened to other laboratories. Consequently, GReD plays a major role in Master and thesis training with a dual attractiveness from the two specialized Universities. The support of GReD by the academic authorities is very strong and matches that of the Région Auvergne which bestowed the label of Center of Regional Excellence on GReD. This signifies the important commitment and recognition of GReD in the Clermont-Ferrand community.

The recent recruitment of brilliant and inspired young investigators, who established their team after being awarded highly competitive grants, is a plus that also illustrates the attractiveness of the GReD. This very positive progression leans upon the presence of excellent teams which have strongly contributed to the reputation of the laboratory. The recruitment of new researchers (a professor, two assistant professors, five CNRS or INSERM researchers) in the last years also denotes the appeal of GReD.

The GReD leaders have been efficient in raising money from a variety of sources, with a noticeable support form the Région Auvergne (Région/FEDER), but also from national agencies (ANR, INCA) and foundations (ARC, FRM, AFM, LNCC).

The funding by the National Plan Campus for the construction of a novel building to host the whole research unit provides an invaluable opportunity for the GReD to get more efficacy and visibility.

The technological platforms run by GReD staff are very well equipped and maintained (microscopy/imaging and Drosophila transformation) and are open to other laboratories and industries. The Drosophila trangenesis platform, originally built with support from a European network, offers worldwide services and is very useful to the French but also the European community.

- Weaknesses and threats

GReD has been efficient at producing good science, and the contribution of several teams is remarkable but the laboratory should globally improve publications in high impact journals. Several groups have the potential to select higher rated journals, which they could more easily reach if they were to develop more focused analyses.

It is felt that, at present, international recognition of the GReD is not at the height of its potential and could be improved. This concerns the rare participation of teams in international consortia (notably European), the still low number of foreign thesis students and post-docs, and the limited participation of the staff in the organization of international scientific meetings.

The uneven distribution of the technical assistance among the teams and the aging population of the technicians and engineers (contrary to that of the researchers) raised the question of the preservation of acquired competences during the five-year period to come, both at the level of the teams and the collective platforms.

The incorporation of teams mostly composed of clinicians evinces the will of GReD and its direction to boost translational research, notably in connection with the future gathering of GReD on the campus of the Université d'Auvergne. Though, the committee observed that medical research projects are still struggling to really benefit from the GReD environment and competences, and they are not optimally integrated.

- Recommendations

The GReD has been founded in 2008 and progressed well since then. It has been recently very successful in recruiting excellent PIs, but it has to reinforce its international attractiveness, in particular towards European scientists and students. While approving the efficient policy to recruit talented and successful PIs, the Committee also encourages to select higher rated journals for publication of research results to foster a better recognition at the international level.

To develop a continuum between basic and medical sciences, it is recommended that concrete collaborative work between clinicians and GReD scientists is encouraged and that a clearer strategy is defined towards that objective.

The grouping of all personnels of the GReD at one site on the campus of the Université d'Auvergne is fully justified. This will however require that the teaching staff from the Université Blaise Pascal finds the proper infrastructure for the academic activities on the campus Les Cézeaux. A novel green house will most likely be installed at Les Cézeaux, close to the already operating mouse transgenesis facilities, but indoor growth chambers should also be installed in the new building. The Committee encourages the GReD direction to pursue its action towards the two institutions to urge finding solutions to these sensitive issues.

While recognizing the efficient policy in recruiting promising investigators, it was generally felt that the GReD could benefit from setting up an external scientific council that would help tracking the progression of ongoing projects and facilitate the integration of newly recruted groups of clinicians, especially during the next five-year period.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	42
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	18
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0,97
A4: Number of HDR granted during the past 4 years	12
A5: Number of PhD granted during the past 4 years	37

3 • Specific comments

- Appreciation on the results

The GReD project covers broad scientifc topics which are well interconnected. GReD has built up a recognized expertise on the analysis of chromatin and gene silencing through the study of epigenetics marks in different models (notably Drosophila and Arabidopsis) and diverse biological situations ; this has provided a core knowledge that is now profitable to many GReD teams. Study of development and differentiation has also led to the emergence of novel and original concepts in telomeres protection, in the formation of early lineages, in the regulatory networks that control the development of muscles and the regulation of cell polarity under stress conditions. The study of sperm maturation has shown its sensitivity to cholesterol homeostasis, which is explored elsewhere via the analysis of regulatory nuclear receptors. Tumorigenesis is also the common thread of several GReD teams which have had a strong impact in the study of adrenal tumors in particular.

The relevance and the originality of the research at GRed is very good. Overall, the teams have brought a significant contribution to science, to academic training and, more modestly, to valorization of research. The GRed has published 156 papers in the last four year period. The IF analysis reflects a very good level of production, with 10 % of the papers in journals rated above 10. However, only a few teams contribute to these high visibility papers. In general, groups leaders are encouraged to aim at journals with higher impact even though it may be at the expense of the quantitative indicator of their production.

Concerning the valorisation aspects, the GReD has supported the development to two innovative technological projects ; one aims at using stem cells to assay toxicity of drugs ; the other is devoted to Drosophila transgenesis and dsRNA injection and is used locally but also by a number of French and foreign laboratories. A few groups have established cooperative projects with local and national industry partners but no patents have been deposited over the 2008-2010 period. The GReD has also developed strong links with the hospitals and with the Centre Jean Perrin for cancer treatments.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

The GReD is considered a priority by the Région Auvergne which in practice provides extra funds for equipment and salaries. Several of the group leaders have been awarded highly competitive grants. The laboratory has been reinforced by the recent recruitment of two young French PIs with high track record and inspiring projects. One of them recently got an ATIP-AVENIR grant while the other obtained a Starting Independent Researcher Grant from the ERC. Some GReD scientists have been often invited to international scientific meetings. Many of them have been also active in the local and regional scientific animation, but only a few have participated in the organization of international congresses. It is felt that, owing to the potential of many groups, this could be improved and would help increasing the visibility of GReD at the European and international levels.

In the last four years, five CNRS or INSERM researchers and three researchers-teachers (1 PR and 2 MCF) have joined. Most young scientists in Clermont-Ferrand are French and many originate from the closer surroundings. The degree of internationality has slightly progressed over recent years, with a few non-French students and postdocs but it could be improved still. The recruitment of post-docs is rather sustained at the local and national levels essentially. The defense of 24 University theses in the past four years and the presence of 29 thesis students at this moment illustrate the attractiveness of GReD for doctoral training.

The GReD teams have been successful in raising a diversity of funds at local (CPER-FEDER, Région Auvergne) and national levels (ANR, INCA, diverse foundations) and two groups participated to European programs, of which one team leader coordinated an impressive Network of Excellence. The same group was labeled by FRM and got a three-year support. Partnership with foreign institutions is variable among teams.

- Appreciation on the management and life of the research unit

The Director has established an efficient connection between the GReD unit and the local academic, clinical and industrial community. This action has been instrumental for the GReD to obtain the label of Center of Regional Excellence from the Région Auvergne and has led to establish GReD as a major and the larger laboratory in basic life science in Clermont-Ferrand. The sensitive issue of the re-localization of the GReD teams at one site (the teams are presently divided in two distant locations) will find a solution through the construction of a new building in downtown Clermont-Ferrand with funds from the National Plan Campus. The new building will accommodate all the laboratory over some 4000 m2. Significantly, it will sit on the medical Campus, which suits the objective of the direction to give a strong inflexion towards interactions with clinicians. Although this is very valuable, the GReD direction has to keep working conditions optimal also for the plant groups which also represent part of the GReD strength.

The discussions with lab representatives (either researchers, teachers, technical staff or students and post docs) have highlighted the quality of its governance, the efficacy of the GReD internal organization, and the prime importance of well-equipped and maintained core facilities within the laboratory. Communication is fluid at GReD, although technicians and engineers expressed that they are not systematically informed of the decisions of the direction on their careers (ranking for promotion, extra bonuses…). Thesis students and postdocs are also satisfied with the GReD environment but wish that their representatives in staff meetings ensure a better information flow about GReD issues.

The scientific animation is excellent with weekly seminars (Les Mardis du GReD) opened to a large audience, and one GReD annual meeting. GReD staff has also taken part in the organization of many scientific meetings held in Clermont-Ferrand.

The Professors and Assistants Professors (MCF) at GReD represent an important body providing continuity, with a staff of 44, among which 14 are clinicians. All have a heavy teaching load and are involved in MCs and thesis education in particular, notably at the Université Blaise Pascal (Les Cézeaux), and in the training of medical students at the Université d'Auvergne. Many of them have key responsibilities in different courses. CNRS and INSERM researchers also take an active part in teaching in Master programs.

- Appreciation on the scientific strategy and the project

The proposed development of the unit defines three main directions, with a critical mass of 4 to 5 teams each. One is the study of Genome Dynamics and Epigenetic Control, the second is the exploration of Reproduction and Development in Health and Disease and the last one the study of Endocrinology, Signalling and Cancer. The purpose of these axes is to confer visibility to the GReD project, but the strategical coordination of the program will still be operated centrally. The proposed projects are feasible, as long as new plant growth facilities become rapidly available to the community working on plants and team 1 in particular which is in urgent need of such an equipment.

The proposal is the result of a rather deep reorganization of the existing laboratory. Two groups have stopped their involvement in GReD, while a previous team leader has joined another group. Two new teams headed by young investigators coming from outside have been established and contributed to reallocate staff of the GReD, while a third one supported by the Université d'Auvergne will also move to the GReD. In addition, the new organizational chart comes along with the evolution of already established groups as, for example, teams 4 and 5 are now led by two scientists. It is felt that all these changes are appropriate and will confer enhanced efficacy. At the same time, this implies that the allocation of human ressources is regularly adjusted considering that there are discrepancies between the different groups for technical assistance and that a significant fraction of the pool of staff technicians and engineers will retire in the years to come.

The renewed project is also sustained by the recent recruitment of youngs scientists. This clearly gives further strength to the research projects. A key to the future development of GReD also lies in the capacity for a few teams to develop more focused approaches.

The will to establish stronger links with the clinical and cancer research in particular has defined a clear orientation in the project and stimulated the incorporation of a novel team. The integration of clinic-driven projects is to be encouraged but implies that a clear strategy is deployed to boost collaborative projects and approach phenomena at a less descriptive and more basic level. Remarkably, the efforts of GReD scientists to incorporate basic concepts towards the development of novel therapies have led to fruitful cooperation with local hospitals and to the incorporation of clinicians in their teams. The development of such interactions is strongly encouraged.

The allocation of resources (other than personnels, see above) is well-established and relevant. The GReD policy experienced during the present four-year period satisfies all the staff and will be maintained.

Importantly, the project is strengthened by the existence of cutting edge projects, carried out by either already installed teams or newly recruited PIs who have rapidly found at GReD an adequate environment and the human resources to organize their team.

4.1. Appreciation team by team and/or project by project projet

- "SIL.EN.T. - Silencing, Environment & Transposons"
  Team Olivier MATHIEU

    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	*3*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	0	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	1	1

In italic : estimation for 2012

    - Appreciation on the results

This so-called "SILENT" team is a very young group with a three research staff. The PI who obtained his CNRS position recently (2008) is only beginning to establish a track record as an independent investigator. His past publications are excellent in number and quality, with papers in the highest impact journals (e.g. Nature, Cell, EMBO Rep, EMBO J, PLoS Genet).

    - Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The group leader is a young but already recognized scientist in the plant epigenetic field. He was particularly productive during his post-doctoral studies in a leading laboratory in Geneva. The team that he has just established will ensure his position at the forefront of plant genetics through continued collaborations with his post-doc advisor but also with other very renowned laboratories in Europe. The PI's promise as an investigator is underscored by his recent award of a Starting Independent Researcher Grant from the European Research Council.

    - Appreciation on the scientific strategy and the project

The primary goal of the team is to understand the mechanisms controlling DNA methylation homeostasis in plants. The project also includes analysis of the impact of environmental stresses on plant gene silencing. The research objectives for the next 4 years are clearly defined and rely on the use of genetics, reverse genetics and high-throughput RNA sequencing. To summarize, the projects aim at:

- Identify the factors inhibiting DNA re-methylation at the FWA locus and analyse their activity at a genome-wide level;

- Understand the mechanisms controlling the rapid and efficient re-establishment of silencing in one generation at the Arabidopsis EVD retrotransposon;

- Understand the mechanisms mediating stress-induced release of transcriptional gene silencing at endogenous and transgenic loci in Arabidopsis.

These objectives are all very well rooted in previous works performed by the PI during his post-doc and constitute an exciting series of integrated projects. Although this continued collaboration is certainly worthwhile, it will be important for the team to develop sufficient singularity to avoid overlap with other leading groups in the field.

The high quality of the past research achieved by the group leader ensures the feasibility of the different projects in the proposed timetable. The highly competitive field in which these projects are taking place will necessitate that this young group efficiently utilizes human resources and available infrastructure.

- Conclusion :

This is an excellent and ambitious young team project which clearly performs at the cutting edge of science. The project is further strengthened by expertise provided by an array of well-established collaborators. The team is clearly an asset to the GReD laboratory and to plant biologists in Clermont-Ferrand and its productivity is expected at the highest.

The team will perform several genetic screens that will require facilities for plant growth. The availability of sufficient space for greenhouses and inhouse plant growth chambers is a condition for productivity of this team (and other plant groups within the unit).

- "Establishment, maintenance and transcriptional regulation of heterochromatin"
  Team Sylvette TOURMENTE

    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	1,80	0,80
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.8 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	2	2

In italic : estimation for 2012

    - Appreciation on the results

Previous work of team 2 has made a substantial contribution to our understanding of the process of 5S rDNA silencing in the plant model system Arabidopsis. The rDNA genes provide an important component of ribosomes, and their balanced expression is therefore essential for protein production in general. The multicopy nature and the diversity of the 5S genomic templates represent an interesting system to study several aspects of gene expression in connection with sequence diversity and DNA methylation. The team has provided clear evidence, based on the use of plant mutants, that a coordinated temporal interplay between DNA methylation, chromatin-related factors, and RNAi components is required to establish gene silencing at part of the 5S rDNA copies. The team members have also identified environmental conditions that trigger modifications of the methylation status at these loci. In parallel, they have shown that PolV, a plant-specific polymerase involved in transcriptional gene silencing, has a specific role in the regulation of a subset of 5S rDNA loci located on the chromosome 4. The work of the team has resulted in several publications in recent years, some of them in high quality journals (PLoS Genetics, Plant Journal, EMBO Rep). Two of the major scientists of team 1 were trained in the team 3 during their thesis projects.

    - Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The group has been attractive for new members from within the unit as well as for young scientists with independent positions and own projects. A young researcher with an excellent background in plant and animal chromatin research and an impressive publication record has recently joined the group as a CNRS researcher and will add to the scientific weight of the unit with new topics, additional funding, methodological expertise and supervision of co-workers. The group has also been very efficient in attracting teachers/researchers (PR, MCF). Despite these positive aspects, the team has not been able to get appropriate funding to sustain its research, nor to create or participate in national or international networks.

- Appreciation on the scientific strategy and the project

The projects are organized along three main lines. The first one aims, in the continuity of the present work, at understanding the epigenetic mechanisms leading to the silencing of the 5S rDNA loci in planta. The second one deals with the analysis of the role of TFIIIA isoforms in the epigenetic control of 5S genes. The third project is a study of the role of SUN-type proteins in the dynamic translocation of target genes at the nuclear periphery. While the last one is a novel research program on epigenetic regulation of gene expression and is interesting regarding the main topics developed in the GReD laboratory, the Committee sees a need to extend or reorient the other research topics. The Committee supports finalization of the PhD project on the variant of transcription factor TFIIIA but would not recommend further investments in this line of research, since the exact nature of the TFIIIA isoforms remain to be clarified. Reorientation on broader questions and a focus on the potentially more relevant parts of current projects will certainly allow better cooperation and interaction with local and international colleagues.

- Conclusion :

— Summary

The team has performed significant work in the domain of plant epigenetics and has a recognized competence in 5S gene regulation. The project leader has been very successful in training and attracting young scientists who will probably add to the scientific competences of the team.

— Strengths and opportunities

The newly hired members have an excellent scientific background and should have the potential to improve and expand the scientific prospects of the team.

— Weaknesses and threats

Some areas of current research need reorientation towards broader and more relevant biological questions. The group could do better to acquire competitive funding to sustain its research.

— Recommendations

In order to remain competitive, the team should focus on promising developments within the projects and collaborations. In particular, the Committee feels that the projects addressing the co-regulation between 5S, 45S rDNA and ribosomal proteins and the role of histone variants and associated histone chaperones in heterochromatin organization are interesting and should be developed with priority. However, the international visibility of the group is presently limited, and external funding should be improved in order to sustain its research.

- "Genetic instabilities and control by the host genome"
  Team Chantal VAURY

    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	*1*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	2	2

In italic : estimation for 2012

    - Appreciation on the results

Team 3 investigates the mechanisms of transposable element (TE) silencing in the fruit fly Drosophila, focusing the analysis on the regulation of two retrotransposon models, ZAM and Idefix. In the recent years, the group has developed sensor GFP transgenes that allowed transposon silencing to be monitored visually during development in the germline and other cell types. From this work, the team has shown that retrotransposon silencing involved different types of mechanisms: 1) In ovarian tissues, silencing most likely takes place at a post-transcriptional level involving the RNA silencing proteins PIWI; 2) In other somatic tissues and cells, the silenced elements are found in a repressed form of chromatin, enriched in H3MeK27 methylation and Polycomb group proteins, and silencing is independent of the Piwi proteins. In parallel to this work, the group has also shown that Idefix can function as an insulator and barrier element, thus enlightening mechanisms through which insertion of this TE can modify gene expression. During the period under evaluation, members of the group published 12 articles in international journals. Of these, group members were either first or last authors on 6 publications. The most significant publications were in well-recognized general journals such as NAR or Retrovirology.

    - Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader is very enthusiastic and dynamic and has managed to develop a solid research project while being also the Director of the GReD with substantial duties in research and administrative management. The team leader has a long lasting experience in the field of TE and has been regularly invited to speak at international meetings. The team has established several collaborations with renowned leaders in the field and has been involved in the organization of several international meetings, including in 2008, the International Congress of Transposable Elements, which was held in France (Saint Malo). The team leader has been able to obtain financial support for her research from local and national funding agencies (ARC, INCA, Région Auvergne).

- Appreciation on the scientific strategy and the project

The project of the team is to further explore TE silencing using the specificity of the two TE that they have analyzed so far (ZAM and Idefix). This will be achieved, on the one hand, by further investigating the different mechanisms responsible for TE silencing in the various somatic tissues. On the other hand, the team intends to develop cutting edge in situ approaches and a genome wide chromosome conformation capture approach (4C) study to better understand the dialogue between TEs and their regulatory loci. For this purpose, the group has already developed a unique DNA/RNA fluorescent in situ hybridization which allows the detection, on the same sample, of a region of DNA and of the transcripts produced in this region. For the 4C approach, they have established an appropriate collaboration with a Dutch research group with specialists in the field. The project is original and, if focused, should be successful.

- Conclusion :

— Summary

The team is already well recognized in the field and develops an original research project. Although the study of TE silencing in relationship with RNA interference is very competitive, the research project of the team has a number of original and specific aspects that should allow developing a niche where the team leader should be able to strengthen her international visibility.

— Strengths and opportunities

There are two aspects of the project that are more cutting-edge and that should be focused on. The mechanism of TE silencing that is not dependent on Piwi protein is original and it should be analyzed in depth. Aspects related to the dialogue between TEs and their regulatory loci involving the DNA/RNA FISH and the genome wide survey (4C) for pairing between TEs and the regulatory loci are very promising. The existence of lines with stable and unstable TE silencing offers a further promising path for a genetic approach to the underlying molecular controls.

— Weaknesses and threats

Given the small size of the team and the high competitiveness in the field of transposon silencing, the team leader should be careful of not dispersing the project too much.

— Recommendations

Keep the project focused on its original aspects, i.e. the two retrotransposons ZAM and Idefix and their regulatory locus (COM/flam), rather than trying to expand it in too many directions (e.g. to I-related elements). Regarding this last aspect, the projects of the permanent researcher that joined the team in 2008 were not very clear: they appeared as side-projects and it was not really clear to the Committee how in silico analysis of TEs in the 192 Drosophila lines could help to decipher efficiently TE silencing processes. As this new permanent researcher has considerable background and experience, she represents a strong force of the team. Given that the team leader is also the Director of the GReD, it is essential that this full time researcher be more directly involved in the main aspects of the project. This should allow developing a niche and increasing further the number and level of the publications.

- "Recombination and maintenance of the genome"
  Team Charles WHITE

    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	*3*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	1,80	1,80
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	3	3

In italic : estimation for 2012

    - Appreciation on the results

Previous works of team 4 concerned three topics. (1) the analysis of kinetics of DNA repair and the study of the hierarchy of the pathways while exploiting genetic and cytological approaches with mutations affecting components of different DNA repair pathways; (2) the analysis of how the open ends of chromosomes are protected from erroneous recombination events that would lead to chromosomal instability; (3) the investigation of elements of the programmed recombination during meiosis.

These are all fundamental and important biological processes, and the team adequately selected the plant model Arabidopsis in which, in contrast to animal models, most of the mutants in the DNA repair and recombination pathway are viable. Past production of the team is very sound and well accepted, with several publications in high quality journals (Plant Cell, Plant Journal, PLoS Genetics, EMBO J). The group has further acquired a substantial amount of grant support in national and international programs.

    - Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team is frequently invited as a partner for international networks, and the PI and research staffs contribute regularly to international conferences. The PI has experience as a network coordinator and organizer of conferences in the field. He is a frequent reviewer for top journals and a consultant for plant industry. Therefore, the qualification of the group leader and the relevance of the topics are beyond doubt. It is fortunate that the group, beside the PI, has qualified and experienced permanent members who contribute to research as well as teaching activities, and a good frequency of post-doc appointments. The current lack of thesis students is regrettable but hopefully overcome by a more pro-active and international advertising of a GReD doctoral school and an inspiring presentation of the group's project in this framework.

- Appreciation on the scientific strategy and the project

The current projects follow three main lines, mostly in continuation of previous work. (1) The group will investigate the role of repair/recombination proteins during meiosis and study the pairing behavior of special chromosomal regions. For this, they have generated several fluorescence-tagged proteins which, together with well-characterized mutants and lines with different chromatin configurations (EpiRILs), result in a valuable toolbox for this project. (2) They want to investigate the consequences of malfunctioning telomere protection with regard to the chromosomal fusions and their consequences for the whole cell. This will include global analysis of RNA profiles after several generations of reduced telomerase activity. (3) Further, the group wants to apply the knowledge about plant repair and recombination to address issues of interest for biotechnology. They will increase or decrease the expression of individual recombination proteins during meiosis or in somatic tissue or during plant transformation, including attempts to increase the rate of targeted integration.

Project 1 will certainly provide valuable insight about the kinetics and localization of individual components. Project 2 and 3 are definitely addressing interesting questions, but they are described in much less experimental and strategic details. Therefore, their potential is currently difficult to assess on the basis of the oral presentation and the written report. However, the project descriptions will have to be elaborated for future grant applications and will certainly receive refinement on this occasion. Further, the group has assembled a large collection of mutant lines defective in various aspects of DNA repair and recombination. These genetic tools position the group to make unique insights. As for the other plant research groups, the question of appropriate plant growth facilities, especially after the planned move into the new building, is of crucial importance. An active role in the planning and joining forces with the GReD colleagues is recommended.

- Conclusion :

— Summary

The team has substantially contributed to the understanding of DNA sequence maintenance and modification in plants. The project leader is an internationally recognized and experienced PI who can contribute with his experience to the GReD beyond his own field.

— Strengths and opportunities

The projects of the group are all biologically relevant and good to study in plants, with the potential to identify principles that are also valid in non-plant organisms. The group has generated interesting tools for further studies. The team is expected to continue its successful grant acquisition, education of young scientists and local and international collaboration.

— Weaknesses and threats

Although material and tools for future work were mentioned, the strategy and detailed plans were not always obvious from the presentation. The group does not currently contribute to the education of PhD students.

— Recommendations

Parts of the projects need more detailed planning in the course of future grant applications; the group is encouraged to recruit and inspire good PhD students, and it should interact with the other plant groups to help finding a good solution for appropriate plant growth facilities.

- "Genetic and epigenetic control of cell lineage commitment during mouse development"
  Team Claire CHAZAUD-Philippe ARNAUD

    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	1,5	1,5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3 + *1*	
N6: Number of Ph.D. students (Form 2.8 of the application file)	1 + *2*	
N7: Number of staff members with a HDR or a similar grade	2	2

In italic : estimation for 2012

    - Appreciation on the results

Team 5 is led by two young researchers who recently decided to combine their expertise in one group project at GReD. The publication record of both is of very high quality, and they have been extremely influential in their fields of research.

One has an important track record from his previous positions in the field of genomic imprinting in mammals, and he published important papers as senior author, in addition to a number of collaborative papers.

The other has a short but high impact production in an extremely competitive area of research (that of early mammalian development), and has contributed seminal papers to the field that have changed the paradigm regarding the specification of the primitive endoderm in the blastocyst. Since she established her group in 2003 in Clermont-Ferrand, she invested in novel areas of research and was well inspired in her research.

As a consequence of their past research positions, both team leaders have established well-balanced partnerships with labs of the highest quality. Both of them as well as other members of the team have actively participated in international and national scientific meetings.

    - Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Due to the recent establishment of their research groups, the team members are only starting to gain visibility in the international research community. It is noteworthy that one of the team leaders has recently been awarded with an ANR Young Investigator Grant. Further, the other has attracted in the past a foreign postdoctoral researcher. At present, the team is funded mainly by small national research grants, but it is foreseeable that in the near future more significant national and international grants will be obtained. One of the two principal investigators is also part of a very active scientific network of European biologists studying early mouse developmental that has recently applied for funding from the European Union through the Marie Curie Initial Training Network Scheme.

- Appreciation on the scientific strategy and the project

The joint research project aims to understand how the first stages of mouse development and the appearance of early lineages are controlled, by both genetic and epigenetic mechanisms. At the genetic level, the projects described for the period 2012-2016 are a well balanced mixture of short and long term aims, that are built on previously generated animal models and methodologies (such as mouse embryo electroporation), and also requires the generation of novel ones (i.e., alleles coding for new fluorescence-targeted proteins involved in early specification). The main objective is to understand the molecular mechanism responsible for the generation of the primitive endoderm lineage and how it acquires its cellular phenotype. The project will tackle this problem with multiple approaches, and is clearly at the forefront of the research carried out in this area. The epigenetic basis of early development will be explored by examining in detail the establishment and control of bivalent chromatin domains in the genome. These are genomic regions that carry a peculiar set of epigenetic signatures, which are believed to mark genes as silent, but being primed (by a "paused" polymerase and concomitant active marks) for a rapid activation in response to early differentiation signals. To do so, previous experience in imprinted genes will be used to study the control of bivalent domains, both their establishment and their resolution. The aim is to go a step further and analyse the molecular mechanisms that are responsible for setting up these bivalent domains. This is a very important and novel aim, also a competitive one, as up to now, much of the published work on bivalent domains has been limited to their description and charting, with little knowledge on the precise factors that are implicated in their control. Another important and original aspect of this part of the project is to explore the connection between misregulation of bivalent marks and cancer.

- Conclusion :

— Summary

Overall, this is a high quality team led by two young researchers who have an excellent track record from their previous research experience and have already produce important publications as senior authors. It is expected that the team will perform excellent research in the future, building upon their previous experience as well as entering novel areas.

— Strengths and opportunities

The strengths of the team are the excellent prior experience that two group leaders possess, together with a very important network of international relationships and collaborations. The research theme to be developed is highly ambitious and addresses very important questions relating to how cells in the early embryo take decisions related to their lineages and fates and how they maintain them through development. These issues are of clear relevance to the field of cell reprogramming, with the obvious implications it has in regenerative medicine. The collaboration of the two principal investigators of the team provides a privileged opportunity to address these issues from different angles (developmental, genetic and epigenetic), which is not common in the field. It will be very important to interconnect both work plans and tackle similar problems using the tools and approaches developed in the past by both.

— Weaknesses and threats

The main weaknesses of the team are those associated with them being of recent formation, in terms of size, funding and scientific productivity. However, it is anticipated that these problems will be overcome once the proposed projects start to produce results. A threat that the team leaders must be very careful to avoid is to develop two independent research projects with only little interaction between them. The Committee supports the current concept of co-leadership in the project, as long as there is coordinated development and fluid collaboration between the two PIs. The close collaboration might even serve as a model for other potential synergisms within the GReD.

— Recommendations

The project is promising and based on very solid track records of the two PIs. Potential synergisms between the PI expertise and field of research could really place the proposed research in a first position at the international level in the coming years.

- "Mechanisms of post testicular male infertility"
  Team Joël DREVET

    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	*1*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	3,32	3,82
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.8 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	1	1

In italic : estimation for 2012

    - Appreciation on the results

The team aims at understanding the mechanisms ensuring the post-testicular acquisition of sperm fertilizing ability within the mammalian epididymis compartment. They mainly focus on investigating the regulation of oxidative stress and of cholesterol homeostasis during epididymal maturation of spermatozoa in mouse through the generation of powerful knock-out mice. This is an important issue given the high impact of defective post-testicular sperm maturation in male infertility. The results of the team, based on analysis of GPx knock-out mice that they generated, show that post-testicular oxidative insults of sperm DNA have strong effects on the issue of reproduction. These results received a lot of attention from the international community. By performing a careful phenotypical analysis of LXRs knock-out models, the team also very convincingly demonstrated that oxysterol and their receptors, LXRs, and more generally cholesterol homeostasis, are crucial for the maintenance of the epididymal epithelium.

These important results in the field of reproduction physiology were published in internationally recognized journals, some of them being highlighted by commentaries. The team was invited to write several reviews and book chapters and its members were regularly invited to give communications in national and international meetings. Three theses were defended. The work benefited from appropriate high quality collaborations, either local (inside the Laboratory) or national or international.

    - Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team attracted good PhD students and will be joined by two MDs. However, no post-docs joined the group during the last period. It should be noted that it is essentially composed of teachers/researchers (PR, MCF) with heavy teaching duties in all biological trainings proposed by the University and that the productivity of the group is good with eleven research papers within the evaluation period.

The team actively participated to an international network where it was the only French partner among 10 international members, and played an active role inside the network until its completion. The PI of the team has recently been contacted by NIH laboratories to participate to a grant proposal.

The team developed active collaborations and was invited to international meetings, a consequence of the novelty of their data on the impact of oxidative stress and cholesterol homeostasis on epididymal maturation of spermatozoa.

- Appreciation on the scientific strategy and the project

The team intends to pursue its two main projects for the next five years period. The generation of a double GPx5/GPx4 knock-out mouse will be used to deeply explore the sperm nucleus defects caused by oxidative attacks. Using the LXR knock-out models, the team will examine the precise sperm defaults caused by impaired cholesterol homeostasis, the impact of hypercholesterolemia caused by a western diet and the involvement of secreted phospholipases. This part of the project will be connected with clinical investigations aiming at investigating the occurrence of dyslipidemia on sperm cells of men attending fertility centers. In parallel, a third project, based on a knock-out mouse will analyse the participation of indoleamine 2,3-dioxygenase in the inflammatory status of epididymis.

The project could be too large given the size of the team and the absence of full-time researchers. Several research axes are presented, some of them being either vague or highly speculative. A strong in depth analysis has first to be conducted in order to precisely characterize the defects in the sperm nucleus compaction resulting from GPx invalidation. After this descriptive and exploratory step, the team should then define an overall clear direction, a probably difficult issue given the potential pleiotropic effects that can be generated. The assumption that an epigenetic process could be impaired, giving rise to the observed compaction defects, is actually not scientifically funded. However, if the phenotypic analysis reveals that an epigenetic process is clearly affected, the team has to develop appropriate collaborations to get the skills required to conduct a deeper analysis.

- Conclusion :

— Summary

The past work of the team revealed the importance of the oxidative status and the cholesterol homeostasis for epididymal functions and the extreme sensitivity of this compartment towards both these factors. The defects of the sperm nucleus caused by oxidative stress and their negative impact on the embryonic developmental program should question the use of ICSI technology. These studies deserve to be continued given their cognitive interest and the major concern represented by human infertility in developed countries.

— Strengths and opportunities

The team has a unique expertise in France, and possibly in Europe, in the field of epididymis physiology. They generated powerful mouse models and obtained important and promising results on the consequences of oxidative attacks of sperm on embryonic development. They have now to carefully choose their future directions to improve their international recognition, to consolidate their leadership in the field and not to divert their efforts.

The arrival of two hospital practitioners in the team in 2012 should be supported. It would strengthen the interface between basic research and clinical research within the team.

— Weaknesses and threats

The multidirectional proposed project diverts the efforts instead of focusing on a clear direction. It is over-sized given the size of the team and the lack of full-time researchers and post-docs. The team has a lack of skills to develop the epigenetic part of the project. This part of the project has no priority and could be irrelevant. The defects of the sperm caused by either oxidative stress or impairment of cholesterol homeostasis could be too pleiotropic to provide a clear research direction. In this case, the project could have to be re-oriented.

— Recommendations

A strong in depth analysis has first to be conducted on the sperm nucleus defects. It should provide the main direction of the project, where the team has to focus. The group should plan to use its own strengths and expertise in post-testicular sperm maturation in order to carve out a unique niche for itself and to improve its international recognition.

- "Diversification of muscle and heart cells in normal development and in pathological conditions "
  Team Krzysztof JAGLA

    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1+*1 2012*
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	*2*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	2	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.8 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	1	1

In italic : estimation for 2012

    - Appreciation on the results

This team aims at deciphering the regulatory networks controlling muscle and heart development programs in Drosophila. Both projects are connected by the central role of the ladybird gene, which codes for an evolutionarily conserved homeodomain factor required for cell fate specification of a subset of muscle and heart cells, in the fly and vertebrates. The team has shown that ladybird acts at multiple levels not only by regulating other identity genes but also late acting genes such as cytoskeleton modulators involved in the morphological process of muscle fibers. In parallel, the team has also worked on the development of the Drosophila heart. This has led to the identification of new heart structures and of genes required for cardiac lumen formation. The team is also studying muscle stem cells and muscle pathologies.

This is a well-established team, with an excellent scientific output and solid international relationships and collaborations. The work of this team led already to an impressive number of excellent papers with primary data in top journals, many of which influenced the research field significantly. Overall, the quality of the papers produced by the team has increased over the last years. Efficiency and productivity of the team is very high.

    - Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The participation of the PI and other team members in international events is very outstanding, and it is noteworthy that the PI has been involved in the organization of a number of these events. The international dimension of the team is illustrated by the stable recruitment of experienced post-doc researchers from abroad, and the participation of the team in international projects. In this regard, it should be stressed that the PI has been the coordinator of an extremely successful European Network of Excellence. Apart from this, the team has obtained constant funding at a high level, both national and international. All this resulted in driving important collaborations with other research groups that contributed to important scientific results.

- Appreciation on the scientific strategy and the project

The team presents a well-designed research project for the next years that balances the previous expertise of the group in Drosophila developmental genetics. The underlying theme of the proposal, in all its different aims, is to understand the gene regulatory networks underlying muscle progenitor (stem) cells, and how specific components of these networks act during the differentiation process.

In parallel, the group plans to use the fruit fly as a model system to better comprehend the physiopathology of human diseases (dystrophies and myopathies). This approach is highly original and also risky, but the existence of more conventional projects will insure the continued productivity of the team. To do so, the project will exploit a variety of experimental approaches, including Drosophila genetics, zebrafish assays, state-of-the-art transcriptomic and genomic studies, and analyses of human clinical samples. The team has a proven expertise in these approaches, and where not, they include the necessary collaborations with other expert research groups.

Overall, the proposed project is of very high quality, and its feasibility is ensured by the composition of the team and its previous expertise.

- Conclusion :

This is a well-structured and productive team that capitalizes on its previous research and, at the same time, proposes novel and original projects.

— Strengths and opportunities

The team and particularly its leader have been strongly involved in the development of outstanding GReD and University technological platforms, as exemplified recently by the lead of an Equipex application. The involvement in a microscopy and imaging center is highly relevant and is an asset for local teams, from the laboratory and the whole Clermont-Ferrand scientific community.

The previous track record, with regards to publications, scientific communication and funding, is excellent

— Weaknesses and threats

No major weaknesses can be pointed out.

— Recommendations

The recommendations are to pursue the future projects with the same success and the same productivity. The forthcoming recruitment of a researcher/teacher will contribute to the stability of the team.

- "Epithelial growth and morphogenesis"
  Team Vincent MIROUSE

    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	*1*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	0	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.8 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	1	2

In italic : estimation for 2012

    - Appreciation on the results

This new team is aiming to decipher the relationship between cell growth and cell morphogenesis and, more specifically, a novel epithelial polarity pathway required under nutrient deprivation. To address these questions, the team is investigating in Drosophila the development of the follicle cells, an epithelial tissue that surrounds the female germline cyst during oogenesis. The organization of the team is very recent (2010). The research program is based on recent work performed by the principal investigator. He established a very interesting link between energetic stress and cell polarity through the relationship between the tumour suppressor LKB1 and AMPK and Myosin II. In parallel, it was shown that the dystroglycan complex linked to the extracellular matrix in relation with the actin cortical network is also involved in the control of the apico-basal polarity under energetic stress. The past work of the young team leader, while a postdoc (2005-2007) or in the group previously headed by his former advisor at GReD was related to this topic. His publication record is in top journals (Cell, Dev Cell, J Cell Biol, Development). He also developed several important collaborations for the realization of the research program of the group.

    - Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Although the group has been established very recently, its attractiveness is very high. Indeed, the appreciation of the group leader is evident from his award of an ATIP/AVENIR grant, which recognizes him as an independent investigator. He received invitations to several prestigious institutes to present his results. The ability and potential of the group to raise funds is very good.

    - Appreciation on the scientific strategy and the project

Understanding the processes controlling cell polarity in Drosophila is a competitive field. However, the connection between cell polarity and energetic stress is novel, original and promising through a more general relationship between cell growth and cell morphogenesis.

The planned research project tackles major, novel and essential biological questions in an experimentally innovative way. Sharing common technologies and having excellent test systems in hand, the success of research efforts is well anticipated at short, middle and long term.

- Conclusion :

There is no necessity to give specific recommendations concerning the research projects of this team since the risk and challenge of the research program are well anticipated, in the auto-evaluation in particular, and since efficient collaboration with renowned partners have been launched.

In summary, this team, which has been very recently created, presents a very promising research program and is very likely to contribute substantially to the scientific weight of the GReD.

- "Metabolic and molecular implications of retinoids during human development"
  Team Vincent SAPIN
    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	12	9
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	1,50	0,50
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.8 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	8	5

In italic : estimation for 2012

- Appreciation on the results

This is a clinical research team which studies the effect of retinoids on the biology of two tissues : the amniotic membranes and the lung during fetal development. The ultimate goal is to exploit biological knowledge towards therapeutic purposes, targeting two pathologies: the prelabour rupture of amniotic membranes and the congenital diaphragmatic hernia. The team was integrated into the GReD 4 years ago to bridge clinical research with the cutting-edge knowledge-driven molecular biology, epigenetics and integrative biology research performed by the other GReD teams. If the potential of such close interactions exists, it could be improved and the association has still to bear fruits. The studies carried out in the present period remain descriptive and still wait to benefit of a better understanding of the involvement and mode of action of retinoids in the treatment of the pathologies under study.

The team is organized around staff members with both teaching and clinical duties who can dedicate only 50% or less to research activities. The publication record of the group is high in number of papers (33), but does not reach yet the level of completeness required for publications in high impact journals.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team has a good local visibility and a fair national visibility, with 13 invitations to national congresses within the review period. The international visibility should be improved and there was a single international invitation (Marocco). No foreign scientists were attracted to join the team and the international collaborations appear scarce and lacking a solid basis. The team has not raised any major competitive grants (ANR, EU …). It received some funding through industrial partnerships but the level of this support and the extent of the collaboration were not clearly mentioned.

- Appreciation on the scientific strategy and the project

The projects are ambitious and aim at pursuing the study of retinoids on amniotic membranes and lungs. Among many objectives, one is to incorporate pan-genomic transcriptomic analysis and epigenetic studies to evaluate the effect of treatment by retinoids. This is encouraged but the experimental models used could leave ambiguities and the protocols should be more deeply worked out to bring clear-cut results that enable the drawing of significant conclusions. The project aims also at answering a quite large spectrum of basic questions; it is felt that besides being more focused, its success strongly depends on the capacity of the team to establish concrete collaborations with other GReD groups. Besides, applied research projects may be fruitful in terms of practical outcomes, as the retinoid treatment of amniotic membranes in the case of corneal injury.

Overall, the proposed strategy does not really bring synergy between the studies on the amniotic membranes and those on the lung.

- Conclusion :

— Summary

The team is too focused on the production of descriptive knowledge. The unifying theme of the team, the retinoids, is not exploited because these compounds are not used in a way that will allow understanding of retinoid biology, mechanisms and physiological functions. Thus, the two main projects of the team hardly overlap and there is no synergy between the lung and the amniotic membrane projects. The benefits one could expect from the integration of a clinical research team within a basic level environment have been only marginally exploited. There is still a long way to go before new ways of thinking and new strategies are implemented to produce high impact biomedical research.

— Strengths and opportunities

The team has clinical expertise and direct connection to pathologies.

The integration within a high-level fundamental research environment with good technical platforms bears a high potential.

— Weaknesses and threats

The two main themes are too loosely connected and lack synergy.

There is too much emphasis on descriptive research. It was felt according to the written self-evaluation that previous recommendations from experts were not sufficiently considered.

The lack of integration between clinical research and fundamental biology weakens the objective of the GReD to integrate these two themes.

— Recommendations

The group should aim at producing more papers of higher visibility, even though if it may mean fewer papers overall.

It is strongly suggested to better integrate clinical research with basic biology questioning. This means establishing stronger links with the other groups of the GReD to obtain support to tackle problems in a less descriptive way.

More synergy between the two research axes of the team should be developed. Experimental pathology journals may be targeted in the future if the team members are able to integrate their findings in appropriate disease models. These journals have a high impact factor and are well respected in the scientific community.

- "Lipid, nuclear receptors and male disorders"
  Team Jean-Marc LOBACCARO
    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	*2*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	0,83	1,33
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.8 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	2	3

In italic : estimation for 2012

- Appreciation on the results

This team is focused on the study of the physiological roles of the lipid sensor nuclear receptors LXR, FXR and SHP in the male genital tract using transgenic and knock-out mouse models. It studies in particular the impact of these receptors and their ligands on the prostate, with an emphasis on prostate tumors, and on the testis, studying both Sertoli and germ cells. The aim is to apply knowledge gained from the study of mouse models to human health. The team is focused on a well-defined project and occupies a niche with high topical expertise that allows it to collaborate efficiently with two of the worldwide top-level groups on these nuclear receptors. The group is essentially composed of teachers/researchers (PR, MCF) with heavy teaching duties and has just been able to recruit a young full-time INSERM researcher that should enhance its productivity and visibility. The production of the group is good with five research papers within the evaluation period where the team plays a central role (first and last authors) published in good quality journals like Oncogene, J Biol Chem and Mol Endocrinol, and a number of collaborative work (including a J Clin Invest, IF 15, signed by the group leader as a last author, and a Genes & Dev, involving the group leader).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader has been invited to two national and one international (USA) conferences. Members of the team have organized two national conferences. The team has obtained a number of national competitive funds (ANR, FRM, Ligue, Canceropole). It is involved in collaborations with several national and international groups, in particular two of the most prominent leaders in the field (Switzerland and USA). This is a clear recognition of its expertise. The tasks of group members were very well presented reflecting an efficient team management. The group has recently attracted a full time researcher and a clinician showing its attractiveness.

- Appreciation on the scientific strategy and the project

The projects of the team are along the line of its expertise and the strategy of niche occupation is stable. The project is relevant both in terms of basic understanding and for its potential incidences on human health. The ambition to exploit better the impact on human health has not been fulfilled yet because of the lack of strong links with clinicians, but the recent recruitment of a clinician in the team should allow these links to be strengthened. Given the ambition of the GRED to combine basic and clinical research, this evolution of the team is laudable, and if successful, will allow it to play an important role in the overall equilibrium of the unit. Prostate cancer projects appear to be reasonable. The selected field has a major importance because of the association of Western diet and fat with prostate cancer prevalence in Europe.

- Conclusion :

— Summary

This small team successfully occupies a niche that allows it to be a recognized partner of major groups in the field. The production is good to very good in light of the heavy teaching duties of most members. The recent recruitment of a full time INSERM researcher and of a clinician will certainly contribute to increase its impact and visibility.

— Strengths and opportunities

The team has cumulated topical expertise in the biology of lipid receptors. The active networking deployed by the team leader has driven outstanding and promising collaborations. The recent recruitments should boost its production.

— Weaknesses and threats

The group should be aware that long term evolution may be limited when the niche will be fully exploited.

Also, the team lacks a robust funding at the moment to sustain the progression of the project. The epigenetic-colored project may not be the most relevant.

— Recommendations

The team should prepare future evolutions of its research projects to anticipate niche shrinking. They should strengthen the links with human health issues while keeping robust basic analyses and expertise. The group should also discuss thoroughly and critically the epigenetic-colored project with the GReD colleagues with expertise in that field. It is recommended to work at raising more stable research funds.

- "Adrenal tumours & adipose tissue homeostasis"
  Team Antoine MARTINEZ
    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	*1*
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	1,30	1,30
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.8 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	3	4

In italic : estimation for 2012

    - Appreciation on the results

The team is interested in the pathophysiology of the adrenal cortex and adipose tissue. The work focuses on the molecular mechanisms involved in adrenal tumorigenesis and in the onset of obesity. The work relies on genetically modified mice. The team has two research domains:

- the regulation of adrenal steroidogenesis and adipose tissue homeostasis. In particular, they explore the mechanisms by which aldo-keto reductases regulate metabolism and differentiation of adipose tissue.
- the adrenocortical tumorigenesis. They explore the mechanisms by which cAMP/PKA and Wnt/ß-catenin pathways ensure differentiation of the adrenal cortex and induce tumor development.

In recent years, the team demonstrated that some murine and human isoforms of aldose reductases are involved in the biosynthesis of prostaglandins. They showed that this prostaglandin synthase activity is involved in the inhibition of adipogenesis and in the resistance to diet-induced obesity. There are important and original results that should bring new data and pathways to understand the onset of obesity.

In the field of cAMP/PKA and Wnt/b-catenin pathways, the group has demonstrated that constitutively active ß-catenin triggers the development of benign aldosterone-secreting tumor suggesting that the Wnt/ß-catenin pathway might be a potential therapeutic target in human adrenal tumors. By generating mice lacking the gene encoding the R1a regulatory subunit of the PKA (PRKAR1A gene) specifically in the adrenal cortex, they induced autonomous adrenal hyper-activity and bilateral hyperplasia that mimic the primary pigmented nodular adrenocortical disease (PPNAD), a bilateral adrenocortical hyperplasia causing hypersecretion of glucocorticoids. This mouse model demonstrates that a deregulation of PKA activity leads to the initiation and development of PPNAD suggesting that it should be considered as a developmental disease.

From these results, it appears that the team has a relevant national and international expertise on the function of the aldose reductase family in steroidogenic organs, on the cAMP/PKA and Wnt/ß-catenin pathways in human adrenal tumors.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

During the 2006-2010 period, the team members have published eight papers among which 2 have an IF>5. There are two high profile publications in which the group leader and a permanent scientist are senior authors published in PLoS Genetics and Human Mol Genetics. Other publications include those in Endocrinology and Mol Cell Endocrinol. Overall productivity is very good.

One article was evaluated and recommended by Faculty of 1000 Medicine. Eight other publications are originating from work carried out in collaboration with other teams or external laboratories. Twelve lectures of the team were invited by organizing committees in national or international congresses, sometimes with the best oral presentation award. There is also a large international project with participation of NIH in which the team is an important participant. International collaboration with a renowned group has a strong potential.

The team has recruited a postdoc from 2008 to 2010 and three PhD students. It has raised funds from the ARC, Ligue contre le Cancer, ANR « Rare Diseases » and ANR "Carney Complex » to support the work on PKA signaling and funds from the ARC and the Ligue contre le Cancer for the studies on Wnt/ß-catenin signaling and adrenal tumorigenesis.

From this year to 2013, the Regional funding CPER "Laboratoire d'excellence" supports the team in the field « Modèles génétiques du cancer prostatique et de l'obésité ».

The team participates to international or national scientific networks. They are involved in the COMETE national network (COrtico et Medullo surrénale, Etudes des Tumeurs Endocrines) and in the ENS@T european network (European Network for study of @drenal Tumors).

- Appreciation on the scientific strategy and the project

The project is based on two subjects: the role of aldo-keto reductases in white adipose tissue homeostasis and the role of cell signaling pathways in adrenocortical neoplasia and differentiation.

The first project consists in studying specific functions of the 3 murine and the 2 human aldose reductases on white adipose tissue. It is based on the use of gain-of-function models in cell cultures and transgenic mice. The impacts of expression of the different isoforms (Tet/on system) will be studied at the level of adipocyte differentiation, oxidative status and lipid metabolism. The work will be conducted in collaboration with two external groups of the CRNH Auvergne, INRA UMR1019 for biochemical analyses of lipid metabolism, and with the CHU of Clermont-Ferrand to provide human samples of adipose tissues. This part of the project is relevant since it will probably provide further information on the anti-radiogenic or obesogenic functions of the aldo-keto reductases.

The second project concerns the cell signaling pathways involved in adrenocortical neoplasia and differentiation during the early phase of tumor development and its progression. The role of PKA activity, of mTOR signaling and the involvement of ß-catenin will be studied in mice lacking the gene encoding the R1a regulatory subunit of the PKA and mice with activation of ß-catenin (collaborative project). This is relevant for understanding cellular signaling pathways in the pathogenesis of adrenocortical tumors. Translational research aspects are well developed.

- Conclusion :

The scientific output of the team in terms of quality, quantity and impact is very good. The team and the projects are attractive since a postdoc and a CR2 CNRS joined in 2008.

One of the strongest assets of the team is to have developed a unique transgenic mice model to study adreno-cortical tumors relevant for human diseases. Another advantage is the opportunity to conduct research at the interface with the clinic by the integration of the group in national and European clinical networks dedicated to adrenal tumors. The team will incorporate two endocrinologists from the CHU of Clermont-Ferrand.

This represents an excellent opportunity to effectively develop the clinical program and to limit the risks. The project is supported by ANR programs and it is planned to recruit a Post-doc (2012) for the PKA signaling studies and one thesis student for the Wnt signaling part of the project.

The project on the functions of aldose reductases on white adipose tissue is risky. To be achieved, the team should receive more technical support. Additional external funds may be also helpful.

- "Steroid hormones signalling and prostate cancer"
  Team Laurent MOREL
    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	0,86	0,86
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.8 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	4	4

In italic : estimation for 2012

- Appreciation on the results

This group is focused mostly on androgen receptor signaling in human prostate cancer. The topic of research is relevant and there is a considerable international competition in this area. A significant contribution of the team was to show the role of nucleophosmin as a new androgen receptor partner, its expression in human prostate cancer, and its implication in proliferation and PSA regulation. This led to one publication from the group with a high impact (Oncogene) in 2008 with senior authorship of a team member.

Previous studies on the interaction between androgen receptors and growth signaling pathways were published in the mid-impact journal J Mol Endocrinol. The group developed also interactions with several partners within the laboratory (teams 10 and 13) which have a potential to advance the visibility of GReD in prostate cancer biology. Another collaborative work concerns the development of a new therapeutic compound with some potential in prostate cancer. Here, the team participated with a Clermont-Ferrand CNRS group of chemists to unravel the properties of a new metallo-compound which led the group leader to sign a paper in Chemistry as a co-senior author. In summary, all three publications at different levels have been prepared mostly by the group.

Three group members have contributed to 3 publications of other GReD groups. The group leader was invited to an international meeting “Androgens 2006” as a speaker.

Overall, considering the high scientific potential in the group and the expertise of 3 researchers, the number of internationally competitive and visible publications remains relatively low.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The group comprises two professors, a teacher/researcher (MCF) and a CNRS researcher. For evaluation, it was not easy to determine the contribution of each staff in charge. However, clarifications were offered during the visit. There is a need to better define the responsibility of the group leader in terms of senior authorship. The group is well known among the community of scientists who work on androgens in Europe. However, they should be more active in the society for basic urological research in Europe (ESUR). This is the best way to increase visibility. There is collaboration with a group from Karlsruhe and it was clarified that a researcher worked on a project with fund provided from Germany (DAAD). Most research grants are obtained from smaller organizations.

A poster award was given to the group during the Symposium of the Journal of Steroid Biochemistry and Molecular Biology.

- Appreciation on the scientific strategy and the project

On the basis of previous results and new developments in the field, the main project is focused on the role of nucleophosmin (NPM) in prostate cancer while the collaboration will be pursued on the development of new anti-tumor therapeutics.

There were successful publications by groups in Europe and US focusing on specific cofactors of AR in prostate cancer. Thus, the role of NPM in steroid receptor co-activators, potentiation of AR activity and overexpression in cancer tissue will be mainly approached at the transcription level with the study of NPM-dependent changes of epigenetics marks. Given the pleiotropic function of NPM, there is a part of risk and the possibility of indirect effects should be carefully considered and controlled.

An additional suggestion is to examine the possibility that NPM is associated with endocrine therapy resistance (the role of NPM in mediating agonistic effects of anti-androgens). This part is translationally interesting but collaborations with urologists in this project are important and should be improved.

The studies on cooperation between NPM and LSD1 in regulating androgen-dependent gene transcription should be performed. They may be time consuming and the results may be expected at the end of the next time period.

During the evaluation it was reported that transgenic mice with human forms of the androgen receptor and NPM are available. The cell lines will be used to assess the development of early malignant lesions and prostate cancer.

Globally, it is felt that the NPM work may be quite important for the next time period. However, as mentioned above, all studies should be carefully controlled.

- Conclusion :

— Summary

This is a group with a good potential and knowledge. One excellent and one very good paper were published but the overall output is relatively low and should be increased in the next time period.

— Strengths and opportunities

The group has built up an innovative scientific and technology knowledge with unique animal (transgenic) models. The projects for the next period are based on solid preliminary data and are quite original. They are also relevant to prostate cancer translational research and may also attract interest from clinicians and pharmaceutical industry.

— Weaknesses and threats

The long time needed to establish the transgenic models probably led to difficulties in terms of publications. Collaboration with urologists and pathologists needs to be improved to insure that projects reach a success. Physicians should be more active in scientific exchange and contribute to meetings and publications preparation.

The main project is devoted to the role of nucleophosmin in prostate cancer, but the pleiotropic properties of the protein may render it difficult to delineate the functions that are relevant to tumorigenesis.

There may be some difficulty after retirement of the CNRS full time researcher.

— Recommendations

There should be some more joint meetings with urologists/pathologists and involvement of a young resident in the project.

The team leader should work at a better distribution of individual tasks within the group to improve efficacy and should continue with his efforts to recruit a new scientist for the group.

The researchers should improve connections to other European groups, attend more basic urological or cancer meetings. More project funds could be obtained from foundations and EU.

- "Exploring and Targeting the Mechanisms of Cancer Escape" Team Pierre VERRELLE
    - Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ETP	2	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2,9	
N6: Number of Ph.D. students (Form 2.8 of the application file)	10	3
N7: Number of staff members with a HDR or a similar grade	7	7

In italic : estimation for 2012

- Appreciation on the results

This clinician team aims at joining GReD during for the coming 5-year period. They focused their work on the clinical relevance of interleukin-6 (IL-6) signalling pathway, telomeric functions and DNA repair as targets to improve standard treatments of malignant glioma (MG) and chronic lymphocytic leukaemia (CLL). The group explored the involvement of these cellular processes in the acquisition of radioresistance of MG and resistance to chemotherapy of CLL. They revealed a significant correlation between the Akt pathway activation and the MG radioresistance and have proposed that a new phosphorylated site of STAT3 (S727) could play a role in this process. They also obtained promising results on the potential of G-quadruplex ligands and Dbait (dsDNA mimicking DNA damages) to overcome MG radioresistance. They explored the involvement of apoptosis signalling pathways and telomere dynamics in the CLL chemoresistance and identified several significant prognostic factors. Functional studies aiming at modulating these processes to develop new therapeutic strategies were also initiated. Finally, they characterized the mesenchymal stem cells (MSCs) of tumor-infiltrated bone marrow, revealing an altered phenotype.

This clinical work provided interesting clues for new therapeutic strategies concerning MG and CLL. This research is very much appreciated by colleagues working in this field. It was carried out with the support of excellent collaborations (Curie Institute in Paris, IMCB in Singapore, ISIS in Strasbourg, DNA Therapeutics company, etc.).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team members devote only 50% or less to research activity, as the rest of their time is dedicated to clinical and teaching duties. The team attracted thesis students but no post-docs and showed ability to raise funds (ANR, INCa, regional Canceropole).

The group developed active collaborations within France and abroad. Members of the group participated actively in international and national scientific meetings. They published very actively (more than one hundred articles in the last five years) in medical journals, they participated to a US patent and they were invited to give numerous conferences in national or international meetings or Universities.

They have a local leadership and benefit from a strong recognition in the fields of MG and CLL. Their position provides them with a high regional and national recruitment of patients with clinical samples, allowing them to develop solid translational approaches.

- Appreciation on the scientific strategy and the project

The team will join the GReD where it plans to develop its project. They will be joined by two teachers/researchers (MCF). However, a very well-recognized cytogeneticist will leave the team. The project is a natural extension of previous work of the group. They aim at targeting survival pathways and DNA repair to increase radiosensitivity of glioblastoma (GBM) cells. A new aspect will explore the role of DNA methylation in MG progression and response to treatment. This is based on the observation of an aberrant methylation of the promoter of the O6-methylguanine-DNA methyltransferase gene in GBM associated with longer survival of radiation-treated patients. It will include an investigation on the contribution of transposable elements in the progression and tumour evolution of gliomas. In parallel, they will pursue their work on factors playing a role in the resistance to chemo-induced apoptosis in CLL, by focusing on the TCL1 (T-cell leukaemia 1A) gene and the MSCs that constitute the bone marrow microenvironment.

Overall, the proposed research project will provide further insight into the mechanisms of cancer escape and the possibility to target them. The project is multidirectional but is not focused enough to address most questions in depth, regarding the absence of full-time researchers in the team and the heavy academic, clinical and teaching duties of the team members. The Committee was not convinced by the strategy or the presence of the appropriate expertise within the team for the development of the epigenetic part of the project. Although two teachers/researchers will join the team and bring a solid expertise in molecular biology, the project on DNA methylation is not yet properly designed, ignoring many critical points and difficulties both at the conceptual and technical levels. More generally, the Committee believes that the team could face a problem of mentoring concerning the fundamental aspects of the project.

- Conclusion :

— Summary

The team is well recognized for its clinical research and proposes a project in continuation with the work carried out in the previous period. It includes new approaches that should take advantage of the new context of the GReD where the team will work.

— Strengths and opportunities

The team has a very strong expertise in France in GM and CLL. Its project provides a solid basis for future synergy between the different teams of the GReD. The Committee believes that the integration of this group in the GReD could be appropriate for the GReD and also for the group itself. On one hand, the teams of the GReD should benefit from the clinical expertise of the team, several of them being concerned by human pathologies, especially cancer. On the other hand, team 13 has to take advantage of the strong and excellent expertise of several teams of the GReD in the epigenetic field, and more generally could compensate their weaknesses in some fundamental aspects of their project by developing strong partnerships with the specific GReD teams. Several collaborations already began (with teams 3, 4, 10 and 12), a good start for a successful integration.

— Weaknesses and threats

The number of projects is too ambitious for the number of members in the group when considering their other duties (clinical and teaching).

As mentioned above, the feasibility of the methylation and transposon part of the project appears not yet mature enough as it is presented now.

Because the team will integrate the GReD, its project was expected to include new fundamental parts. As it stands, the project is still largely clinical.

Because the two types of cancer (GM and CLL) studied by the team do not fall within the main topics of the GReD, it was not clear to the committee what this integration will bring to the GReD. The main threat concerning the team relies on its scientific integration. It is at the same time a clear opportunity.

— Recommendations

The team has to develop collaborations with other GReD researchers specialized in the field of epigenetic (methylation, transposon elements).

The Committee strongly encourages the team to take advantage of the rest of the Unit for the development of basic and fundamental parts of the project. There is a potential for development of novel cellular models, especially for IL-6 studies. In particular, constitutive STAT3-S727 phosphorylation provides a good opportunity to study IL-6 action in haematological malignancies.

At present, most of the proposed research is focused on analysis of clinical samples and may be correlative -if not supported- by adequate models. The role of suppressors of cytokine signalling in these diseases may be further studied. If not, the team will continue its excellent clinical research work that does not require its integration into the GReD. There is the potential for fruitful interactions, and this has to be exploited by a clearly defined and determined strategy.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
GRED: GÉNÉTIQUE, REPRODUCTION ET DEVELOPPEMENT	**A**	**A**	**A+**	**A+**	**A**
CONTRÔLE GÉNÉTIQUE ET ÉPIGÉNÉTIQUE DE LA DÉTERMINATION DU LIGNAGE CELLULAIRE AU COURS DU DÉVELOPPEMENT DE LA SOURIS [VAURY-ARNAUD-CHAZAUD]	A	A	Non noté	A	A
MÉCANISMES DE L'INFERTILITÉ MÂLE POST-TESTICULAIRE [VAURY-DREVET]	A	A	Non noté	A	A
DIVERSIFICATION DES CELLULES MUSCULAIRES ET CARDIAQUES AU COURS DU DÉVELOPPEMENT ET DANS DES SITUATIONS PATHOLOGIQUES [VAURY-JAGLA]	A+	A+	Non noté	A+	A+
LIPIDES, RÉCEPTEURS NUCLÉAIRES ET PATHOLOGIES MÂLES [VAURY-LOBACCARO]	A	A	Non noté	A+	A
TUMEURS DE LA SURRÉNALE ET HOMÉOSTASE DU TISSU ADIPEUX [VAURY-MARTINEZ]	A+	A+	Non noté	A+	A+
SILENCING, ENVIRONNEMENT ET TRANSPOSONS [VAURY-MATHIEU]	Non noté	A+	Non noté	A+	A+
CROISSANCE ÉPITHÉLIALE ET MORPHOGENÈSE [VAURY-MIROUSE]	Non noté	A+	Non noté	A+	A+
SIGNALISATION PAR LES HORMONES STÉROÏDES ET CANCER DE LA PROSTATE [VAURY-MOREL]	B	B	Non noté	A	B
IMPLICATIONS MÉTABOLIQUES ET MOLÉCULAIRE DES RÉTINOÏDES AU COURS DU DÉVELOPPMENT HUMAIN [VAURY-SAPIN]	B	B	Non noté	B	B
ETABLISSEMENT, MAINTIEN, ET RÉGULATION TRANSCRIPTIONNELLE DE L'HÉTÉROCHROMATINE [VAURY-TOURMENTE]	A	A	Non noté	A	A
INSTABILITÉS GÉNÉTIQUES ET CONTROLE PAR LE GÉNOME DE L'HÔTE [VAURY-VAURY]	A	A	Non noté	A+	A
EXPLORATION ET CIBLAGE DES MÉCANISMES DE L'ÉCHAPPEMENT CANCÉREUX [VAURY-VERRELLE]	B	B	Non noté	A	A
RECOMBINAISON ET MAINTIEN DE L'INTÉGRITÉ DU GÉNOME [VAURY-WHITE-GALLEGO]	A+	A	Non noté	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

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Clermont-Ferrand, le 8 juillet 2011

Le Président

et

Le Vice-président du Conseil Scientifique

à

Monsieur Pierre Glorieux
Directeur de la section des unités de recherche
AERES
20 rue Vivienne
75002 Paris

OBJET : Rapport d'évaluation S2UR120001916 – GReD : Génétique, Reproduction et Développement – 0631262E

Direction de la Recherche

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N/réf. :DR-IR/AL/2011 N°216

Monsieur le Directeur,

Je vous prie de bien vouloir trouver ci-joint les observations de portée générale concernant le rapport d'évaluation de l'unité « GReD » dirigée par Chantal Vaury, envoyé le 14 avril 2011, observations que j'approuve bien évidemment.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de mes sentiments les plus cordiaux.

Professeur Philippe Dulbecco
Président de l'Université d'Auvergne

Professeur Alain Eschalier
Vice-président du Conseil Scientifique

GENETIQUE REPRODUCTION & DEVELOPPEMENT

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Reply to the AERES report UMR/CNRS6247, Clermont Université, INSERM U931

General comment:

We thank the committee for its in-depth review and very positive assessment. It clearly recognizes the high research potential of the GReD. The successful research projects over the last four years have been emphasized as well as the use of original and unique set of plant and animal models. The committee noticed the efficient GReD organization that provides a rich environment for research, a lively atmosphere and involves the whole staff.

For the years to come, the committee clearly acknowledges the high intrinsic research potential due to the recent recruitment of brilliant and inspired young investigators, the cutting edge projects of the teams and the well-equipped technology platforms.

We are grateful to the committee to have pointed out that some teams have had excellent results and gained unique expertise with an international recognition although being mainly composed by teacher/researchers with heavy teaching duty.

We thank the committee to encourage the integration of clinic-driven projects as we proposed. We will take into account the committee's suggestions and work on deep interaction and collaborations with these two groups so that they can succeed in their fundamental research projects. We believe that our strong research environment will offer these clinically oriented teams the conditions for an efficient translational research.

The committee noticed that a major difficulty we will have to face is the impending retirement of many technicians and engineers. We will work on keeping the lab skills and we hope that the Universities and national agencies (INSERM, CNRS) will help us in this task. The staff allocation will thus be an important issue and will be determined by a mutual decision from the scientific committee as has been always the case.

It has been and will be one of our priorities to give young researchers the resources to work. To that respect, we are happy to have got the opportunity to associate two researchers with a permanent position or teacher/researchers to each of the two young teams (teams 1 and 8) as soon as they started their project in the GReD.

A new building will host the whole research unit within 4 years. It will provide an invaluable opportunity to increase efficacy, team interactions and visibility of the unit. We will pursue our action

towards the four institutions to invest into well equipped laboratories where everyone can work with its model organism, plants, Drosophila and mice. It is to be strengthened that the University Blaise Pascal in concertation with all plant laboratories of the Cezeaux has been working for several years on the financial support to build a new green house and we are rather optimistic that its construction will start soon. Furthermore, since the AERES visit, the unit direction got in touch with the CNRS to help with this issue. They formally agreed to provide financial support for an indoor growth chamber useful for the three plant teams of the GReD in the very near future.
As well, we will follow the committee advice to work with a SAB.
Overall we find the report very fair and useful.
Few team leaders wished to add comments or point out omissions noticed in their team reports. They are added below.

Team 4
Recombination and maintenance of genome integrity
Team Charles White

We thank the committee for their appreciative remarks and take this opportunity to highlight what we feel are some minor misunderstandings and omissions in the report text.

1/ Thesis students and Teaching.

We feel it is necessary to clarify the position of the group with respect to thesis students and teaching in general. The team has had one or two thesis students at any given time since its inception. The fact that we do not have a thesis student at the moment is unusual and due to a number of factors, with two theses finished recently (2009, 2010 - now post-docs at London and Québec). A promising Master 2 student last year (2009-2010) unfortunately did not fulfill our hopes concerning his potential during his time in the lab for his master project work (we have since aided him to find a PhD project in a good lab in Canada). Our potential thesis students must succeed in the competition for fellowships from the Ministry of Education.

We participate very actively in training and each year have two or three young people in the group to participate and learn (Licence 3, DUT, BTS ...). Two members of the group have full teaching loads in genetics (Maître de Conférences, Professor) and Maria Gallego is currently in her third year as head of the Genetics and Developement Master II program.

2/ Contributions to the scientific environment.

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We feel that we did not clearly transmit to the committee the importance of the contribution of the team members to the general material and scientific environment. The team (and particularly Elisabeth Allain and Annie Depeiges) runs and assures the maintenance of the plant growth facilities used by the UMR - including modifications to the existing facilities to meet biological containment rules and preparation of the documents requesting permission for the use of genetically modified organisms. This is complemented by a leading role in planning - for example we initiated and submitted a collaborative request (with the other plant groups of the UMR and the two other plant UMRs on the Cézaux campus) to plan and finance construction of a new research greenhouse. Since our installation at Clermont-Ferrand, we have very actively collaborated (and often initiated and led) in purchases of equipment (microscopes, molecular biology equipment, ...) and in general tasks for the community (seminars, committes ...). Our effort in these areas has been particularly important over the last 3 years with the rapid growth of the plant community of the UMR.

2/ Projects and planning.

As evidenced by our publications, collaborations and consistent success in financing and coordinating projects at european and national levels, we cannot agree we have a weakness in clear and coherent scientific planning and regret that we did not fully succeed in communicating to the committee some aspects of our research strategy and plans. This comment perhaps results in part from the evolution of our projects in the year separating the written document and the oral presentation - in particular our success in the developement of tools for analyses of recombination and repair of chromosomal breaks and dysfunctional telomeres led to the decision to group these as a single "project" in the oral presentation. The development of new tools and approaches is an important part of our work, and this successful technical evolution is both driven by, and serves as the base on which we construct experimental strategies for specific biological questions. Thus, although this modification to the presentation may have led to some confusion, we believe it to be both scientifically coherent and well adapted to grant applications (an ANR project recently submitted).

Finally, we note a minor error in the report - we are very excited with our results on the mechanisms of meiotic chromosome pairing and have clear evidence for differing implications of recombination in heterochromatic and euchromatic regions of the genome. We are not however using epi-RIL lines in this work. This confusion perhaps comes from our collaboration with the Paszkowski group, which used this approach to examine influences of chromatin structure on gene-targeting recombination in somatic cells.

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Team 6
« Mechanisms of post-testicular male infertility »
Team Joël DREVET

First of all, we would like to thank the reviewers and the committee for their general appreciative remarks. However, reading the report carefully we have found some discrepancies and misinterpretations that we would like to bring into focus and to clarify.

Appreciation of the results:
It is indicated « that our work was « *published in internationally recognized journals*.. ». This statement does not truly reflect the quality of our production. One of our major paper in 2009 was a *J. Clin. Invest*. (IF : 16) and it was acknowledged by a commentary in the same issue (only 2 to 3 papers in each monthly issue are highlighted in that way). It was regarded by the CNRS and the INSERM has a landmark contribution of the institutes in their respective 2009 annual reports (published in 2010). Some of our other papers in the same period are *J. Lipid. Res* (IF: 5) and *The J. Biol Chem* (IF:5.7).

Appreciation on the scientific strategy and the project:
It is indicated, "*that a strong in depth analysis has first to be conducted in order to precisely characterize the defects in the sperm nucleus compaction resulting from GPx invalidation*". We are surprised by this statement since this is exactly our project for the next months and years and it has already been implemented through: confocal microscopic analysis, Chromatin IP with the anti 8-oxodG antibody, chemical modifications of oxidized sites on the sperm DNA associated with deep sequencing (collaborative work in progress with the US team of Stephen Krawetz, Detroit, Michigan, USA). We apologize if this has not been clear enough both in the AERES written proposal and during the presentation of the group leader.
In the same paragraph it is also indicated "*the assumption that an epigenetic process could be impaired, giving rise to the observed compaction defects is actually not scientifically funded*". This is a complete misinterpretation of what we have stated both in the manuscript and during the visit of the committee. On the contrary, we postulate that the oxidative alterations and compaction defects of the sperm nucleus may alter the epigenetic marks as well as the reprogramming of these epigenetic marks upon fertilization and during the embryonic developmental program potentially leading to trans-generational impacts. The pro-mutagenic effect of DNA oxidative alteration is scientifically funded.

Conclusion (recommendations)

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Again the report indicates that: "*a strong in depth analysis has first to be conducted on the sperm nucleus defects*". As said above this is the main part of our project for the coming months. It is also indicated "*the group should carve out a unique niche for itself and to improve its international recognition*". As it was noticed by the committee and written in the paragraph "strengths and opportunities" the team already has its niche and international recognition. We agree with the committee that scientific achievements can be always improved and we hope to do so in the future. My main concern as the leader of a team composed of academics will be to maintain the level of our international recognition.

Team 9:
Metabolic and Molecular Implications of Retinoids During Human Development
Team Team Vincent Sapin:

First of all, the members of our group thank the committee for its reviewing, recommendations and its encouragements for the integration of our clinic-team in the project of the GReD. We clearly identified the strong opportunity to be boosted in our translational research, by the high level of fundamental science generated by the other teams of the GReD. We began to work with Lobaccaro's team (*cf.* co-published papers) in the past period and will of course reinforce this collaborative aspect with other GReD teams implicated in epigenetics. We agree that the past activity was probably too focused on descriptive researches; but this first step was, to our opinion, necessary to build the actual projects more mechanistic as we proposed with our ambitious approaches: pan-genomic transcriptomic and epigenetic studies. Note that at the end of our past –activity, we began to publish in this mechanistic field (*cf.* the paper by Borel *et al.,* 2010). We clearly followed the most important recommendation from the previous experts committee: the focusing of our scientific projects. In this context, the two themes seem to lack synergy. We are convinced that the mechanistic aspects that we will propose in terms of retinoids biology will be a real bridge between the two axes (amniotic membranes and lung). If the team didn't raise yet any major grants (ANR, EU…), we want to underline that two members of our team (D. Gallot and V. Sapin) obtained some nationally competitive INSERM contracts called "Interface Hospital". In addition, this obtaining was the first for D. Gallot and a renewal for V. Sapin. We really plane to target the team's publications in higher IF, compared to the past period, as already proved by our last year publication (Borel *et al.,* 2010) in J. Cell Mol. Medicine (IF 2009: 5.23).

Team 10
"Lipids, nuclear receptors and male disorders"

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Team Jean-Marc LOBACCARO

First of all, the lab members would really like to thank the evaluation committee for the project analysis as well as the comments.
We would also like to raise some questions as well as point out some misinterpretations of the project we submitted last year and presented for the visit in March.

· **Appreciation of the results:**

o We would like to add that the cited JCI was also signed by the Young researcher that joined the lab last year as well as the cited Gene and Dev (both as first author). Besides, a second JCI has been omitted where the group leader is involved.

o The committee stated "5 research papers within the evaluation period where the team plays a central role". This fact should be corrected since there are actually nine research papers in which the team played a central role (among a total of twenty-seven papers). It was probably a mistake resulting from the 5 papers from the group leader.

· **Appreciation of the impact, attractiveness…** The committee underlined the two ANR grants obtained during the period. It should however be enlightened that one was obtained in collaboration. The second one has just been obtained by a young researcher and runs until the end of 2015. Likewise, the committee omitted the "Nouveau–chercheur" grant obtained by a young associate professor that allows the enrollment of a post-doc for two years (until February 2013) and the functioning.

· **Scientific strategies and the project:** The lab members have been highly surprised by the fact that half of research project for the next 5 years has never been cited in the report nor during the visit: a full-time researcher, an associate professor, a physician, a grad-student and a 3 year post-doc are involved in this project. It regards the role of the bile acids in the testis physiology, as well as the role of the nuclear receptor SHP in the retinoid pathway. This probably explains why the committee underlined the fact that the team has a "stable niche occupation" and missed the fact that we are preparing de facto the future, as suggested in the recommendations, and this started last year…

· **Conclusions of the committee:**

o The production was qualified of "good to very good" and we really thank the committee for this. Conversely teaching members of the team have been chocked by the comment "in light of the heavy teaching duties". Indeed, as pointed by the committee in the specific comments about the unit "10% of the papers" (from a total of 156) were published "in journal rated above 10". We would like to focus that among the 16 papers rated above 10, **three papers came from our research team**. And one of it was done within the unit, and not outside... This point needed to be enlightened.

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o Weaknesses and threats: as pointed before, we are really surprised by the assertion that we did not prepare our future evolution. As stated above, half of the group works on new projects and the other half developed what was considered a risky project on prostate cancer. We are not leaving in "stable niche occupation"!
o The lab members do not really understand what is considered as a "robust funding", since we obtained for the next 4 years an ANR grant and a grant from the region, both allowing the enrollment of 2 post-docs, a master 2 student,... for a total of 400 000 €. Moreover, we also regularly get grants that allow the day-to-day functioning of the lab. Should we consider applying ONLY to European grants?
o "The team should prepare future evolutions of its research projects to anticipate shrinking".
We really want to apologize since the message was unclear for the committee on the written application as well as at the oral presentation: as already presented half of team works on a new research project (cf. above).

Team 12
"Steroid Hormones Signalling and Prostate Cancer"
Team Laurent MOREL

I would like to thank the international committee for their constructive evaluation of the team « Steroid Hormone signalling and prostate cancer ». The reviewers supported our scientific project and particularly highlighted its originality and its relevance to prostate cancer translational research (coll. with chemists and clinicians) based on "solid data". They also pointed out some bottlenecks that we had already identified and exposed in the SWOT section of our written report. In order to insure the development of our scientific program in the best conditions, we will carefully take into account these recommendations although answers to these bottlenecks have already been anticipated:

- *"Network and joint meetings with urologists and pathologists should be extended"*.
  Joint meetings are already regularly taking place (every 3 months) with Pr L. Guy (Urology dept of the CHU Clermont), Pr JL Kemeny (Pathology dept, CHU Clermont) and Pr P. Verrelle (Radiotherapy dept, CLCC Jean Perrin). These meetings gave us, and will continue to give us, the opportunity to design experiments with the critical point of view of clinicians. In this sense, we have started in 2010 a clinical study with a retrospective analysis over 5 years to answer the question of the role of NPM in predicting the radio-response of prostate tumors.
  Together, we have also been collecting human prostate samples in a "Prostate library" (both tumor and contra-lateral normal tissues are stocked) containing at time more than 50 frozen biopsies. This library is dedicated to the production of mRNA and proteins representative of

different stages of tumor progression and will allow mechanistic analyses in human that will complement those obtained with the specifically developed animal models (NPM transgenic mice).

- *"Young clinician resident in the project"*.
  Although having frequent meetings with urologists (see above), we have not yet any clinician working in the team. We have already planned to have a young clinician for a two years stay during which he will get formed to basic research in the courses of the Master "Genetics and Physiology".
- *"Recruitment of a new full-time researcher"*.
  Aware of the need of reinforcing our researcher potential, we have been tagging a young researcher who is doing a post-doc fellowship at Mc Gill University in Montreal in Dr Giguere's lab. There, he is improving his knowledge in the field of nuclear receptor that will fruitfully complement our skills. Following a "retour" fund in the lab, he will apply for a CNRS position in 2013.
- *"Increased visibility*".
  - National level: L. Morel is a coopted member of the SAB of the ARTP (Association pour la Recherche sur les Tumeurs de la Prostate) since January 2011. This network aims at putting in relation urologists and basic researchers in a translational perspective. This will help us to expand our own clinician network. ARTP is also the organizer of national meetings in basic urology.
    L. Morel is also involved in the steering of the Canceropôle Lyon Auvergne Rhône Alpes (CLARA) as scientific coordinator of the "Tumor escape & Cell plasticity" axis.
  - International level: ARTP is also the co-organizer of European meetings together with ESUR (*e.g.* 9th Congress on Urological Research, Innsbrück, 2011) and to which we will attend.
    C. Beaudoin participated to the "Young Prostate Researcher" meeting held in London in 2009 to build a new European network in this field and in connection with the Androgens research network into which we are active participants for 10 years.

Team 13
"Exploring and Targeting the Mechanisms of Cancer Escape"
Team Pierre VERRELLE

We thank the Committee members for their constructive remarks. We will take into account these recommendations notably in the aim of a better scientific integration of our team into the GReD.

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The already existing collaborations we developed with teams from the GReD have led us to engage during the 4 past years discussions about the common interest concerning our integration into the GReD.

The decision of Anne Fogli and Catherine Vaurs-Barrière (already working in a GReD team which deals with genetic neurodegenerative diseases and will stop its activity at the end of the year) to join our group has reinforced our perspective of GReD integration and has made possible the emergence of this new project. Today, DNA methylation and transposable elements investigations appear to be promising to better understand cancer progression mechanisms. We are aware of our lack of expertise in this field; that is why this recent part of the project is currently built in close interaction between the teams of Olivier Mathieu (DNA methylation) and Chantal Vaury (transposable elements).
Moreover, in close collaboration with Laurent Morel team (cell signaling), we already plan to extend the STAT3-S727 phosphorylation studies to LLC (as recommended by the Committee) leading to a common approach applied to the study of both types of cancer.

Regarding the poor outcome of malignant glioma patients and our promising preliminary results, we think that our implication in radiosensitizing approaches must be continued but limited to the proof of concept in collaborative projects and clinical trials supported by the local INSERM Clinical Investigation Center.

Beside the help of GReD to bring scientific explanations to our clinical interrogations, we think that our pathological and translational expertise will be useful to link genes and/or biological functions newly described in model organisms to human oncogenesis and tumor progression.

Chantal Vaury