Génétique, immunothérapie, chimie et cancer

Rapport Hcéres

▶ **To cite this version:**

Rapport d'évaluation d'une entité de recherche. Génétique, immunothérapie, chimie et cancer. 2011, Université François-Rabelais de Tours, Centre national de la recherche scientifique - CNRS. hceres-02035153

HAL Id: hceres-02035153

https://hal-hceres.archives-ouvertes.fr/hceres-02035153

Submitted on 20 Feb 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Section des Unités de recherche

AERES report on the research unit

Genetics, Immunotherapy, Chemistry & Cancer (GICC)

From the

Université de Tours

CNRS

January 2011

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

Section des Unités de recherche

AERES report on the research unit

Genetics, Immunotherapy, Chemistry & Cancer (GICC)

From the

Université de Tours

CNRS

Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

January 2011

Research Unit

Name of the research unit: Genetics, Immunotherapy, Chemistry & Cancer (GICC)

Requested label: UMR CNRS

N° in the case of renewal: 6239

Name of the director: M. Patrick GAUDRAY

Members of the review committee

Committee chairman

M. Claude SARDET, Université de Montpellier

Other committee members

M. Jean-Luc TEILLAUD, Université Paris Descartes

M. Mike CHANDLER, Université Paul Sabatier, Toulouse

M. David SHORE, University of Geneva, Switzerland

Ms. Fawzia LOUACHE, Université Paris Sud

Ms. Sandrine PIGUEL, Université Paris Sud

M. Francois LEMOINE, Université Paris 6 (CNU)

M. Thierry GRANGE, Université Paris Diderot (CNRS)

Observers

AERES scientific advisor

M. Jean ROSENBAUM

University, School and Research Organization representatives

M. Michel ISINGRINI, University of Tours

Ms. Martine DEFAIS (INSB, CNRS)

M. Gerard DELERIS (Chimie, CNRS)

Report

1 • Introduction

The review took place January 14th at one of the 2 present sites of implantation of the unit (Université François Rabelais/Faculty of Pharmacy-Tours). Oral presentations describing past and future research programs of the unit were made by the proposed director (P. Gaudray) and by the 5 team leaders/PI (G. Paintaud, O. Herault, MC Viaud-Massuard , M. Charbonneau and C. Augé-Gouillou) participating in the new project. The review group also met separately (in the absence of the direction/team leaders), with the technical staff, researchers with permanent positions, non-permanent lab members (Students, Post-docs) and the representatives of institutional authorithies. All members of the review group were present from the beginning to the end of this visit and have returned independently their argued comments to the chairman. The review group thanks the GICC Staff for their kind welcome and their receptiveness.

GICC was created in 2008 by the CNRS & the University of Tours to welcome seven local teams with complementary biomedical and biological expertises (genome, cancer, chemistry, immunology, pharmacology and cell. & mol. Biology) aiming at developing basic as well as potential gene-drugs scientific knowledge that could eventually lead to the identification and development of new tools for targeted therapies. This interesting but challenging initiative was fostered by the first director of the GICC (Y. Bigot) until the beginning of 2010. At that time, he abruptly resigned and was replaced by the deputy director. Of note, this first director of the GICC and part of the staff of his team (team 2 of GICC1) are currently moving to another reseach unit and will not participate in the new GICC project and therefore have not been evaluated by our review group.

The initial GICC configuration suffered from the fact that the teams were, until recently, spread out on three distinct sites located on two distant campuses (hospital, pharmacy & science university). This situation slightly improved in 2010 with the regroupment of GICC lab members on two sites (Hospital & Faculty of Pharmacy) rather than three.

The evolution of GICC has been rapid but is far from being fully developed. It is approaching the critical mass required to be considered as an institute. Hence, the new project that we have reviewed, termed GICC2, involves around 80 people (29 permanent staff), reorganized in five teams supported by a common administrative team. The proposed GICC2 management team consists of a director (P. Gaudray) and of a deputy director (MC Viaud-Massuard), both former team leaders of GICC1. This reorganization is a complex combination of former teams of GICC1 that have choosen to merge, and of new incoming teams. The research field of GICC1 was rather broad, as are GICC2's proposed projects that integrate the new subjects of incoming teams.

In brief, the new GICC2 team1 entitled “Antibodies, Fc Receptors and clinical responses” (headed by G. Paintaud/ 11 permanent staff), is a large team (26 people) corresponding to a fusion of three teams with medical interests: the former team6 (Immunogenomics and therapeutic antibodies, headed by H. Watier) and team7 (Pharmacology & clinical investigation, headed by G. Paintaud) of GICC1, and an incoming team of inserm U618 (Tours) working on heparin-induced thrombocytopenia and tissue factor in lung cancer (headed by Y. Gruel).

The new GICC2 team2, entitled “Leukemic Niche and redox metabolism”, headed by O. Herault, is also large (19 people / 11 permanents) and results from the fusion of the former team3 of GICC1 (“Signaling and leukemogenesis”, headed by F. Gouilleux) with two medical teams of Tours University (EA 3852, “Physiopathology of arterial wall” headed by V. Eder, and EA3855, “Hematopoeisis & stem cells microenvironment, headed by O. Herault and J. Domenech).

The new GICC2 chemistry team3, entitled “therapeutic molecular innovation”, involves 12 people (4 permanent staff) headed by MC Viaud-Massuard. It remains unchanged and corresponds to the former GICC1 team 5, “Organic and therapeutic synthesis”.

The new GICC2 team4 (8 people/7 permanent staff), entitled "Telomeres & genome stability", results from the fusion of members of the former GICC1 team4 "Genomic Instability and cancer" that was working on the role of the tumor suppressor Menin in the control of genome stability (headed by the proposed director of the GICC2 project), with two CNRS DR/CR working on telomere maintenance who moved very recently from Lyon (M. Charbonneau, former member of the team "G2 Cell Control, telomere protection and control of their size" at UMR5239, ENS Lyon). The team will be headed by M. Charbonneau and will focus on Telomeres functions and regulations.

Finaly, the new GICC2 team5 (10 people/6 permanent staff), entitled "Genome & transposases relationships", Headed by C. Augé-Gouillou, is composed of former members of GICC1 team2 (headed by the former director Y Bigot) that merged with GICC1 team1 ("Biochemistry of Mariner transposases", C. Augé-Gouillou).

- Staff members

Of note, four out of five teams (1, 2,3, 5) involved in the new GICC2 project are composed only or mainly of permanent researchers (total 29) from university and/or medical faculties, who have the usual heavy teaching and /or clinical loads so characteristic of the French University system. Only four researchers have CNRS positions (2 in team4, 1 in team2, and the proposed director), but none of those are recent recruitments. Despite the strong medical orientation of two of the five teams (Team1 & 2), there are no INSERM researchers involved in the GICC2 project. A high fraction of permanent researchers have an HDR (25 people) and presently supervise a total of 12 graduate students and 8 post-docs involved in GICC2. The CNRS contributes half of the permanent technical Staff of GICC2 (7 out of 14). The University and the Hospital contributes the other half as well as several non-permanent technical or sientific staff (mainly in team1).

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	14	20
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	15
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	9.5	15
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	7	
N6: Number of Ph.D. students (Form 2.7 of the application file)	11	
N7: Number of staff members with a HDR or a similar grade	17	24

2 • Overall appreciation on the research unit

• Summary

GICC1 was a first attempt to regroup several research teams working in the fields of biomed, chemistry & biology, but spread out over Tours university campuses, within a single institute. This goal has yet to be attained. Initiated in 2008, this interesting project suffered from the lack of common lab space dedicated to housing all teams on one site. However, the project clearly continues to reflect a strong desire of both the university management and of the staff of local research teams. The GICC2 project reviewed by our committee now involves new incoming teams that reinforce both the medical and fundamental subjects of GICC. The review group strongly encourage GICC2 staff to pursue that path, hoping they will finally succeed in regrouping and creating attractive facilities on a single site within the next four years mandate. This is a unique opportunity to create a multidisciplinary research center with a national visibility and capacity to continue to attract/create additional teams.

Yet, the past and proposed orientations are still very broad for a medium size research centre and the number of separate projects is quite large. This might foster interdisciplinary projects but also decreases the overall visibility of the research that is conducted in some of the teams. Nevertheless, the overall scientific production of the participants in the GICC2 project can be considered good but could be improved by focusing on a more limited number of projects, by a more ambitious and aggressive approach to publications in top journals and participation in international networks.

• Strengths and opportunities

The reorganization and fusions of several groups are sensible and appropriate decisions. The scientific production of the new incoming teams is good.

The new direction team has a strong expertise in lab management and in the administration and popularization of science. It has the support of most team members at all levels.

GICC2 will regroup valuable and complementary expertises in chemistry, molecular biology and medecine and will have access to clinical connections. Most of the GICC Staff have the willingness to move work in a translational direction.

Considered as a whole, the overall scientific production of the current GICC1 and of incoming teams can be considered as good by French standards, although significant differences exist among the different groups. This production can even be considered as very good if one takes into account that the vast majority of the senior scientists of GICC2 have also heavy teaching, administrative and /or clinical duties.

Several new projects are promising. With active management, commitment to compete and the application of appropriate resources, some of these promising projects have the potential to become internationally competitive.

All teams have been active in raising funding from various regional and national agencies.

• Weaknesses and threats

The teams are at present located on two distinct and distant sites and the common facilities are sub-optimal.

Four out of five teams involved in the new GICC2 project are largely or only composed of permanent researchers from the university and/or medical faculties and who are actively involved in the teaching, training and organization of the Tours faculties of Science, Pharmacy and Medecine. The positive side of this situation is that GICC is central in the formation of young researchers in Tours university, and that it has a true and permanent access to the best students on the one hand and to patients for clinical samples on the other. However, the number of full time permanent researchers appears currently sub-optimal.

From the written application and the presentations at the site visit, the program tends to appear as a list of interesting but self-standing mini-projects rather than an integrated program. This appears as a program in transition that needs to be more focused. In other words, there are too many sub-projects. This period of change should be

taken as an opportunity to focus on groups strengths and matching these to unmet needs in the field. Indeed, although advances are being made in several fields this is a weakness in that the headcount devoted to any one topic is necessarily too restricted to develop simultaneously and rapidly all these research projects in a competitive way (publication in top-journals).

Although the science is good, GICC, as a whole, lacks publications in high impact multidisciplinary journals and the invitations of the most successful groups to international conferences does not necessarily match the good quality of their work. This is clearly detrimental to the visibility and attractiveness of GICC.

- Recommendations

Overall, this is an interesting and forward looking application, that might take time to reach fruition but which justifies funding. The review committee feels that the multidisciplinary profile of the unit can be an asset, however, careful attention should be given to better promote interfaces between the Biology/Chemistry and the Medical Researchs areas of GICC.

The review group strongly encourages GICC2 staff and management team to pursue their objective to regroup on ONE site as soon as possible, to create attractive facilities.

The review group recommends that priorities be identified and that the number of projects be reduced to make timely headway on subjects that have the best chance to be considered as milestones and to be published in high-profile journals. Concerning the choice of such projects, the help of a scientific advisory board that would meet on a regularly basis, would be an asset (see also below/ our evaluation team by team). The creation of such external advisory board should be prioritized.

It is recommended to develop a more ambitious and aggressive approach for publications, patents, grants and participation to international networks. Both PIs and staff scientists/post-doc are encouraged to attend more international meetings.

It is necessary to improve the external communication of the GICC2 project, locally and internationally, to more efficiently attract Ph.D. students and post docs, as well as permanent researcher and PIs, from abroad.

Although the review group takes note that the lab-space and dispersion over two sites are not currently optimal, the recruitment of additional full time researchers (permanent/EPST and post-docs) as well as young PIs with starting grants, should be prioritized.

The committee strongly recommends GICC2 PIs to put more money in common to support the creation of common platforms and facilities and to give the possibility to the management team to develop a scientific policy and GICC2 communication. Similarly, the review group strongly encourages GICC to develop a policy for sharing technical staff in order to develop better facilities and technical platforms.

- Production results

these numbers correspond to GICC2 project, including incoming teams and researchers

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	19
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	3
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	22/23
A4: Number of HDR granted during the past 4 years	7
A5: Number of PhD granted during the past 4 years	25

3 • Specific comments

(each item of the appreciation should be justified)

- Appreciation on the results

Since 2006, significant results have been published or patented by GICC1 teams and by incoming teams participating in the GICC2 project. This led to 11 PhD graduations, 8 patents and participation in more than 250 publications (including original articles, reviews and medical communications, more than 110 of those being with GICC2 members in position of first or last author). These publications were mainly, if not all, in specialized journals of uneven impact factor. Nevertheless, some have been published in the best journals of their specialty and some have been recognized as milestones, as indicated by their good citation index. This is particularly true for team 1 some of whose studies have been published in clinical journals with a large audience.

Considered as a whole, the overall scientific production of the current GICC1 and of incoming teams can be considered as good by French standards, although significant differences exist among the different groups (see evaluation team by team). This production can even be considered as very good taking into account that the vast majority of the senior scientists of GICC2 have also heavy teaching, administrative and /or medical duties.

Altogether, the multiple themes (chemistry, genome organization and dynamics, cancer, pharmacology, immunology, haematology, stem cell biology) addressed by GICC publications have played an important role in maintaining a broad presence of GICC in many fields of biology, medical science and chemistry and have also fostered some successful or promising internal collaborations. The down-side of covering so many topics with a limited number of teams involved in each subject is that it becomes difficult to achieve breakthroughs in each domain and to be considered as highly competitive at the international level.

Thus, GICC, as a whole, lacks publications in high impact multidisciplinary journals and the invitations of the most successful groups at international conferences do not necessarily match the good quality of their work. This is clearly detrimental to the visibility and attractiveness of GICC. The review group encourages the GICC2 PIs and staff scientists to develop, collectively, a more organized, ambitious and aggressive approach for publications, to attend more international meetings, and to improve the recognition of their very valuable expertise and of their work delivered through collaborations with remote investigators. Publication in top-journals will also certainly require focusing strength on a more limited number of projects.

Of note, several clinical trials were also set up by members of GICC2 Teams 1 and 2, some directly resulting from GICC projects, and as so, should be considered as concrete and highly significant results of GICC research activity.

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

GICC1 is clearly a first, but yet unachieved, attempt to regroup, within an institute, biomed research teams spread out in Tours university campuses. During the visit on site, the review group observed that this objective clearly continues to reflect a strong demand of both the university management and of several incoming research teams that wish to join the GICC2 project. They particularly adhere to the mid/long term objective of GICC to regroup on one site in order to reach the critical mass of people required to support a competitive and operative multidisciplinary research center in Tours with common facilities, fruitfull scientific exchanges, visibility and capacity to attract new high profile scientists. In that respect, the 2010 local attractiveness of the research unit can be considered as good. However, this might not last if GICC2 fails to achieve this objective within the next four years.

Meanwhile, all teams have been active in raising funding from various sources to the point that these funds represent 85% of the total operating costs of the current GICC2 teams. Indeed, in addition to the institutional support from CNRS and Tours University, the different teams of the GICC2 project have been reasonably successful in obtaining industrial contracts (Servier, Amgen etc…) as well as competitive funding from the ANR and from other French or local (Region Centre) governmental agencies (DGCIS, FUI). Although one EEC FP grant (2005-2009) was

obtained by the team of the first director of GICC who is currently leaving, some effort should certainly be made towards European and international funding agencies. In that respect, significant differences exist among the different teams concerning the participation in international or national scientific networks and to stable collaborations with european partners. This should be prioritized and encouraged by the future management (increase the frequency of speaker invitations financed by the GICC core budget, dedication of GICC funds and support for symposium organization, establishment a scientific advisory board composed of well-established, non-french, EEC researchers, etc…).

In the same vein, it is necessary to improve the external communication locally and internationally, to attract Ph.D. students, post docs and PIs, from abroad more efficiently. Indeed, although the overall number of PhD students and post-docs is correct by French standards, too few are foreigners or from other doctoral schools. The management of GICC2 should prioritize this objective. In that respect, the multidisciplinary approach advocated by GICC, its good scientific production and the overall attractiveness of the Tours region and university campuses constitute assets that are insufficiently used. A financial and administrative support dedicated to these recruitments and to external communication could be asked to the university and/or to the local government (Region Centre).

Careful attention should also be given to improve the format and English version of the GICC web site, according to the CNRS charter, and to update its content (notably the profile and scientific activity of several teams that are currently blanks).

- Appreciation on the strategy, management and life of the research unit

The initial scientific strategy of GICC was to encourage multidisciplinary projects that could, eventually, lead to the identification and development of new tools for targeted therapies. The review committee feels that, while fruitful collaborations have been set up between chemists and fundamental biologists, it is not persuaded that interactions with the medical staff of GICC have been fully achieved. Once again, the committee feels that this objective has been strongly hampered by the dispersion of the teams over several sites. It appears that important efforts still have to be made in this direction during the next GICC2 project. Hence, during the visit on site, all PIs (including those of new incoming teams) and staff strongly reaffirmed to the review group, their willingness to increase internal collaborations and accordingly, presented convincing projects that fit with this objective. In this respect, the future expansion of GICC2 staff and the fact that it will be located on two sites in the near future requires an improvement of the communication within the unit. This could easily start by immediately increasing the frequency of mandatory public lectures, given by students and researchers, and attended by all the staff of the institute; and If possible on a weekly basis and in English.

In 2010, only two years after its creation, the GICC organization was transiently destabilized by the resignation of the first director and is already emerging in a new format that is currently headed by the deputy director who is to be congratulated for managing this difficult transition period. However, the first director of the GICC should also be thanked for the enormous energy he has invested in the initiation of the project. This turbulent time also coincided with the regroupment of GICC staff on two sites (Hospital & Faculty of Pharmacy) rather than three and by the elaboration of the GICC2 project that will welcome additional staff. Although, there is still room for improvement (One GICC on One site), this first step can be interpreted as an important affirmative answer of the local institutional authorities to the creation of a viable GICC.

Four out of five teams involved in the new GICC2 project are composed only or mainly of permanent researchers from university and/or medical faculties, who are actively involved in the teaching, training and organization of the Tours faculties of Science, Pharmacy and Medicine. The positive side of this situation is that the GICC is central in the formation of young researchers in Tours University, and that it has a true and permanent access to the best students and to patients. However, one could also consider that the number of full time permanent researchers is sub-optimal. Only, four researchers of GICC2 have CNRS positions (3 in team 4, 1 in team 2), and none of those are recent recruitments. Moreover, despite the strong medical orientation of Teams 1 & 2, there are no INSERM researchers involved in the GICC2 project. Although the review group takes note that the lab-space and dispersion over two sites are not currently optimal, the recruitment of additional full time researchers (permanent/EPST and post-docs) as well as young PIs with starting grants (ANR jeune chercheur, ATIPE/AVENIR, ERC etc..), should be prioritized by the future management. To help with this, an external scientific advisory board should be formed as soon as possible. This board would also help to evaluate the pertinence of GICC strategies during this transition period and help to focus on a more limited number of subjects.

Concerning the financial strategy, GICC contractual budgets received from the university and CNRS are evenly distributed between all the research teams and the administrative teams. No levies are presently collected on grants. Although that « fiscal » policy has allowed the GICC1 unit to function properly until now, the committee strongly recommends GICC2 PIs to put more money into a « joint investment fund » to support the creation of common platforms and facilities and to give the posibility to the management team to develop a scientific policy and GICC2 communication. Similarly, the review group strongly encourages GICC to develop a policy for sharing technical staff in order to develop better facilities and technical plateforms. Concerning this point, the committee notes that the number of technical staff with stable jobs is uneven from one team to another. Although this is certainly the result of the « local history » of each team, we recommend further consideration of an alternative scenario that would promote an equal presence of the technical staff in each team of GICC2 and/or its reaffectation to shared facilities, at least partially. These « sharing » policies should be prioritized if GICC2 objective is to function as an institute.

- Appreciation on the project

The proposed new director of GICC2 is currently the PI of one of the GICC1 teams. He is a man of energy and drive who has expressed the desire to devote himself to the management of GICC2. He has a strong expertise in lab management and in the administration and popularisation of science. Hence, to the detriment of his own scientific production, he has been « Directeur Scientifique Adjoint/DSA » at the CNRS central adminstration and more recently, strongly involved in the very time-consuming French National Ethics committee. These expertises and his willingness to be involved full-time in the management of GICC2 should be encouraged and seen as an asset for structurating GIGG2 and to improve its communication.

The evolution of GICC is rapid but far from being fully achieved since the new project is a complex combination of former teams of GICC1 that choose to merge, and of new incoming teams (from the Tours university hospital and ENS Lyon). It is now approaching the critical mass required to be considered as an institute. There is a clear adhesion of the staff (of GICC1 and of incoming teams) to this new GICC2 project and to the idea to regroup on one site. This regroupment is also seen by the university as an important initiative to federate the biomedical research in Tours. Although deadlines are unclear, local institutional authorities have mentioned that they have already considered to offer room to GICC2 in an hospital building that should be renovated before 2015. The review group strongly encourages this scenario, considering that GICC regroupment on one site will be essential to its existence as a viable institute, i.e. a place to share and develop the technology & administrative platforms, daily scientific exchanges, and collaborations required to support GICC ‘s objectives to combine medical /chemical /pharmacological and biological expertises. This desire to work together should also be accompanied by an increase of the mutual funds and by pooling technical staff to develop shared facilities. This important point is not addressed in the GICC2 project. Although this multidisciplinary profile of the unit is seen as an asset, careful attention should be given to promote interfaces between Biology/Chemistry and the Medical Researchs of GICC more effectively.

The research themes of the GICC1 were rather broad, as are those proposed in GICC2 which integrate several new subjects of incoming teams. Overall, the scientific content of the project appears very good. Some of the GICC’s projects were judged as excellent and highly feasible, although a few others clearly require rapid adjustment, as detailed below.

The management team, together with the board of team leaders, is encouraged to define clear priorities for GICC2 and to focus on a smaller number of projects. Concerning the choice of such projects and mid/long term strategies, it would be wise to seek the assistance of an external and permanent scientific advisory board.

4 • Appreciation team by team and/or project by project projet (to be pasted as many as needed)

Team 1: Antibodies, Fc receptors and clinical responses

Project leader: Gilles PAINTAUD

This proposed Team1 of GICC2 is a fusion of three teams with medical interests: the former Team 6 (Immunogenomics and therapeutic antibodies, headed by H. Watier) and team 7 (Pharmacology & clinical investigation, headed by G. Paintaud) of GICC1 UMR 6239, and an incoming research group of INSERM U618 (Tours) working on hemostasis ("heparin-induced thrombocytopenia and tissue factor in lung cancer-headed by Y. Gruel).

- Staff members:

	Past*	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8	8
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	9
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	6	8

- Appreciation on the results

The work developed by the two ex-teams 6 and 7 of GICC1 had been based on their scientific knowledge of the pharmacogenetics, pharmacokinetics (PK) and pharmacodynamics (PD) of therapeutic antibodies. One has to recall their major contribution to the field of therapeutic monoclonal antibodies (mAbs) with the 2002 Blood paper (Cartron et al., 2002) demonstrating for the first time that the response to a therapeutic antibody (the anti-CD20 mAb rituximab) was dependent on the polymorphism of FcgammaRIII (FcgammaRIII/CD16). Thus, following this major discovery (cited more than 600 times), the two Teams (6 and 7) have pursued their research in the field of antibody PK/PD and on their interactions with Fcgamma receptors over the last four years.

They have obtained interesting scientific and clinical results. In particular, they could decipher the genetic evolution of the FcgammaR encoding genes in humans and non-human primates. Moreover, they have investigated the association between FCGRIIIB-NA1/NA2 polymorphism and response to therapeutic antibodies in several diseases.

The two teams have also developed studies on the role of FcgammaR when expressed on human NK cells with interesting results. Notably, an assay that makes it possible to classify NK cell patients according to their ability to degranulate, to produce IFNgamma and to modulate FcgammaRIIIa has been set up and patented.

Finally, studies on FcRn have been also developed. This receptor plays a major role in the control of IgG half-life and these studies are logical to develop with regard to the other works developed by the teams on PKs and PDs. However, convincing results have been difficult to obtain and studies are ongoing to alleviate these difficulties.

PKs characteristic of therapeutic antibodies are also key-parameters in the clinical efficacy of these molecules. The teams have studied whether the allotypes of the IgG monoclonal antibodies infused into patients have an impact on the PKs by inducing anti-allotype antibodies, in collaboration with a team from Montpellier. They could demonstrate that the clinical efficacy of an anti-TNFalpha, infliximab (a chimeric antibody), was not dependent on the response against allotypes, but that anti-Ig antibodies have a profound impact on the infliximab half-life. Studies on serum level of infliximab (thanks to a dosing method developed in the laboratory) have made it possible to propose a dose adjustment in rheumatoid arthritis patients based on therapeutic drug monitoring. Similarly, the Teams have developed a PK-PD model for rituximab that allows the maintenance of a therapeutic response based on the change of the dose/dose regimen of rituximab.

Overall, all these studies have been conducted in a logical and coherent way, bringing interesting lights on the in vivo behavior of therapeutic antibodies in relation with their clinical efficacy.

A large number of papers and reviews (more than 150 of which 65 include a team member as a first and/or senior author) have been published over the last four years by the proposed members of this team. Most of have been published in very specialized journals dealing with PK and PD drug studies. However, others, corresponding to the publication of the main results summarized above, have been published in good clinical and scientific journals with a large audience (Cancer Res., Ann. Oncol., Lancet, Blood, J. Clin. Oncol., Nucl. Acid Res, PNAS, Clin. Chem etc..). The publication record is very good with regard to the number of workers in each team and the teaching/clinical duties of the group leaders/senior scientists of the teams, and despite the absence of full time researchers from INSERM or CNRS.

Numerous conferences and seminars have been given in the last four years. A large number of these have been given in France. However, it should be pointed out that work on inflammation and RA has been largely publicised abroad. There is a low number of scientific communications about the work of the teams on antibodies in major meetings on antibodies in Europe, not to speak of the US. This does not match the quality of the work and is clearly detrimental to the visibility and attractiveness of this team. The review group recommends to attend more international meetings to improve the recognition and visibility of their very valuable expertise.

Although poorly documented in the scientific report, members of the proposed GICC2 team 1 have been directly involved in a number of clinical research activities integrated within cooperative clinical research groups (French Vasculitis Study Group; Etanercept European Investigators network…) or that focus work on nationwide cohorts of patients.

Some partnerships on antibody studies have been indicated by the members of the ex-Teams 6 and 7 of GICC1. They have been funded by the "Region Centre" ("Polyphar" and "Aeromac" projects) and involve the CNRS UPS 44.

There also are other partnerships with Biotechnology companies.

Finally, four PhD students have graduated under the direction of present members of the new team1 (ex Team 6: 2; ex Team 7: 2).

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

All permanent researchers of this proposed Team1 have faculty and /or medical positions and are actively involved in the clinical and teaching duties of the Tours University-Hospital. One has to highlight their strong involvement in the transfer of their work towards the hospital laboratories for routine monitoring of treated patients, as well as their involvement in obtaining new patents and in defending the intellectual property they already possess.

Three patents have been submitted during the last years. Moreover, previous patents have been licensed and sublicensed to biotechnology companies.

They are actively involved in the animation of the french community working on medical aspects of antibody therapy. Hence, one professor of Immunology is one of the founders and the present Head of the GDR CNRS n°3260 "Anticorps and ciblage thérapeutique" that includes more than 70 research groups and biotechnology companies working in France on antibody engineering and antibody therapeutics. Moreover, members of this team have been

rewarded by prizes (Jacques Oudin prize from the French Society of Immunology in 2008), belong to the international Antibody Society and are members of the Editing Committee of the new international journal mAbs. Projects helped by the "région Centre" and partnerships with biotechnology companies, as well as ANR grants, allowed most members of this proposed Team 1 to get significant funding during the past two years.`Finally they are coordinating a "LABEX" project on therapeutic antibodies in collaboration with a team in Montpellier.

Despite this good record, the international visibility and attractiveness of the team are sub-optimal and could be improved with appropriate communications. So far, as already mentioned, there is no indication of any invitation to high impact international conferences or of already fruitful academic collaboration with foreign partners (although one starting new collaboration with an academic foreign partner (Jefferson University, Philadelphia, USA) is indicated). Moreover, the recruitment of students appears to be mostly local and no scientist from abroad is indicated (Post-Doctoral fellow or visiting scientist).

Another weakness is that there are presently no full time researchers from INSERM or CNRS in the Team 1 to be created. Again, this does not match the quality of the work and should be prioritized to strengthen the experimental approaches of the proposed projects.

Finally, the initial scientific strategy of GICC1 was to encourage multidisciplinary projects that could, eventually, lead to the identification and development of new tools for targeted therapies. The review committee feels that, while fruitful collaborations have already been set up between chemists and fundamental biologists, it is not persuaded that such interactions have been fully achieved with the medical team members participating in the proposed team1 (ex-team6 and 7 of GICC1). Although there is room for improvement, there is also hope, as indicated during the visit on site by a proposed project aiming to explore the biochemical properties of antibody solutions, in collaboration with team3 (chemistry/«Therapeutic Molecular Innovation»).

- Appreciation on the project

The team to be created is composed of clinicians/biologists with teaching and medical duties (PU-PH, MCU-PH). The written document is not very informative on the new team organization and management. Indeed, this team involves several natural and senior leaders that already manage their own research groups. Although there is a strong coherence in the overall scientific project and decision to merge, it is unclear whether the choice of the Team1 leader is based on management qualities, disponibility or results from his scientific skills. However, it should be stressed that these team members have worked closely for several years. Thus, there should be no major management problem.

The scientific projects of the team are coherent with and in the continuity of the previous research works (see supra). The group foresees three main lines of research:

1. The impact of IgG structural characteristics on the in vivo half-life of therapeutic antibodies, with the study of cohorts of patients receiving different antibodies. This is an important project, developed in association with a biotech company,

2. The role of the FcgammaR polymorphism expressed by circulating cells in IgG clearance. This is an original project that may shed new insights on the control of IgG serum levels.

3. A third project concerns the activation of effector cells through FcR and the impact of IgG concentrations on this activation.

Thus, the long list of projects appears as a continuation of the previous studies on Fcgamma R polymorphism and on the control of antibody half-life and bio-disponibility. However, it also includes new and innovative research areas, in particular on the role of platelets in antibody clinical efficacy. The arrival of scientists/clinicians specialized in platelet studies has make it possible to propose a set of studies on platelets and therapeutic antibodies that might lead to important advances for the clinical use of therapeutic monoclonal antibodies. Indeed, this opens new opportunities to develop original projects on the role of platelets and platelet Fcgamma receptors in the control of antibody half-life and bio-disponibility. These interesting projects should provide additional opportunities of funding to this team.

Altogether, this project is well constructed and ambitious, although some of the sub-projects should be carefully considered in terms of feasability, planning and questions to be addressed.

The team funding relies both on academic, region, government and private fundings. There is no clear description of how the ressources obtained will be shared between the different project leaders. However, most of the people have already worked together and the management would presumably be similar to that used previously.

- Conclusion :

— Summary

Three of the ten top selling drugs are currently therapeutic antibodies and six out of ten will be in the ten top selling drugs in the next ten years. The members of this team have acquired an international recognition in this major field of human medicine, thanks to their studies on the role of Fcgamma receptors interactions with therapeutic antibodies that impact the clinical efficacy of these molecules. The new project integrates the different know-how (therapeutic antibodies and hemostasis) of the three teams that will merge to create this team 1. This creates a large group composed of scientifically productive hospital and university faculty members with significant clinical activities. The aims of the proposed scientific projects are in direct line of the previous work and integrate a number of areas that should give new insights into the parameters that influence the clinical efficacy of therapeutic antibodies. These projects are coherent, logical, and should provide new insights into the mode of action and control of half-life of therapeutic antibodies. Considering the rapid development of the clinical use of antibodies, most of these projects have good chance to be funded by French research agencies.

— Strengths and opportunities

First, the senior scientists involved are experts in the field of therapeutic antibodies as well as in the fields of pharmacokinetics and pharmacodynamics. Thus, they can gain very rapidly original and new insights into the parameters that modulate the clinical efficacy of therapeutic antibodies.

Second, the senior scientists of team 1 are also clinicians that have easy and direct access to cohorts of patients. Projects directly related to questions based on the use of these cohorts should be favored.

Third, the team expertise and projects deal with clinically relevant questions on antibodies that are very valuable for biotechnology/pharma companies. This should generate new patents as well as funding from these companies.

Finally, this fusion of teams also creates new opportunities that should be strongly encouraged. Thus, some aspects of the project (platelets and antibodies) are innovative, and should be prioritized.

— Weaknesses and threats, and Recommendations

First, the theme of therapeutic antibodies is highly competitive and requires a critical mass of investigators per subject that might be difficult to obtain on all the projects. In that respect, the priority given to the different projects seems unclear. At present, it is difficult to understand who is doing what among the senior scientists in the new Team 1 with regard to the different projects presented. The recruitment of young full-time scientists (CR level) should be a priority as all the senior scientists of this team are medical doctors that spend less than half of their working time in research activities.

Second, Publication in top-journals will certainly require focusing efforts on a more limited number of projects. In view of the fact that the scientific content of the past publications is of good quality and had an impact on the antibody field, the review group encourages team 1 to develop a more ambitious approach for publications in high impact journals.

Similarly, although the research achievements of the senior scientists of the team are well known by a large number of academic and biotech scientists, their presence on the international scene (meetings, conferences) is low and should be improved.

Finally, while fruitful collaborations between chemists and fundamental biologists of GICC are already in place, such interactions have not been fully achieved with the medical faculty members of team 1. There are multiple opportunities that have been so far insufficiently explored.

Team 2: Leukemic Niche and RedOx metabolism (LNOx)

Project leader: M. Olivier HÉRAULT

This proposed team 2 of GICC2 results from the fusion of three teams with medical interests; the former team 3 of GICC1 ("Signaling and leukemogenesis", headed by F. Gouilleux) and two medical teams of Tours University (EA 3852, "Physiopathology of arterial wall" headed by V. Eder, and EA3855, "Hematopoeisis & stem cells microenvironment, headed by P. Charbord (till 2007) and Jorge Domenech (since 2008) hey have been joined by Olivier Herault (proposed to be the head of the new team 2 of GICC) in 2007.

- Staff members

	Past*	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	4
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)	0	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	6
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 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	1	5

- Appreciation on the results

The research groups that compose this new team 2 have worked on: i/ the role of mesenchymal stem cells (MSC) and of their microenvironment in normal and pathological hematopoiesis and in vascular differentiation, and ii/ on Stat signaling in leukemogenesis.

Significant results from members of this team include: i/ a better characterization of normal MSC biology (MSC migration potential and role of hypoxia in mobilization), ii/ an exploration of the role of CD31 and CD38 surface markers in the adhesion of leukemic cells to bone marrow microenvironment, iii/ an evaluation of the impact of SDF-1 polymorphism on blast dissemination, iv/ a demonstration of the oncogenic properties of Stat5. This led to major accomplishments, notably on the impact of Stat signaling in acute myeloid leukemia and on the mobilization of MSC by hypoxia.

Altogether, the members of the team have published more than 50 original papers or reviews (including 18 as first and/or senior authors), since 2006. Several have been published in good scientific and biomedical journals with a large audience (Blood, Stem cells, Faseb, Leukemia, Haematologica, Am J. Physiol, Oncogene, Cancer Res., J. Biol. Chem etc… …).

This publications record is good with regard to the number of workers in each sub-group and the heavy teaching/clinical duties of 5 (out of 6) senior scientists involved in the project.

Many (12) PhD students have graduated or are in the process of graduation under the direction of team 2 members.

Most conference invitations were to French meetings. Although the different group members have contributed posters at numerous national and international meetings, there are almost no oral communications in major international meetings. As mentioned for team 1, this is clearly detrimental to the future visibility and attractiveness of the new team. The review group recommends attendance at more international meetings to improve the recognition and visibility of their very valuable expertise.

Although all senior faculty members of this new team have been able to raise funds in the past, most of the present funding is provided by the proposed PI sub-group whose projects are currently well financed. The declared larger size of the new team will require additional funding. This could become a potential area of weakness that should be prioritized.

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

5 out of the 6 permanent researchers of this proposed team 2 have faculty and medical positions and are actively involved in the clinical/molecular hematology/cardiology and biology teaching duties of the Tours Science University and University-Hospital.

The proposed team leader is also head of a molecular hematology lab at the Tours hospital. This is an asset , giving privileged access to the biological ressource and technical facilities of the hospital required for the GICC2 team 2 project (FACscan, cytogenetics, genomics and proteomics core facilities and leukemic cell banks).

He has developped a very valuable panel of assays to evaluate the antioxidant defenses of cancer cells. This led to an European patent that have been registered (but not yet licensed) in 2010. He has developped a fruitful and intensive collaboration with an excellent lab in Montreal (IRIC) that has a strong expertise in animal models designed to study the in vivo behaviours of the normal hematopoeitic or leukemic progenitors. This ongoing collaboration will be an asset for the development of team2 projects.

Other members of the team are actively involved in the French research community (CHO) and French Cooperative Groups (GOELAMS, GFM) working on hematopoeisis and blood diseases.

Several members of the team have been directly involved in the setting up of regional clinical and interventional biological studies directly related to team 2 subjects, notably aiming at evaluating antioxidant genes expression and MSC functional properties in MDS, AML and CML patients from various cohorts and in close collaboration with French cooperative groups (GOELAMS, GFM etc..).

As mentioned for the other teams, despite the good quality of their research, the international visibility and attractiveness of the various sub-groups that merge to form team 2, are sub-optimal and should be improved. As already mentioned, there have been very few invitations to high profile international conferences and the recruitment of students appears to be mostly local. Nevertheless, with appropriate communication, the review committee believes that the new organisation of the team, its larger size and the cutting-edge questions that are addressed, should provide the opportunity to improve the visibility and attractiveness of the group.

- Appreciation on the project

The team to be created in 2012 is composed of a DR CNRS and of clinicians/biologists with teaching and medical duties (PU-PH, MCU-PH). It is a complex merger of three teams with interest in stem cell microenvironment and hematology. As mentioned for team 1, although there is a strong coherence in the overall scientific project and decision to merge, the application is not very informative about the organization and internal management of the new team. Indeed, as team1, team2 is a merger of several natural and senior leaders who already managed their own research groups. However, several faculty members have already worked together and have co-published articles. The research themes and objectives of the clinicians within the project are unclear. This point should be clarified.

The main project aims at investigating the contribution of oxidative stress and oxidative defenses on the biological properties of leukemic progenitors, blast cells and of the supporting niche (marrow microenvironment, MSC cells). Three complementary approaches have or will be set up. i/ ex vivo, using co-cultures of various leukemic cells with MSCs; focusing on the impact of these co-cultures on the oxidative metabolism, the stress-responses (ROS, intra and extra-cellular antioxidants responses, Stat signaling, etc…) and the oncogenic properties of the leukemic cells (engraftment, reconstitution); ii/ in animal models, using a sophisticated murine model of leukemia developed by a Canadian collaborator of the PI, that allows in vivo studies of leukemic cells interactions with marrow microenvironment and MSCs. iii/ in human AML/MDS and Bone marrow (progenitors & other cell types) samples

obtained from the GOELAMS and GFM cooperative groups. This interesting translational aspect of the projects aims at evaluating if these redox parameters could be used for prognostic or diagnostic of leukemia. Altogether, this is a very interesting, ambitious and cutting-edge domain of research, but this is also a very competitive subject. However, the project is based on pertinent experimental models and takes full advantage of the complementary expertise of the three sub-groups that are merging to form team 2 (Stat5 and hypoxia, redox metabolism, MSCs and microenvironment and leukemic progenitors). Moreover, it is also based on convincing and original preliminary results. Notably, in collaboration with the Canadian lab, they might have identified a novel exciting key player of the antioxidant-response that would be specifically involved in this MSCs-stem cells (leukemic and normal) dialogue. While the review group encourages this fruitful collaboration, careful attention should be given to ensuring the recognition of their work delivered through this collaboration with a remote and well established investigator. The review group also expresses one methodological concern about the fact that most ex-vivo experiments have apparently been, so far, performed without taking care of the abnormal O2-exposure of the cell-cultures. To avoid artifacts, it is recommended to rapidly improve this aspect of the project by working in incubators and chambers at lower and well-defined O2 levels.

These complementary models will also benefit to internal collaborations planed with teams 3, 4 and 5 of GICC, aiming at exploring the impact of the ROS exposure on leukemic and MSCs cells genomic stability, and to test the biological effects of novel Stat5 chemical inhibitors.

- Conclusion :

— Summary

This new team is composed of productive researchers with complementary expertises in stem cells, hematopoeisis, transcription and redox signaling. Their common project is well designed and aims at exploring the impact of the redox status/signaling of the stem cells “niche” on normal and leukemic stem cells homeostasis.

— Strengths and opportunities

First, the senior scientists involved in the project have the complementary knowledges required to develop and interpret this interesting project.

Second, several senior scientists of team 2 are also clinicians or hospital biologists that have been directly involved in the setting up of regional clinical and interventional biological studies directly related to team 2 subjects. They have direct access to the cohorts of patients required to validate the medical relevances of the hypotheses raised by this new project. This is an interesting aspect of the project that will nicely complement ex vivo and animal-based experimental approaches.

Third, this project has been very recently well financed and has a good chance to be further supported by the charitable as well as public research agencies. However, this promises to be a very ambitious and expensive project (animal models, stem cells culture etc…) and the declared larger size of the new team (19) will require additional funding. This could become, at least transiently, a potential area of weakness.

— Weaknesses and threats, and Recommendations

The theme of hematopoeitic stem cells and their microenvironment is highly competitive and requires a critical mass of investigators per subject that might be difficult to obtain on all the aspects of the project, as all but one of the senior scientists of this team are medical doctors and professors that have other duties. This might be a weakness, particularly when dealing with complex animal models. The recruitment of additional young and full-time scientists (CR level or post-doc) with strong expertise on mouse models should be prioritized.

In general, like the other GICC teams, team 2 members should improve their presence on the international scene (meetings, conferences, collaborations & international networks and grants, foreign students and post-docs).

Team 3: Therapeutic molecular innovation

Team leader: M.-C. VIAUD-MASSUARD

The new GICC2 chemistry team 3, entitled "therapeutic molecular innovation", involves 12 people (2 University faculty members (PU, MCU) and 1 clinician from the university hospital (PH)) and is headed by MC Viaud-Massuard. This team is identical to the former GICC1 team 5, "Organic and therapeutic synthesis".

- 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)	0	0
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)	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)	4	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The research directions described in the report are very diverse, including: i/ synthesis of inhibitors against diverse biological targets (medical and biological chemistry developped on targets that interest team5 and 2, ii/ encapsulation of hydrophobic molecules in order to develop smart molecules, iii/ analytical studies aiming at understanding the solubility and stability of monoclonal antibodies.

Several families of N-containing heterocycles have been obtained with diverse biological targets showing the expertise of the group in the field of heterocyclic chemistry. Notably, in collaboration with team 5, they have obtained the first set of inhibitors of the Mos1 transposase that all contain a bis-(heteroaryl)maleimides scaffold.

Nine full papers (7 as first and/or senior authors) were published in specialized journals with average impact factor (for instance Bioorg Med Chem Lett, European Journal of Medicinal Chemistry, Heterocycles, Synlett. Etc..).

In addition, 3 patents have been registered (one international patent in 2006 and two national patents in 2008 and 2010, no license).

This record of publications and patents is correct taking into account, the small size of the group, the fact that the three senior researchers have either heavy teaching (MCU and PU) or medical (PH) duties, and the fact that the PI was deputy director (2008-09) and then director (since 2010) of GICC1.

Altogether the team has contributed to 16 posters in international and national conferences which show that it is active in its field. Although there are also a couple of invitations to conferences, these were not to major meetings. Overall, the international visibility of the team is sub-optimal and should be improved.

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

The group is organized around university faculty members. It has been and is still very active in recruiting post-docs, Ph.D and Master students. However, this recruitment appears to be mostly local. The group has built up a few academic and industrial collaborations (Servier, University of Poitiers, University of Mohammedia in Maroc) and is actively participating in local networks through two programs : "Cancéropôle Grand Ouest" and "Cosmetic Valley Competitiveness Pole". The cosmetotextile project, on the synthesis of micrcocapsules and encapsulation has already led to one patent and is currently funded by FUI. They have also been successful in raising other french funds from industry (Servier) as well as from regional public organization ("Cancéropôle Grand Ouest" and "Région centre").

The initial scientific strategy of GICC was to encourage multidisciplinary projects involving chemists,biologists and clinicians. The review committee feels that, while fruitful collaborations are already in place between the chemists of team 3 and the biologists of team 5 (co-authorship on publications and patents), it is not persuaded that interactions with the medical staff of the first GICC1 was fully achieved. However, as indicated during the visit on site and in the team report, there is a clear willingness to improve these interactions, notably with projects aiming to explore the biochemical properties of therapeutical antibodies solutions (collaboration with team1) or aiming to identify Stat5 inhibitors (with team 2). A hospital pharmacologist (PH) has recently joined the group in 2010, presumably to develop this new program on the solubility and preparation of therapeutic monoclonal antibodies (collaboration with team 1).

- Appreciation on the project

The scientific projects of team 3 presented during the visit on site are all in close collaboration with the biologists involved in the GICC2 proposal. Together with team 5, it is proposed to continue the derivatisation of maleimide inhibitor scaffold as a tool to further decipher the various enzymatic steps of Mos1-mediated transposition. While this approach might provide some insights, it would be of great interest to also develop a molecular model-building strategy of this question; this is feasable since the X-ray structure of Mos1 is now known. This additional strategy would be an asset not only for this project but also to improve the technical expertise of the team that would benefit to other GICC biology-chemistry based projects in the mid-long term. Another project, with team2, aims at developping compounds that interfere with Stat5 ativities and signaling, based on known modulators of PPARs. The review group expresses some concerns about the specificity of inhibitors that will be isolated by this approach. Overall, the chemistry involved in such projects is related to nitrogen-containing heterocyclic chemistry but only a few words appear in the report concerning the type of chemistry that will be developed.

- Conclusion :

— Summary

This chemistry group states a broad range of interests based on scientific collaborations outside and inside the unit. Their main topic is the design of nitrogen-containing heterocyclic structures to target biochemical processes that could become potential candidates for therapeutic development.

— Strengths and opportunities

The group has a strong expertise in heterocyclic chemistry.

Consistent with the initial objective of GICC, the group has developed collaborations with biologists. A fruitful internal collaboration with the molecular biologists of team 5 has been set up, with co-signed patents and publications. The new organization of GICC2 provides the possibility to extend these collaborations to two new groups with medical interests.

The group has been successful in obtaining funds and students for its projects.

— Weaknesses and threats and Recommendations

This team is isolated in terms of "chemical environment".

The presence of the team on the international scene is low and should be improved.

Since the senior scientists of this team spend a large part of their working time in teaching and administrative duties, it is recommended to avoid dispersion of the research subjects. Among the multiple projects proposed in the report, the group should focus on subjects that can create a synergistic effort with their biologist colleagues, such as the development of inhibitors of DDE enzymes which already gave significant results with the identification of the first Mos1 transposase inhibitors.

Considering the medicinal chemistry programs that are proposed, the lack of expertise in molecular modelling might preclude contribution on inhibitors at the forefront. It is recommended to develop this expertise asap.

The group should be reinforced by the recruitment of a researcher at the CR level, if possible with expertise in molecular modelling.

Team4: Telomeres and genome stability

Team leader: Michel CHARBONNEAU

The new GICC2 team 4 (8 people/7 permanent staff), entitled "telomeres & genome stability", results from the fusion of the technical staff of the former GICC1 team 4 "genomic instability and cancer" that was working on the role of the tumor suppressor Menin in the control of genome stability (headed by the proposed director of the GICC2 project), with two CNRS DR/CR working on telomeres maintenance who moved very recently from Lyon (M. Charbonneau / N. Grandin, former members of the team "G2 Cell Control, telomere protection and control of their size" at UMR5239, ENS Lyon). They have been joined by one Research engineer (IR, Tours university) from the former team 6 of GICC1 with expertise in human molecular genetics. In 2012, they will be joined by two medical faculty members of Tours University Hospital (PU-PH) with interest in oncology and surgery. The team will be headed by M. Charbonneau and will focus on Telomere function and regulation.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	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)	1	2
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)	2	
N7: Number of staff members with a HDR or a similar grade	3	5

- Appreciation on the results

The team leader is an accomplished geneticist with a strong track record over the past 15 years of novel contributions to the field of telomere biology, all of which have been published as last author in top journals (e.g. Genes & Dev, EMBO J, and Mol Cell Biol). Most notably, he, together with only one collaborator, has discovered two essential telomere-capping proteins, the Stn1 and Ten1 components of the CST complex, now recognized to be a widely conserved RPA-like complex. He was also the first to discover a role for Hsp90 type chaperones in telomere maintenance, now shown by biochemical studies (B. Freeman and colleagues) to be crucial for promoting protein dynamics essential to telomerase action and regulation. More recently, he developed and exploited clever genetic screens to uncover additional new aspects of telomere biology, one related to DNA replication stress and alternative recombination-based telomere elongation pathways, another involving a possible novel telomere-specific DNA damage checkpoint pathway involving the highly conserved RPA single-strand DNA-binding heterotrimer.

It is important to emphasize that these accomplishments have been achieved with for the most part a single collaborator, and on a very limited budget. The productivity/cost ratio of the team leader is likely to be in the top 10% of the field. The recent 2006-2010 record of publication is constant and correct if one takes into account this productivity/cost ratio and the good quality of the results (Nuc Acid Res 2007, Mol Genet Genomics (2007), Cell Cycle (2008), Mol Cell Biol (2009) etc..)

The research engineer who has joined the team has a good record of publications obtained in the former team 6 of GICC1 in the field of immunogenetics and therapeutic antibodies (last author in J Clin Oncol (2008); and J Urol (2010), and co-author of 7 other publications in medical journals).

The two medical faculty members PUPH that will join the team for 10% of their time have a record of medical publications and letters in average, mainly in specialized journals focusing on neurosurgery or oncology.

- 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 internationally recognized in the field of telomeres biology and his work is widely cited. His "visibility" in the field, as measured by other criteria such as presentations at international meetings, meeting organization, recruitment of students/postdocs, etc. has been lower than would be expected from the published record and from the novelties of the results. However, the very recent (2010) move of the team to Tours, and its expansion and adoption of mammalian cell models, as well as a number of innovative collaborations on site, offers the promise of a significant increase in visibility in the coming years. Together with the recent award of a Nobel Prize in the telomere field, these new developments should increase the attractiveness of the team to students and postdocs.

The review group encourages this new team to develop a more ambitious approach for their communication, to attend more international meetings, and to improve the recognition of their very valuable work by initiating international collaborations (notably, European networks).

Although all senior faculty members of this team have been able to raise funds in the past, the funding of this new and larger team is unclear. This could become a potential area of weakness that should be prioritized by the team and by GICC. In that respect, the proposed extension of the PI results to the mammalian systems, should provide additional opportunities of funding to this team.

- Appreciation on the project

The team to be created is composed of two CNRS researchers whi have recently arrived from Lyon, with a strong expertise in yeast genetics and telomeres, and of a technical staff (3) with expertise in mammalian biology and genetics. Although it is too early to judge the efficiency of this association and although there is a strong coherence in the overall scientific projects that are proposed (centered on telomere biology in both yeast and human), They should be joined in 2012 by two PUPH with very heavy teaching and medical duties. The research themes and objectives of the clinicians within the project are unclear. This later point should be clarified.

A logical and exciting series of projects are proposed that build upon recent (largely unpublished) results using the budding yeast system. These recent studies open interesting perspectives on a possible novel, telomere-specific checkpoint activation pathway, mechanisms of telomerase holoenzyme assembly and/or cytoplasmic/nuclear trafficking, and DNA damage-induced cohesin modification. Pursuit of these studies in yeast should be strongly encouraged as they have a good chance to be published in top-journals. A proposal to extend the checkpoint work to human cells in culture also appears promising and is likely a potential asset to obtain additional funding from cancer agencies.

However, proposals to develop two different shRNA-based genetic screens in human cell lines are not well thought out and do not at this time appear feasible. The applicant would be advised to proceed step by step to establish first a regulatable telomerase cell line, while at the same time carefully considering possible external collaborations for the genetic screens that are proposed, which are likely to require access to sophisticated high-throughput screening platforms and expensive sh/si RNA and cDNA libraries. The regulated telomerase line will also be necessary in a collaboration proposed with the Augé-Gouillou team, which aims to test an interesting though highly speculative hypothesis.

The scientific and medical values of the projects proposed with the two clinicians that plan to join the team are unclear. These projects still need to mature.

- Conclusion :

— Summary

The new PI is an internationally recognized yeast geneticist in the field of telomeres biology whose innovative work is widely cited. He has, so far, achieved this significant contribution to the field with a single collaborator, and on a very limited budget. His very recent (2010) move to GICC is accompanied by creation of a team of 8 people and extension of his projects to mammalian cell models.

— Strengths and opportunities

The PI has a past track record of novel and original contributions to the field of telomere biology. His ongoing mechanistic studies in yeast open interesting perspectives that have good chance to be published in top-journals. His association with mammalian biologists and the proposed extension of this work to human cells in culture also appears promising and is likely an asset to obtain additional funding from cancer agencies.

There are several innovative collaborations proposed on site.

— Weaknesses and threats, and Recommendations

Other aspects of the projects in mammalian cells (ShRNA and cDNA screens, ALT/glioblastoma) should mature and will require external collaborations and additional funds. Notably, the review group recommends further consideration of how realistic it is for a new group that still need to crystallize to carry out the large and expensive genetic screens in mammalian cells that they propose.

The funding of this new team is currently limited. This could become a potential area of weakness that should be prioritized, with the help of GICC.

In conclusion, some thought should be given to the limited personnel resources available and to the effort which will be required to advance each of the individual projects in a competitive manner. This will certainly require to focus strength and funds, at least at the beginning, on a more limited number of projects that directly derive from the ongoing yeast studies.

Team 5: Genomes and Transposase Relationships

Team leader: Corinne AUGÉ-GOUILLOU

This new GICC2 team 5 is composed of former members of GICC1 team 2 (headed by the first director of GICC, Y Bigot) that merged with GICC1 team 1 ("biochemistry of Mariner transposases", C. Augé-Gouillou). The 3 permanent researchers of this proposed team5 have faculty (MCU) positions and are actively involved in the teaching of biology at the Tours Sciences University. Four members of the team have a HDR, including a Research engineer (IR CNRS).

- 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	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)	3.5	3
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 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	4	3

- Appreciation on the results

The group has worked for many years on transposition of the Mos1 transposon. They have made some inroads into understanding Mos1 transposition at the biochemical level and the results are quite complementary to those obtained elsewhere with other DNA transposons. In addition, a large effort was invested in biotech aspects - construction of vectors for mutagenesis and gene delivery. So far this has not been fruitful in the case of human cells but may yet be useful for other model organisms such as C. elegans.

The availability of a crystal structure of the Mos transposase with one of its DNA substrates provided the group with a scaffold for understanding and predicting the behaviour of transposase mutants isolated by them and also by the group responsible for the structure. This has confirmed, for example, the presence of a regulatory checkpoint requiring the formation of a synaptic complex before any chemistry can occur as has been found with other transposons but which had been problematic for Mos1. They have also provided some evidence that transposase activity might be regulated by phosphorylation. Together with GICC2 Team 3 (chemistry), the group has identified maleimide derivatives effective in inhibiting Mos1 transposase activity and, in collaboration with another group, have shown that these molecules are also active on another distantly related member of this family, the HIV integrase. Although it is too premature to judge, it is possible that maleimide might be tailored to become an effective therapeutic agent and join the existing integrase inhibitors which have been developed by the large Pharmas.

The group members have an acceptable, but not strong, publication record: 21 articles in peer-reviewed international journals of which 12 research articles and one review directly concern the transposon project. These are not published in journals with high impact (Biochemistry, J Mol Biol, Mini Rev Med Chem, Mol Genet Genomics, Gene, Genetica, PloS One, BMC Mol Biol). The remaining articles appear to be associated with older projects (e.g. DNA viruses) or with new members of the group.

There are also 2 patents concerning the isolation of hyperactive transposase mutants and, with team 3, the identification of maleimide inhibitors of DDE/DDD transposases.

The PI has been invited to two national and one international meeting (the most recent international workshop on Site-specific recombination, transposition and chromosome dynamics) and different group members have contributed posters at numerous national and international meetings.

Three PhD students have graduated under the direction of present members 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

The three permanent scientists of the group are university faculty who have the usual heavy teaching loads so characteristic of the French University system. The PI has been successful in attracting and financing students & more recently, postdocs (2). However, none have come from abroad. It seems that this team is now just beginning to expand and this may provide it with the opportunity to make a much bigger impact in the field than it has been able to make to date.

The PI is responsible for a French network of laboratories (GIS) interested in mariner and related eukaryotic transposable elements and has participated to an EU Strep programme (coordinated by the first director of GICC1) concerned with the use of mariner as a delivery tool in gene therapy.

The group has been successful in attracting funding at the local (Région Centre) and national (ANR, CNRS) levels. Many (if not all) projects are financed.

- Appreciation on the project

There are three major projects:

1) **DDE inhibitors**. This is an ongoing project funded by Région Centre. Together with Team 3, it is proposed to continue the derivatisation of the maleimide inhibitor scaffold as a tool to probe the mecanism of Mos1 at the atomic level. These compounds will be tested on HIV integrase in collaboration with another group. While this might provide some insights it will necessitate an additional, molecular model-building approach as the PI recognises. The group also has access to a chemical library from a small biotech company which they will test. This is an extremely competitive area of research. The competition includes some large Pharmas such as MERCK. However, it is very difficult to judge the potential for success since there is a large component of serendipity involved. Inhibitors might be used to probe mechanism but this is not addressed here in any detail.

2) **SETMAR and Hsmar1 expression**. This is a new two-pronged project. On the one hand, the role of a primate-specific gene fusion between a mariner transposase and a histone methyltransferase will be investigated and its expression will be analysed and on the other, the effect of expression of the human relative of Mos1, Hsmar1, on global gene expression (which is strangely called functional genomics here) will be analysed. The interest of the latter is based on the observation that many Hsmar1 fragments might be embedded within genes and therefore the expression of these genes may be influenced by Hsmar-mediated RNAi. While the committee had some reservations concerning the RNAi part of this project, it was felt that exploration of the reported effects of SETMAR on DNA transactions (e.g. enhanced Topo-II function) and its possible enhanced expression in carcinogenesis would be worthwhile. In particular its potential role in leukemic cells (in collaboration with group 2) and in the ALT pathway of telomere maintenance which occurs in come cancer cells (in collaboration with group 4).

3) **Mariner as an engineering tool**. There are several avenues which will be explored here. An ongoing collaborative project financed by the ANR concerns C.elegans and will exploit the hyperactive Mos1 transposase mutants previously isolated by the group to improve the efficiency of an established Mos1-based protocol for targeted gene delivery in this organism. It is also proposed to generate "improved" transposon and transposase delivery systems. The second avenue of exploration will be to use Hsmar1 and/or piggyBac (which have both previously been shown by others to transpose in human cells) to investigate e.g. double strand break formation and repair. It is argued that not only is this important in revealing the transposon-host interface(s) but is a prerequisit for further developing tools.

- Conclusion :

— Summary

The group is composed of three university faculty. It has many years experience with the Mos1 transposon from Drosophila and has developed an in vitro system to analyse its transposition mechanism. This has had some success. The group has also developed a useful collaboration in identifying transposase inhibitors. On the other hand the use of Mos1 as a gene delivery system and genetic engineering tool has not progressed rapidly and, except for C. elegans, its use appears limited. The related (Hsmar1-RA) and unrelated (piggyBac) systems appear more tractable for use in a variety of cell lines and organisms. The projects proposed may provide opportunities for the group to evolve more towards cell biology and the interface between transposons and the host cell.

— Strengths and opportunities

The team has been very successful in attracting good fundings and most projects are financed. Two new post-docs joined this small team in 2010; this should contribute to speed ongoing project development and provide the opportunity to make a much bigger impact in the field than has been achieved to date.

These projects have the advantage of the opportunity afforded by the unit for collaboration with other groups - in particular the ongoing collaboration with group 3 on DDE inhibitors (with patents) and potential interesting collaborative projects with the future groups 2 and 4 of GICC2 on the influence of SETMAR on cell proliferation.

— Weaknesses and threats

The proposed projects are all in very competitive research areas. DDE inhibitors are already on the market and are presumably being expanded by the big Pharmas as well as several large research institutions. The goal of this project should be clearly defined. The group should also perhaps have explored the viability of the proposed projects by obtaining some preliminary results. Other groups are actively working on SETMAR and on Hsmar1 transposition. The systems are complex and often less tractable than they might initially naively seem (e.g. the absence of Mos1 transposition in human cells as this group experienced).

The absence of publications in top-journals is detrimental to the international recognition and long-term survival of this team.

— Recommendations

It is imperative that the collaborations outlined in this project are consumated and that this group can find its "niche". Some thought should be given to the limited personel resources available and to the effort which will be required to advance each of the individual projects in a competitive manner at the international level. Rather than spread the available resources thinly, it would be more logical to concentrate efforts into fewer projects. Hence, publications in top-journals will certainly require to focus strength on a more limited number of projects.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
GÉNÉTIQUE, IMMUNOTHÉRAPIE, CHIMIE ET CANCER	**A**	**B**	**A**	**A**	**A**
RELATIONS ENTRE GÉNOMES ET TRANSPOSASES [GAUDRAY-AUGE-GOUILLOU]	B	B	Non noté	A	B
TÉLOMÈRES ET STABILITÉ DU GÉNOME [GAUDRAY-CHARBONNEAU]	A	B	Non noté	A	A
NICHE LEUCÉMIQUE ET MÉTABOLISME REDOX [GAUDRAY-HERAULT]	A	A	Non noté	A	A
ANTICORPS, RÉCEPTEURS FC ET RÉPÔNSES CLINIQUES [GAUDRAY-PAINTAUD]	A+	A+	Non noté	A+	A+
INNOVATION MOLÉCULAIRE THÉRAPEUTIQUE [GAUDRAY-VIAUD-MASSUARD]	B	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**

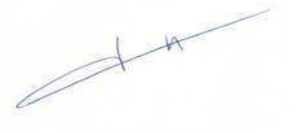
UNIVERSITÉ
FRANÇOIS - RABELAIS
TOURS

SERVICE DE LA RECHERCHE ET
DES ETUDES DOCTORALES

Tours, le 6 avril 2011

REPONSE DE :
GENETICS, IMMUNOTHERAPY, CHEMISTRY AND CANCER (GICC)

Le Vice-Président,
Chargé de la Recherche



Michel ISINGRINI

3 rue des Tanneurs
BP 4103
37041
Tours Cedex 1

Tél. : 02 47 36 64 12
Fax : 02 47 36 65 62
Mél. : red@univ-tours.fr

UMR6239
Dir. Marie-Claude Viaud-Massuard

Response to the AERES report on the research unit GICC from the University of Tours

First, we want to thank the review committee for both the time and work that it devoted to our project, to a so careful and in depth investigation of our strengths and weaknesses, and for the nice scientific atmosphere during the review last January.

We appreciate that the review committee has perceived the efforts that have been made since the beginning to create an active interdisciplinary research unit, and the complexity of the restructuration that was started during the last year. This restructuration has driven the deliberate choice of group leaders on the basis of their scientific and managing skills, and their willingness to coordinate both scientific projects and the persons in charge of conducting them.

The management of the unit will certainly take good notice of the advice that is given to reduce the number of projects and of their necessary prioritization. We are very grateful for the positive outcomes and for the encouragements that are given throughout the report.

We also value the recommendations and criticisms that have been underlined. Most of the "negative" comments refer to the relative lack of international visibility. One could quickly answer by paraphrasing the French 17th century author Pierre Corneille: *we are young, it is true but for the well-born hearts, value does not await the number of years*.

More seriously, every team will respond for itself, but, at the level of the unit, we would like to stress out new positive elements (achievements):

1- Although we do not want to reduce our efforts, we have to point out that GICC is a major team and the pilot of a selected "laboratory of excellence" (Labex) on therapeutic antibodies (in collaboration with four teams of Montpellier) referred to as *MabImprove* (PI Hervé Watier) that is one of only 23 biology and health Labex in France and the only one in the north-west quarter of France.

2- We have just learnt that a manuscript has just been accepted in Nature Biotechnology (IF = 29.5)[1] that involves two members of team N°5 as second and last author.

3- The relative weakness of some teams has been opposed to the ambitiousness of their projects. This is particularly the case of medicinal chemistry programs and of the *lack of expertise in molecular modeling that might preclude contribution on inhibitors at the forefront*. The group has been reinforced by the recruitment of a MCU, Christophe MAROT, from Orléans, who has a good expertise in molecular modeling.

4- With the help of CNRS, the recruitment of a "Chaire d'excellence" has been set up (at the level of MCU), and since there are around 90 candidates for this position, we are confident that we should find somebody who will complement and reinforce the Chemistry team.

5- Three PhD fellowships (starting in September 2011) have been awarded to teams 2,4, and 5 that will reinforce their scientific projects.

[1] Palazzoli F, Bire S, Bigot Y & Bonnin-Rouleux F. Landscape of chromatin control element patents: positioning effect in pharmaceutical bioproduction. 2011; accepted for publication in *Nature Biotechnology* MS#BT-PT25515)

6- On a more practical aspect, the Web site of GICC is being totally rebuilt, and an emphasis will be put on (i) its simplicity, (ii) its readability by lay people, (iii) its English version. Each team will become responsible for the maintenance of its specific pages.

Concerning the advice of the review committee to share more resources between teams, we take good notice that money sharing could give the managing team the opportunity of an actual scientific policy. Conversely, we doubt that we can manage the personnel as it has been proposed. Permanent staff would certainly not appreciate to be considered as pawns in a chess game, although we are aware that neither CNRS nor the University are in a position where they can create permanent technical positions for our unit.

We fully agree with the committee that the unit would benefit of the advice of a permanent scientific advisory board. Although we know that it is difficult to solicit top-level foreign scientists who are already over-solicited, our priority is to set up such a council as soon as possible.

Finally, we cannot be more in frame with the committee's recommendation of "*one GICC on one site*", and we will act to even speed up the process so that we are all on the same spot before 2015.

Patrick Gaudray
Directeur de recherche au CNRS
Project manager

Responses from GICC teams to the AERES report

Team N°1 - **Antibodies, Fc receptors and clinical responses (A2RC)**

Lab Head: Gilles Paintaud

Team N°1 wishes to thank the review committee for this sound analysis of its background and of its scientific project. We appreciate that our publication record has been recognized as very good, although we acknowledge the fact that the team should target major journals of a more general audience.

We would like to complete the information given to the committee in January by a few facts that were not presented at that time:

1°) Hervé Watier is the leader of a selected "laboratory of excellence" (Labex) on therapeutic antibodies called *MabImprove* ("Optimization of therapeutic monoclonal antibodies development"), in collaboration with four teams of Tours and four teams of Montpellier. It is one of only 23 "biology and health" Labex in France and the only one in the north west quarter of France. Our team plays a major role in this Labex as Gilles Paintaud, Gilles Thibault and Hervé Watier are co-managers of 3 of the 5 work packages. This recognition of our leadership in the development of tools to use monoclonal antibodies as biopharmaceuticals will give us high level support for the next ten years, in addition to having a major impact on the image of the entire GICC

2°) Concerning the place of our research on the international scene, we can add to written report that : (i) the three senior scientists of the project have been cited 323 (HW), 205 (YG) and 178 (GP) times in 2010 (*Web of Science*); (ii) the Second "Charles Richet and Jules Héricourt" international

workshop on Therapeutic Antibodies and Anaphylaxis will be organized by team N°1 in Tours May 31st - June 1st 2011; (iii) Gilles Paintaud is invited to give a lecture at the next meeting of the European Association of Clinical Pharmacology and Therapeutics (EACPT, Budapest, June 2011).

3°) Team N°1 agrees that our major investment in clinical research was poorly documented in the written report due to a lack of space. In fact, the team is involved in 30 (mainly multicenter) clinical studies devoted to pharmacokinetics and/or pharmacogenetics studies of therapeutic antibodies. In addition, the team is involved in 5 animal studies. This valorizes the recognized major implication of most senior scientists of the team in bedside application of biological research.

Team N°2 - **Leukemic Niche and redOx metabolism (LNOx)**

Lab Head: Olivier Hérault

The Team 2 thanks the review committee, and notices that it has concerns regarding the governance of the team, the financial and technical resources required to support our project and the international influence of the team as well as intellectual property regarding some aspects of the project. The committee also asked to clarify the clinical part of the research project.

1) Governance of the team

Team 2 results from the merger of three formerly independent groups with different areas of expertise: EA3855, EA3852 and Team 3 of GICC1. Since last September, the three teams are located in the same building. They use common experimental models and methods and work effectively together, and two of them have already joint publications. The new Team 2 has two scientific meetings weekly. Senior scientists also meet weekly to coordinate projects, lab organization and human resources management.

2) Financial, technical and human resources

Even if the financial resources obtained in 2010 by Team 2 were important, we fully agree to the suggestions made by the committee to strengthen them. Along this line, Team 2 is applying to become "équipe labélisée" of the charity "Ligue Nationale Contre le Cancer". We agree also that the *in vitro* experiments in our project may be confronted to the problem of abnormal O_2 environment. We want to stress out that funding for a "hypoxic workstation" is now acquired, and such equipment will soon be available to allow inclusion of the "hypoxia" parameter in the modeling of the leukaemic niche.

3) Presence on the international scene

We appreciate that the committee underlined the good publications record of Team 2 and we agree that our presence on the international scene was sub-optimal until now. However, we have to emphasize that (i) we had three published abstracts at the last American Society of Hematology annual meeting, (ii) we will apply to an upcoming international ANR Grant (France-Austria project: "Targeting Stat5 proteins in myeloid malignancies" coordinated by Fabrice Gouilleux, a senior scientist of our team), (iii) all our international collaborations described in the written project will be maintained, as well as ongoing projects with different teams in Canada, USA and Austria.

4) Intellectual property of the project

Although our model of primary leukemic stem cells, and the primary results obtained from this model were initiated in the lab of Guy Sauvageau (Montreal), its use by our group will neither interfere nor overlap with the Canadian's projects. In fact, their lab focuses mainly on the epigenetic regulation of HSC self-renewal. Ours focuses on the oxidative metabolism and GPX3 expression in the leukemic niche. We are aware to be in a highly competitive field, but we trust that the expertise and knowledge that have merged in our group will help us to find our own "niche" in a near future.

5) Clinical projects

The committee has underlined that a strength of our project is our capacity to develop translational aspects starting from *ex vivo* / *in vivo* (mouse) models to patients. Clinical studies benefit from (i) our presence at the head of the Biological Hematology Department of the University Hospital of Tours, (ii) an easy access to various collection of patients samples (official "cytothèque" of the Department of Biological Haematology [9,000 samples from ≈2,500 patients], and the national "GOELAMSthèque"), (iii) a local access to normal hematopoietic stem cells from human marrow, peripheral blood and cord blood ("CoSMMOS", "OPTICYT" and "OPTICORD), and (iv) an active participation in the clinical research programs of GOELAMS and GFM. Three types of projects are planned (all funded, excepted "MILESYM" as yet): (a) validation on patient samples (acute myeloid leukemia [AML], myelodysplastic syndromes [MDS]) of results obtained *ex vivo* and in animal models ("MILESYM" project aiming at studying molecular and functional characteristics of marrow MSCs from patients with MDS and AML compared to MSCs from healthy marrows); (b) evaluation of diagnostic and prognostic relevance of identified biological markers ("PROXYMYL" and "LEUSIGNOX" projects centered on the antioxidant signature of hematologic neoplasms [European Patent No. 10306483.8-1222 "Method for diagnosing hematological disorders"]); (c) evaluation of the antioxidant signature as a predictive tool for therapeutic response ("OXYDAZ" project).

Team N°3 - **Therapeutic molecular innovation**

Lab Head: Marie-Claude Viaud-Massuard

The Team N°3 appreciate that its *strong expertise in heterocyclic chemistry* has been acknowledged by the review committee. We are fully aware that our critical mass needs to be enhanced, so that we no longer appear as being *isolated in terms of "chemical environment"*, and we take good notice of the Committee's concerns about the necessary improvement of our presence on the international scene. We wish to respond to comments, criticisms and recommendations that have been made, especially as several points that have been underlined have evolved since the visit of the Committee in January.

1°) The review committee points to a relative dispersion of the chemistry projects and ask for more focus on themes that can increase the *synergistic efforts with their biologist colleagues*, we believe within GICC. From this point of view, we have given up on a time consuming and low productivity project on alkaloid compounds mimicking marine sponges products that target tubulin, and thus to focus on our main chemical interests, maleimides, in particular.

2°) We have received confirmation that a position referred to as MCU-Chaire CNRS 0328 is officially opened at the University of Tours. It will allow the recruitment of a researcher (with light teaching duties) with an expertise in heterocyclic chemistry aiming at tumor targeting. Since we have learnt that there are ≈90 candidates for this position, we believe that the recruitment will be successful. The person who will be hired will contribute strengthening the collaboration of our group and team N°2, in particular concerning Stat5 function and signaling.

3°) The review committee has expressed concerns about a possible lack of expertise in molecular modeling that *might preclude contribution on inhibitors at the forefront*. In September 2011, Christophe Marot (MCU-HDR from Orléans) will join our group. His expertise in molecular modeling will create a positive environment to our study of the mechanisms of inhibition of both transposases and HIV integrase by maleimides-derivatives. It will also provide a tutoring to the bioinformatics engineer who is already in charge of part of this project. The study of structure-activity relationships will allow us to reinforce our strong collaboration with team N°5, on which the InhDDE project is based and give it the opportunity to publish in higher-ranked journals.

4°) Our team will also benefit from the creation of the Labex “MabImprove” in which a "Physical Chemistry of monoclonal antibodies" platform has been identified. This platform will be invaluable to study and evaluate factors that may influence the formation of monoclonal antibodies aggregates. This is studied by Jean-François Tournamille (pharmacologist PH at the University Hospital) within our team and will strengthen the collaboration with team N°1.

5°) Concerning our place and relations on the international scene, we trust that the strengthening of our group by three new scientists and thank to the change in the managements of the unit by somebody else than team N°3 leader will help us to increase our publication level. This is a prerequisite for gaining invitations to prominent international meetings. We can add two points that are –and will be important for our international image, namely:

- Collaboration with the laboratory of Zoltan Ivics (MDC, Berlin) for the use of our maleimides molecules
- Participation in the framework of an “Erasmus” draft between the University of Tours and the University of Barcelona for a cycle of teaching- conferences (12 hrs).

Team N°4 - **Telomeres and genome stability**

Lab Head: Michel Charbonneau

We are very grateful to the AERES Committee both for its encouragements and criticisms. We totally agree with its analysis, as you will see along our answers below.

1°) Our greatest preoccupation is to rapidly raise money to develop our projects. As you rightly noticed, the principal reason to operate a move from the yeast model to the human model for telomeres (while keeping the yeast model) was to increase our efficiency in raising funds. Taking advantage of the Cancéropôle Grand Ouest recent call for funding, collaboration could be set up with Lucie Karayan-Tapon (MCU-PH - CHU of Poitiers and INSERM U985) on glioma cells. Her group has access to stem-like cancer cells that they derive from glioblastoma patients. This collaborative project will be submitted soon to Cancéropôle and the LIGUE Grand Ouest. We have also applied to a call for funding from the Fondation de France, implicating our group only. The role of the two physicians in the group, Claude Linassier and Patrick François, will be reconsidered. Another positive point in this matter is the attribution of a doctoral fellowship to our group, starting October 2011.

2°) Concerning the genetic screens on mammalian cells, we agree that the approach with sh/siRNA libraries might be very costly and difficult to set up technically. We will follow the suggestion made by the AERES Committee to undergo such an approach in collaboration with groups expert in that matter (or in dedicated technical platforms). Before the AERES Committee report was issued, we had already decided to simplify our approach by using, for instance, the specific telomerase inhibitor BIBR1352. Together with the hTERT transgene constructed here, we will have good tools at hands to manipulate glioma cell lines and study the ALT and telomerase pathways.

3°) We appreciate the encouragements of the Committee to actively pursue our studies on budding yeast telomeres. We also welcome the suggestion to derive the mammalian projects to come from our knowledge of equivalent mechanisms in yeast. Indeed, the projects on ALT/telomerase in glioma were derived from our previous studies on the equivalent ALT pathway in budding yeast.

We will apply the same reasoning concerning a second major project concerning human cells on the CTC1-STN1-TEN1 and Shelterin complexes, given our expertise in the Cdc13-Stn1-Ten1 homologous complex in budding yeast. We propose to study mechanisms linked to the role of CST and Shelterin in leukemic cells. In fact, the *MLL* gene, which is rearranged in acute lymphoid and myeloid leukemia, encodes a Set methylase that functionally interacts with the shelterin protein complex in the transcriptional regulation of telomeres, as proposed by the group of Jay Hess in 2009.

4°) Our participation to international meetings depends on our ability to raise enough money, as our clear priority is given to bench money. Indeed, we need to take into account that working with the top two model systems in telomere biology, humans and the budding yeast, requires more benefit from the international telomere community. In addition, we will try to organize an international meeting on telomeres in Tours.

5°) Finally, we have planned, together with Charles White, head of the telomere group in the CNRS/INSERM Unit in Clermont-Ferrand, to apply to ANR grants by the end of this year, combining our projects on *Arabidopsis*, *S. cerevisiae* and humans to study the conserved CTC1/Cdc13-STN1-TEN1 complex of telomere maintenance in these three organisms. This could represent a starting point for more ambitious programs on telomeres at the international level.

Team N°5 - **Genomes & Transposases relationships**

Lab Head: Corinne Augé-Gouillou

The review committee must be thanked for the encouragements and criticisms brought to our project. The criticisms concern mainly the limited forces in presence and the international attractiveness of the team. Some additional information can be given as a response to those comments.

1°) We would like to shed light onto the DDE inhibitors project. This project has begun 5 years ago, and the “proof of concept” has been achieved. It led to publication, patent and funding for a post-doc. In addition, this project is one of the strongest collaborative projects within GICC. In order to reinforce the rational design of improved maleimides, the unit was successful in attracting one person (C. Marot) devoted to modeling and drug design. A second person is expected at the end of 2011 by the way of a Studium[2] contract (Région Centre) that permits the welcoming of a senior scientist.

We probably were not informative enough in our presentation of the aims of the project, which are: to setup tools to probe mariner transposition, and to check whether or not mariner transposases can be powerful surrogates to screen new HIV-1 integrase inhibitors, especially in human cultured cells. As the committee observed it, Mos1 is inactive in human cells. This is the reason why we are developing Hsmar1 transposition assays in human cells. In addition, DDE inhibitors could be used to better control the transposase activity in the gene transfer. This point is currently assayed in Zoltan Ivics’lab (MDC, Berlin) with our maleimide derivatives.

2°) We agree that the proposed projects (ongoing and new) are all in very competitive research areas. Therefore, we consider with attention the recommendation of the committee to focus strength on a more limited number of projects, especially with the aim to publish in top-journals. However, we paid particular attention that the new projects are not in direct competition with the well-established groups (especially working on SETMAR), in order to find easily a “niche” in highly interesting topic. As pinpointed by the committee, we are in a period of transition that allows us accumulating preliminary data on the new projects in order to identify priorities to focus on our strengths. In complement to what was indicated in the written project, we decided that this period of transition would end at the end of 2012. At this time, we will chose 2 topics between the 4 main axes (DDE inhibitors, transposon-tools, SETMAR expression and effect of Hsmar1 expression on global gene expression) in order to focus on topics that have the potential to become competitive subjects at the international level.

[2] Research institutions (CNRS, for instance) and Universities of "Région Centre" have created in LE STUDIUM® an innovative program for bringing together high-level foreign researchers within laboratories for one -or two-year periods.

3°) To conclude, we would like to stress out that most of our current projects are funded, and thus allow hiring post-docs. Since the site visit, a doctoral fellowship was attributed to our group to reinforce our ability to speed up project development.

In addition, the group leader has been an invited speaker to an international meeting focused on eukaryotic mobile DNA (FASEB conference, august 2011). This is a first main step in developing “a more ambitious and aggressive approach to attend international meetings”, as recommend by the committee. Finally, two members of the team, Solenne Bire and Florence Bonnin are respectively second and last authors of a publication accepted in Nature Biotechnology (IF 29.5).

From these recent instances, we trust in our ability to achieve breakthroughs and to publish in high-profile journals.
