CTO - Ciblage thérapeutique en oncologie

Rapport Hcéres

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

Section des unités de recherche

AERES report on the research unit:

Therapeutic targeting in oncology

From the

University Lyon 1

May 2010

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Unit

Name of the unit: Therapeutic targeting in Oncology

Requested label: Equipe associée

No. in case of renewal: EA3738

Unit director: M. François-Noël GILLY

Members of the expert committee

Chairperson:

M. Dietrich AVERBECK, Institut Curie, Orsay

Other committee members:

M. Thierry PATRICE, University of Nantes 1, France

M. Pompiliu PISO, Klinik und Poliklinik für Chirurgie de Universität Regensburg, Germany

Ms. Sandrine FAIVRE, Hôpital Beaujon, U728 Inserm, Université Paris VII, Clichy ;

M. Michel VIDAL, Université Paris 5, Paris, France

Reviewer(s) nominated by the staff evaluation committees (CNU, CoNRS, CSS INSERM ...):

M. Etienne TISSOT, (CNU)

Representatives present during the visit

Scientific delegate representing AERES:

Mme Marie-Annick BUENDIA

University or School representative :

M. Pierre FARGE, University Lyon 1

M. Germain GILLET, University Lyon 1

M. Lionel COLLET, President of University Lyon 1

Report

1 • Introduction

- Date and conduct of the visit

The visit took place on February 3rd, 2010 at the University Lyon Sud, Charles Mérieux Medical School, Oullins. After a brief closed-door gathering of the visiting committee, the laboratory director made a general presentation of the teams' main achievements and activities within the Lyon research and clinical networks. Each group leader then presented past results and projects and answered committee members' questions. The committee met with representatives from Lyon I University, who expressed strong support of the activities of the team, and then heard separately the students and post-docs, the scientists, and the technical staff. The visit concluded by a 3h closed-door meeting of the committee.

- History and geographical location of the unit and brief description of its field of study and activities:

The research unit EA 3738 "Therapeutic targetting in Oncology" created on 2003 initially included 3 research teams: Team 1: "Chirurgical targetting and peritoneal carcinomatosis", Team 2: "Targeting by chemotherapy and pharmocokinetics", Team 3: "Targeting by physical agents". It was reconducted in 2007 conserving these 3 teams and enriched by a fourth team: "Cellular and molecular radiation biology" (headed by C. Rodriguez Lafrasse, from a previous INSERM UNIT). The research unit is localized on the university campus Lyon-Sud Charles Mérieux- University Claude Bernard Lyon 1, UFR Médecine Lyon Sud at Oullins. Its scientific activities include clinical, translational and fundamental research with special emphasis on peritoneal carcinomatosis (chemo-hyperthermia and peritonectomy) and trophoblastic tumours, pharmacokinetic modelling and chemotherapy, modern radiation therapy (stereotaxic) with on board imaging system, and cellular and molecular radiobiology in connection with Hadron therapy and the project ETOILE.

The unit occupied in 2009 260 square meters research facility and recently extended to a total of 300 m^2. Team 1 and 3 are located inside the hospital area, whereas teams 2 and 4 are within the university area of the campus.

- Management Team:

The Director of the Unit is assisted by 4 Deputy Directors and they meet regularly to assure a smooth management of the unit.

- Staff: (according to the dossier submitted to AERES):

	In the report	In the project
N1: Number of professors (see Form 2.1 of the unit's dossier)	21	22
N2: Number of EPST, (Public scientific and technological institution) or EPIC, (Public industrial and commercial institution) researchers (see Form 2.3 of the unit's dossier)	2	5
N3: Number of other professors and researchers (see Form 2.2 and 2.4 of the unit's dossier)	4	4
N4: Number of engineers, technicians and tenured administrative staff members (see Form 2.5 of the unit's dossier)	4	4
N5: Number of engineers, technicians and non-tenured administrative staff members (see Form 2.6 of the unit's dossier)	0	0
N6: Number of doctoral students (see Form 2.8 of the unit's report dossier and 2.7 of the unit's project dossier)	12	12
N7: Number of persons accredited to supervise research and similar	23	26

2 • Assessment of the unit

- Overall opinion

The Unit combines original know-how and many complementary competences at the same site, exploring 4 domains: chirurgical targeting of peritoneal carcinomatosis, modeling of tumour biology and optimization of anticancer effects, targeting by physical agents such as radiation and hyperthermia, and cellular and molecular radiation biology. The research unit has successfully developed clinical research in oncology and improved targeting, which is a major challenge for successful chemotherapy and radiotherapy. It has also generated a junction between fundamental and clinical research. A salient feature is the technology of chemo-hyperthermic intraperitoneal treatment (CHIP) using an animal model with peritoneal carcinosis and evaluating combined peritonectomy plus CHIP treatments. The Unit has obtained the national INCA label as a Center of Reference of rare peritoneal tumours, and the constitution of the national Network RENAPE as a reference center for trophoblastic tumours. Moreover, it has developped and validated pharmaco-kinetic models of chemotherapy and stereotaxic high precision imaging for controlled radiation therapy. Its range of activities has been considerably extended by incorporating the team of cellular and molecular radiation biology of Claire Rodriguez-Lafrasse implicated in Hadrontherapy and the project ETOILE, as well as in research on radiation resistance and sensitivity. This gives rise to a coherent entity using well-integrated and coordinated scientific approaches towards more effective antitumour therapies. Although input is wide ranging, outside visibility is not evident because it concerns rather specialized domains of research, and publications could be of higher impact. The Committee recognizes an outstanding teaching activity and University School activity. Overall, the Unit is attractive for the arrival of new researchers and students and it has a high potential with a new dynamic drive that deserves support.

- Strengths and opportunities:

The Unit with its 4 teams has proven its capacity of innovation and provided scientific and technological advances for improved therapeutic tumour targeting. The scientific projects follow original and well designed approaches ranging from better understanding of mechanisms underlying individual sensitivity up to individualisation of antitumour treatments. For this, analyses of genomic polymorphisms and proteomics of patients and tumours, mechanisms of cellular signaling will be carried out for a more efficient therapeutic tumour targeting, optimization of exposures for optimal tissue tolerance and development of complementary treatment modalities taking into account individual treatment responses. All this aims at more individualised therapeutic treatments. The development of Hadrontherapy offers new very promising possibilities in radiation therapy. The scientific basis and therapeutic modalities need further exploration. The Unit is already prepared and ready to go for this.

- Weaknesses and threats:

Because of the general tendency towards individualisation of therapeutic treatments, particular attention should be put on the development of new suitable biomarkers for clinical use. The scientific survey of this domain will be important in order to apply recent methodological advances made in laboratories of the research unit or through national and international collaborative studies for the patients benefits. The international visibility of the Unit needs to be further increased by a broader participation in international congresses and collaborative studies as well as by improving the impact of publications and setting up an appropriate Website and or a Newsletter.

- Recommendations for the unit director:

The unit has a wide range of research capacities in combining several chemo-and radiotherapeutic modalities. It is thus recommended to be more ambitious in constituting a centre of excellence and reference in Europe, and to build a European center of Peritoneal tumors within RENAPE together with other pathologists. For this, participation in european and international projects needs to be increased as well as the recruitment of post-doctoral fellows. It is recommended to define and focus on selected diseases, e.g. peritoneal surface malignancies. The work on new animal models and the mechanism of peritoneal cancers, with and without metastic capacity, and research on the biology of other rare diseases could be reinforced in order to find new clues. Team 2 should become more involved in this work. The research links with the forthcoming center of Hadron therapy have to be carefully worked out as part of the ETOILE project strongly involving team 4, and, if possible, team 3. Because of the departure of some researchers due to retirement, it is essential to take this opportunity to reinforce and enlarge the most pertinent research lines, such as new combined chemo-radiotherapeutic cancer treatments, individualised therapies, stem cells, cancer-stem cells and individual radiation sensitivity. Better focus and interactions between the teams would increase the visibility of the Unit. Collaborations between teams of the Unit could be improved by a newsletter published monthly for all four teams members and an annual meeting presenting finished and ongoing trials, including one day of intensive “brain storming“ on common projects.

- Data on work produced :

(see http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	27
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	25
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	25/27
A4: Number of HDR granted during the past 4 years	ND
A5: Number of PhD granted during the past 4 years A6: Any other relevant item in the field	10

3 • Detailed assessments:

- Assessment of work produced and scientific quality:

  – Relevance and originality of the research conducted, quality and impact of the results:

During the last years, the research unit has succeeded in federating 3 teams of clinical researchers involved in surgery of peritoneal carcinomatosis with pertinent animal models, peritonectomy, HIPEC and the original development of intraperitoneal chemo-hyperthermia treatments with CAVITHERM (Team1), in oral chemotherapy and targeted therapies with pharmaco-kinetic, population, in silico modeling and Phase I platform studies (Team 2) and in radiation therapy with physical agents (see development of 3D radiation therapy, Gating, IGRT, stereotactic RT, combined treatments, phase I, II and II studies, targeted tumor destruction and IGRT) (Team 3). It has also attracted and incorporated a team of fundamental researchers involved in cellular and molecular radiobiology and in the National ETOILE project on Hadrontherapy (Team 4) around a main theme of very high clinical relevance, i.e. the therapeutic targeting in oncology. The committee noted in particular the high originality and innovative nature of the research as evidenced by the invention of CAVITHERM for intraperitoneal chemo-hyperthermic treatments of tumors, the set up of a suitable animal model (rat) for peritoneal carcinomatosis, the achievement of labelisation by INCA as a National Center of rare peritoneal tumors, and structuring of the national network RENAPE (involving 20 centers) taking care of the national Tumour register and the international network as well as the recognition by INCA as a center of reference for trophoblastic tumors, the development and validation of pharmacokinetic models in chemotherapy associated with Phase 1 studies, the development and evaluation of new technologies for high precision radiotherapy as well as in molecular targeting of radioresistant tumors (such as radioblastoma). The results are outstanding and four-fold: patents on CAVITHERM, Hsp27 antisense sensibilisation, Bodytherm; 1st European HIPEC and gene therapy trial in surgical oncology; several national and international awards; a wide-range of international collaborations and partnerships.

  – Quantity and quality of publications, papers, theses and other work:

Knowing that most researchers of the unit are heavily involved in university teaching (Lyon1 Medical School), the scientific production is considered as outstanding with a total of 219 publications, mostly in journals specialized in clinical research, with impact factors up to 28.4, but varying from team to team. Twelve Ph.D. students graduated during 2006-2009, and 12 Ph.D. students are at present still ongoing.

  – Quality and solidity of contractual relations over time:

The high quality and solidity of the work is reflected in the high number of research contracts providing very substantial financial support (PHRC, INCA, ARC, EUROPE, ETOILE, CLARA) and many partnerships of each team with private companies (Team 1: EFS Electronics SA, Institut Mérieux, Mectronics, Genzyme; Team 2: Pfitzer, Angen, OOPI, Sanofi Aventis, Astrazeneca, Nezrvianorm; Team 3: Varant, GE, Brain Lab; Team 4: Oncogene, Pharma Mar, Erytech Pharma, NanoH). These industrial relationships are quite exceptional and show the capacity of this research unit to validate its results.

- Assessment of the influence, appeal and integration of the research unit in its environment:

  – Number and reputation of the prizes and distinctions awarded to the unit members, including invitations to international events:

The director of the Unit is dean of the Lyon-Sud Medical School, and president of the CCEM of the University of Lyon and of the regional cancer network CONCORDE. Several national and international awards (6) and a considerable number of invitations to congresses demonstrate the recognition of the research unit in and outside of France.

– Ability to recruit top-level researchers, post-doctoral and other students, especially foreigners:

The unit takes some profit of its high engagement in university teaching and of its many international collaborations to assure a regular flow of recruitment of master students, Ph. D. students and, to a lesser extend, post-doctoral fellows (mostly French). Also, the attraction of new researchers is high since there are apparently no problems to replace 7 researchers who retired or are going to retire.

– Ability to obtain external financing, to respond to or launch calls for tenders and to participate in the activities of competitiveness clusters:

The unit has obtained external financial support from industries (Pharma Mar, Erytech Pharma, Mérieux, Pfizer, Amgen, OPI Consulting, Medtronics, EFS) or national (French Research Ministry, Rhône-Alpes County Council, ARC, LNCC, INCA, Cancéropôle CLARA, RTRS Synergie Lyon Cancer, PHRC) or European support. The participation in competitive European and international calls needs, however, to be enhanced.

– Participation in international or national programs, existence of important collaborations with foreign laboratories:

One of the great strenghts of the research unit is its solid implantation in a wide range of national (Platform Gerland-Lyon Sud of CLARA, CTRS "Synergie Lyon Cancer, Centre Oscar Lambret in Lille, University of Bruxelles, Belgium, GANIL in Caen) and international network of collaborations (NCI-US, NCI-Canada, US Gyneco group, EORTC, ESTRO, University of Pennsylvania (US), Karolinska Institute, University of Upsala (Sweden), Peritoneal Surface Malignancy Network RENAPE (Weizman Institute, Israel), University of Liège (Belgium) GSI (Darmstadt, Germany), European project ENLIGHT).

– Valuation of research and socio-economic or cultural relations:

Several patents were deposited (CAVITHERM (Team1); Treatment of squamous cell carcinoma with Hsp27 antisense oligonucleotides and radiotherapy, ONCOGENEX, (Team 4); "Association of a TLR3 ligand and an apoptotic inducer in cancer treatment", Hospices Civils de Lyon, University Lyon 1, proof of concept (CLARA) (Team 4), and teams 1, 2 and 4 have a number of contracts with 8 industrial partners (Pharma Mar, Erytech Pharma, Mérieux, Pfizer, Amgen, OPI Consulting, Medtronics, EFS Electronics). This clearly indicates that the research unit puts considerable efforts on industrial validation of research.

Furthermore, the team leaders regularly participate in public manifestations in the framework of the regional network of cancerology, the "open university" in Lyon and after request of patient associations and the "Ligue contre le Cancer" in order to present biological and clinical advances in cancer research. Also, they help dissemination of information on cancer research in high schools.

- Assessment of the strategy, governance and life of the unit:

  - Relevance of the unit's organization, quality of its governance and internal and external communication:

Since its creation the unit has been well organized and follows a well-defined scientific strategy. Decisions are taken by the director of the unit together with the heads of the 4 teams. General laboratory meetings of the unit are organized twice a year to stimulate scientific interactions between the different teams and discuss general organization and practical, scientific or financial issues of the unit. Interview of the committee with permanent researchers, Ph.D. students and postdoctoral fellows and administrative and technical staff revealed that all were satisfied with the overall management. Hygiene, safety and security matters are dealt with by the ACMO who is responsible for ensuring safety teaching and controls in the unit. Each new member joining teams 2 and 4 (including students as well as senior scientists) undergoes a specific safety training. Concerning ethical issues, EA 3738 members have signed and accepted the Lyon 1 University ethic chart as well as the GIP. Team 2 members undergo an additional training for conducting clinical phase 1 trials.

In addition, the unit takes part in the organisation of the monthly scientific program of the Lyon Sud Medical Research Council in order to facilitate exchanges between different research units on the site.

  - Relevance of initiatives aimed at scientific coordination and the emergence and taking of risks:

The inherent dynamism of the research unit to participate in new research initiatives, collaborations and projects is in line with the strong promotion of new therapeutic targeting modalities in oncology. The research unit easily agrees to take the leadership, to coordinate clinical trials and new projects and also to organise scientific meetings in this domain. Open mindedness in research work is the true and vivid driving force of the unit. However, there is a possible risk of dispersion.

  - Involvement of the unit’s members in teaching activities and in organising research in the region:

Most unit’s members are highly involved in university teaching, licence (L) and master M1, M2 courses in (L) human anatomy, biochemistry, Molecular Biology, human sciences, physiology and in (M1) digestive pathology, medical oncology, radiation therapy, pharmacology, (M2) medical physics, cellular biology, mathematics and life engineering. In addition, they are active in promoting excellence in regional projects such as RTRS “Synergie Lyon Cancer”, in coordinating the RENAPE network and national centers of trophoblastic tumour registers.

- Project assessment:

  - Existence, relevance and feasibility of a medium- or long-term scientific project:

The research project for the next 4 years is well-defined and well-embedded in current regional and national concepts of cancer research. Research efforts concerning the effective targeting and treatment of cancer and new therapeutic developments are absolutely necessary and a leading factor for the promotion of successful cancer research in the region of Lyon-Rhone-Alpes. The roles of the research teams are highly complementary. Teams 1 and 2 will concentrate on obtaining labelisation for new cancer treatment approaches and for further development of national and international clinical research networks of excellence. They take advantage of their skills in conducting Phase I clinical trials for the treatment of peritoneal, trophoblastique and other rare tumours, together with biopharmacological modelling. The project of model application in the framework of the ETOILE-hadrontherapy project is part of a highly multidisciplinary coordinated effort involving regional and national institutions. Indeed, recent progress in the evaluation and amplification of sterotaxic radiotherapy and therapeutic targeting in nuclear medicine by team 3, the promising data in treatment of radioresistant tumours (glioblastoma), and advances in radiation therapy with carbone ions versus photons by team 4 will be of decisive importance for this project. Due to the future location of the Hadrontherapy facility, some relocation of the teams or sub-groups will be useful in a few years for practical regrouping and possible reinforcement of available forces. In this view, the unit has clearly a seeeding responsabiliy.

– Existence and relevance of a resource allocation policy:

Due to its large involvement in regional, national and international research networks and numerous partnerships with industry the unit EA3738 has over the years built up a sound allocation policy. The follow up and establishment of existing and new contracts will ensure the budget in the four coming years. The unit could increase its engagement in forthcoming European and international research projects in order to increase scientific exchanges and input.

– Originality and risk-taking:

The research program of the unit covers original and important niches in cancer research, such as improvement of the treatment modalities or some specific and rare cancer types and the launching of the ETOILE project and the Hadron therapy. It occupies a crucial and well integrated position in developping and maintaining an effective regional network of cancer research. The future installation of Hadrontherapy in Lyon is likely to require reorganisation and possibly autonomisation of a subgroup or the whole team 4 in order to join the center ETOILE in 2014, in agreement with involve in accord with the regional direction of INSERM, the Hospices Civils de Lyon, Lyon 1 University and the region Lyon-Rhone Alpes. Independently of this, the unit partnerships with local institutions (Hospices Civils de Lyon, Universities of Saint-Etienne and Grenoble, and the Ecole Normale Supérieure de Lyon) as well as national and international networks (network RENAPE, network for trophoblastic tumours, EORTC, Weizman Institute, GSI Darmstadt) are already well acquainted and ready to extend into the near and far future.

4 • Team-by-team

Team E1: Chirurgical targeting and peritoneal carcinomatosis

Team leader: M. Olivier GLEHEN

- Team staff or staff allocated to the project (according to the dossier submitted to AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	9	9
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	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 other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	3
N7: Number of staff members with a HDR or a similar grade	9	9

- Assessment of work produced and scientific quality:

  - Relevance and originality of the research conducted, quality and impact of the results:

The major research theme (peritoneal surface malignancies) is a relevant topic in clinical research. Thousands of patients suffering of different tumor entities may develop carcinomatosis – in most countries treated by systemic chemotherapy alone with poor results. The research conducted is original, and this team was in fact the first group in Europe to perform multimodality treatment of peritoneal surface malignancies, having a major major impact on the management of peritoneal carcinomatosis and its implementation (e.g. French guidelines). Since a prospective evaluation of the results and tolerance of Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) is ongoing within a phase III study, these results are likely to be of high quality and represent an important breakthrough in the clinical management of patients. A world congress with more then 400 participants was organized in Lyon as a recognition of the special role this team in the field. The team was chosen as center of reference by a national evaluation committee.

  - Quantity and quality of publications, papers, theses and other work:

A total of 64 original papers in peer-reviewed journal have been published, including 30 papers with a member of the team as first or last author. Among these, 12 papers are devoted to the main research project of the team. Others originate from collaborative reasearch or deal with other fields. About 13 publications are in journals with IFs between 2 and 17, but most papers are published in journals with lower impact factor. However, continuous progression has been noted, and it should be considered that surgical journals have impact factors around 4-5 going up to 8 (Ann Surg). Of particular clinical relevance was the publications of French data in the monography of AFC as a result of excellent interaction with the Paris group and other centers, and the publication in the multicentic study in J Clin Oncology 2009.

The 2 PIs (FN Gilly and O. Glehen) qualify for a high number (51) of invitations in national and international institutes and meetings. They have organized the 6th International Workshop on Peritoneal Surface Malignancies in Lyon 2008. Three PhD thesis have been defended and junior surgeons have been incorporated into the team to prepare PhD.

  - Quality and solidity of contractual relations over time:

The team has developed a solid contractual relation with the industry (EFS Electronics) resulting in the Cavitherm device for the hyperthermic intraperitoneal chemotherapy – the second generation (Cavitherm II) is in preparation.

Main partnerships are with French centers within RENAPE and with foreign countries within the PSOGI (Peritoneal Surface Oncology Group International).

- Assessment of the influence, appeal and integration of the team or the project in its environment:

Team 1 research activities had a major impact on the treatment of peritoneal carcinomatosis, a until shortly considered incurable disease, now cytoreductive surgery and HIPEC represent gold standard of treatment in France. This opens great opportunity of research. The groups cooperating with Team1 are well known in this particular field but also in the clinical research related to surgical oncology (e.g. Washington Cancer Center). The PI is involved in organisation of the European Trial project on oncogastric cancers that will be published in Brit J Med. Collaborations are also ongoing with local teams (team 4 on HSP27 and team 3 on complete imaging workout for peritoneal carcinomatosis).

  - Number and reputation of the prizes and distinctions awarded to the members of the team or to the participants in the project, including invitations to international events:

The PIs were distinguished by several prizes and distinctions, including 2 national awards and a local award, Victoire de la Science. Members of the team have been invited to many international events, in France and worldwide.

– Ability to recruit top-level researchers, post-doctoral and other students, especially foreigners:

The team was able to recruit good researchers, post-doctoral and other students, as well as foreigners. The team has regular program exchange with junior surgeons from other teams including a team in Washington, which is expert in the field.

– Ability to obtain external financing, to respond to or launch calls for tenders and to participate in the activities of competitiveness clusters:

The team was able to obtain external financing for a total of 490000 Euros over the last four years, which shows an excellent capacity to raise funds.

– Participation in international or national programmes, existence of important collaborations with foreign teams:

The team participated in international and national programmes. The leadership of RENAPE, a well functioning national network, is relevant for stable cooperations with 20 centers. Foreign partners from the PSOGI (Peritoneal Surface Oncology Group International), e.g. Washington Cancer Center, are continously working with Team 1 and partners together. The one year spend by the team leader in Washington enables easy and active communication – important for planning new projects. Collaboration with a team from Rome on gastric cancer is ongoing. The team is also involves in the labelisation by INCA for the Guidelines of good surgical practice in peritoneal carcinomatosis.

– Valuation of research and socio-economic or cultural relations:

The partnership with EFS Electronics was finalized in the production of CAVITERM, a special HIPEC designed device associated to the "Bodytherm" software.

The formation of specialists for PSM from teams in France and abroad has concrete results as the learning curve can be shortened substantially. Due the reduced morbidity, many costs can be saved for thousands of patients. HIPEC has now very good device for cancer treatments that is not yet standard.

- Assessment of the strategy, governance and life of the team or project:

The team has a high potential and is very reactive. Due to the presented aspects, the future strategy of development is excellent. The team leader has managed to strengthen this team in the time of Pr. Gilly absence due to administrative reasons. The team is well organized with clear responsibilities, having a positive dynamic.

– Relevance of its organisation, quality of its governance and internal and external communication:

The team is well organized. It has interactions with several regional groups outside of the unit especially in Grenoble, St. Etienne and in whole France such as Paris, Nantes. Research students are well trained and regularly supervised by their PhD director. They are encouraged to present their results in national and international meetings. They participate occasionally to external seminars.

– Relevance of initiatives aimed at scientific coordination and the emergence and taking of risks:

The initiatives aimed at scientific coordination are relevant in particular within the RENAPE, but also international, e.g. phase III trial conducted by an Italian collaborator on gastric cancer and HIPEC. No major risks are taken.

- Involvement of the members in teaching activities and in organising research in the region:

Many team members have high commitment in teaching activities and are involved in the organisation of the research at local level.The approach to teach surgeons and get them into research work inside a surgical department is quite outstanding.

- Project assessment:
  - Existence, relevance and feasibility of a medium- or long-term scientific project:

The team shows positive dynamics with a high number of young motivated surgeons. The long term scientific project is related to peritoneal carcinomatosis. This subject is of high relevance, the number of publications dealing with this subject is increasing yearly. Many aspects of the treatment can be improved in the future. RENAPE is already a success and its development is an important issue for Europe, as other countries might join this registry.

Pharmacokinetic issues related to human subjects are essential for defining optimal dosage of i.p. chemotherapy, considering that surgery is a very individual treatment and its extent is highly variable. A related project - the i.p. antibody-treatment- represents a new field now opened by studies performed with Catumaxomab worldwide.

More details should be provided about the project on selection based on radiologic imaging by fusing images and performance of 3D reconstruction. This is a very tempting project which might drastically reduce the rate of surgical exploration without effective treatment.

Finding prognostic parameters based on proteomics and genomics might be an important tool, however, it should be more than descriptive to avoid ending with huge amount of data without the ability to find clinical correlations and implications.

As only few Phase III trials have been performed for HIPEC and PSM, planning a phase III trial for ovarian cancer is a very important issue considering that most women do have a recurrence at peritoneal site.

Training of French and foreign clinicians for CRS and HIPEC is the best way to implement this method. Due to the complexity of preoperative selection, treatment itself and management of complications, the training in a center (like Lyon) is more important than for other « single-organ» malignancies.

The ongoing collaborations with other internal and external teams will undoubtly contribute to further improve the scientific and publication level of team 1.

The team follows an overall resource allocation policy which is sound and well-acquainted. There are no major risks taken.

- Conclusion:
  - Opinion:

Team 1 had an impressive activity over the last years, positive dynamics and challenging future projects for the next four years. This team has managed to interact with all teams of the unit and with others in France and worldwide, being now an established international « opinion leader » in the field of peritoneal surface malignancies. This is an original project and the number of groups dealing with this condition is increasing every year, therefore clinical and fundamental research in this field has a high potential. Current studies and high capacity of patients inclusion are expected to have major impact on clinical management and treatment of peritoneal carcinomatosis. Another positive point is the current evaluation of clinical practice by performing a multicenter phase III prospective study.

– Strengths and opportunities:

The main strength of Team 1 relies on clinical activity: the treatment of peritoneal surface malignancies. As mentioned, it is clearly „opinion leader" in this field worldwide. Many surgeons from different countries learn special skills at this University hospital. The team is thus well represented in the international competition. Moreover, the training of young surgeons to translational and clinical research gives a strong opportunity to encourage surgeons to lead or participate in research teams. All the aspects gives the team a unique opportunity to actively influence the main research stream.

The team is gaining on expertise in several other fields involved in the research of peritoneal surface malignancies, having not only surgeons but also engineers, pathologists and radiophysicians as team members.

– Weaknesses and threats:

Although many cooperations are listed, a concrete interaction is not yet evident for some of them. Common publications of Team 1 and 2 refer mostly to rectal cancer, not to peritoneal carcinomatosis. Only one publication (Hepatogastroenterolgy 2006) deals with chemohyperthermia, although many other projects were mentioned.

One of the projects was performed in Washington DC, members of Team 1 being only indirectly involved. This is rather a cooperation than a own project of Team 1.

A peritoneal carcinomatosis mouse model has been described, however, no further research projects or publications could be found. It would be interesting to use this mouse model for studying the origin of peritoneal carcinomatosis : hematogeneous, or direct due to i.p. tumor cells, or both. Possibly, some more modeling could improve the efficacy of synchronous treatments, surgery (resection of tumour mass) plus drugs and HIPEC.

– Recommendations:

The team leaders should increase collaborations with other pathology teams within the RENAPE network and work on the creation of a center of lymphomas. The interactions with other teams of the Unit could also be more evident, specially with team 2. It is recommended to concentrate on less but better designed projects, from descriptive to therapeutic studies. Many planed projects are interesting, e.g. bevacizumab i.p., gene alterations in patients with peritoneal metastases, but the final design of such studies has to be carefully determined.

Team E2: Modelisation of tumor biology

Team leader: M. Gilles FREYER

- Team staff or staff allocated to the project (according to the dossier submitted to AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	9	9

- Assessment of work produced and scientific quality:

  - Relevance and originality of the research conducted, quality and impact of the results:

Relevance and originality of the research essentially relies on the numerical modelisation of tumour biology and the optimization of anticancer effects. The integration and simultaneous analysis of experimental and clinical observations allows prediction of therapeutic treatments and guide further therapeutic progress. Team 2 used its excellent competences in mathematics and engeneering informatics as well as diverse collaborations (ENS, Lyon, INRIA, etc...) to modelize tumour growth including the cellular microenvironment and angiogenesis as well as the effects of chemotherapy using pharmacokinetic and pharmacodynamic models. This team interacts directly with the laboratory of cytotoxic agents dosage and the platform of phase I clinical trials, both located on the Lyon Sud hospital center. This allowed to optimise the posology of some agents and to increase tumour targeting. The main results concern a still ongoing study on mice with colic tumour transplants, in which modelling tumour proliferation and angiogenesis takes into account vascular density and hypoxia. The model is clearly more reliable than the classical gompertzien model. On this basis a second study has been launched for treatment of the same xenografted mice by an association of 5-fluorouracil, IRINOTECAN and the SUNITINIB antiangiogenic agent. This can be expected to give rise to new chemotherapeutic treatment modalities with optimized effectiveness according to biological rythms. The impact of these studies can be measured by the mutual engagement of collaborations with the Weizmann institute (Israel) and also in the framework of the ETOILE project for specific effectiveness of heavy ion radiation.

Furthermore, several models on pharmacodynamic-pharmacogenomic aspects have been developped, including the effects of INOLIMOMAB from plasmatic exposure to tumoral efficacy and clinical outcome. This gave rise (1) to a new monoclonal antibody to control the immune response in ABMT patients, leading to the creation of a new start –up and european registration of the drug, (2) to modelisation of the evolution of Hand Foot Syndrom in 603 patients treated daily with capecitabin for breast or colorectal cancer, (3) to prediction of patients survival in a phase 3 trial on the basis of a previously developed tumour growth model after 5-FU treatment, and (4) to models based on biomarker decrease such as PSA or dealing with spatiality such as efficacy of ciclosporin on GVH disease.

  - Quantity and quality of publications, papers, theses and other work:

The team has produced a total of 47 publications in peer-reviewed journals during the last 4 years, and 5 have been accepted recently. Among the publications, 26 have a member of the team as first or last author, generally in good journals such as Ann Oncol (IF 4.9). This makes for 12 researchers roughly 1 paper per person/year. 11 papers result from multicentric collaborative studies, including one in J Clin Oncol, and 4 papers are published in French journals.

The PI has been regularly invited to prestigious international meetings such as ASCO in 2006, 2007, 2009, and ESMO in 2006, 2007, 2008. Finally, 3 PhD theses have been defended during the last 4 years.

  - Quality and solidity of contractual relations over time:

Several national and international collaborations are noted, such as the INCA project on antiangiogenesis, the large ANR project with the Centre Léon Bérard, and the collaboration with Uppsala, Sweden, and Weizmann Institute, Israel). This team participates in the pharmacokinetic studies of the "RTRS" project "Synergie Lyon Cancer".

- Assessment of the influence, appeal and integration of the team or the project in its environment:

Team 2 is a very interactive group open to many collaborative projects.

  - Number and reputation of the prizes and distinctions awarded to the members of the team or to the participants in the project, including invitations to international events:

The PIs have got several prizes and distinctions and the head of the team is regularly invited to international meetings.

- Ability to recruit top-level researchers, post-doctoral and other students, especially foreigners: pas de recrutement of foreign et post doc, on the contrary some excellent students

Only one post doctoral student was recruited during the past 4 years. On the other hand, the team regularly attracts new Ph.D. students or M2 students.

- Ability to obtain external financing, to respond to or launch calls for tenders and to participate in the activities of competitiveness clusters:

Different resources have been obtained through the RTRS "Synergie Lyon Cancer", a CLARA financial support (collaboration with the Weizmann Institute), ARC, LNCC, and industry for a total of 759200 euros over the last 4 years, which shows an excellent capacity to raise its own funds.

- Participation in international or national programmes, existence of important collaborations with foreign teams: collaboration avec les etrangers

Many collaborations with different countries are in progress: collaborations in France with INCA project, ANR project with other teams in Lyon, and collaborations with Uppsala, Sweden, Weizmann Institute, Israel, Margaret hospital, Toronto).

- Valuation of research and socio-economic or cultural relations:

The capacity of the team to include patients into large phase I and II clinical studies has to be noted.

- Assessment of the strategy, governance and life of the team or project:
  - Relevance of its organisation, quality of its governance and internal and external communication:

The organization of the team is adequate and open to multiple interactions with other anticancer centers. Research students are well trained and regularly supervised by their PhD director within the team (weekly presentation). They are encouraged to present their results in national and international meetings. This team regularly receives invited researchers.

- Relevance of initiatives aimed at scientific coordination and the emergence and taking of risks:

Collaboration with a group in St Etienne is interesting, as this group develops biomarkers with predictive value.

- Involvement of the members in teaching activities and in organising research in the region:

A great majority of team members have teaching activities and are involved in the organisation of the research at local level.

- Project assessment:

  - Existence, relevance and feasibility of a medium- or long-term scientific project:

Team claims different projects including optimization of the association between either angiogenesis inhibitor or BCRP inhibitors (Gefitinib, Imatinib and MBL187, a new molecule issued from Grenoble and Lyon laboratories) with cytotoxic drug (irinotecan), helped by mathematical modelling.

Another point concerns the Modelisation of Iatrogenic Medication errors In Cancerology (MIAMIC) to develop a multivariate risk-prediction model and reduce medication errors in cancerology.

A third one concerns the modeling of efficacy of Patient Education Program (PEP). It aims at reinforcing adherence to oral cancer treatments, introducing adherence as a variable in efficacy model and evaluating PEP effect in treatment efficacy model. This project will have its own financial support (InCA, Roche, LNCC) and will be coordonated through the "centre régional de ressources pour la prévention, l'information et l'éducation sur les cancers" (cancéropôle Lyon, Auvergne, Rhône Alpes).

Feasibility does not seem problematic as all human forces are complementary to ensure the successful realization of these projects (clinicians, pharmacokinetic pharmacologists, biostatisticians, mathematicians). The approach to include biological and clinical data in modeling is excellent and very promising. However, further improvement and optimization of the biological models should be taken into account.

  - Existence and relevance of a resource allocation policy:

Team 2 is able to find its own financial supports.

  - Originality and risk-taking:

Modelisation of the effect of etoposid in lymphoma is a very original project. However, althoug the team has excellent tools, most projects do not apply to very original topics. Subjects chosen are a little too dispersed. A main research line could be focused on modelisation of the trial on VGF ZEROTEC with 60 patients.

- Conclusion:

  - Opinion:

The team has a great capacity to perform modeling studies on patients as well as on mice, and to include in the models predictive biomarker studies. The modeling approaches on clinical subjects are very valuable. The capacity to include studies from bench (mice) to bedside (patients) is quite unique in the unit. The capacity to include patients of Phase I studies as well as animal models is clearly outstanding and provides opportunities of interaction with other research groups, in particular with team 4 for molecular mechanisms. However, some focalisation on stream line and more original subjects are required to avoid dispersion.

  - Strengths and opportunities:

The main strength of Team 2 is its excellent capacity for modeling and its capacity to recruit patients for clinical studies. Interaction with all other teams of the Unit, using new modeling devices should be strengthened and further explored.

  - Weaknesses and threats:

There is a danger of dispersion with multiple modeling opportunities, and the team should focus on more recent, original and competitive problems. The choice of some topics and originality of some projects are questionable; projects on the risk of therapeutic errors, and on ABC transporters should be given low priority, as they seem to increase thematic diversity without added value to the project. Further adaptation of the animal models to actual needs including clinical and fundamental research work is a permanent threat for this team to be kept in mind.

– Recommendations:

Since the team has validated its modeling methodology on classical tumour markers such as PSA, the team should select additional topics that are more competitive internationally. This could help reaching journals with higher impact to publish the work. For example, the team may apply this method to new plasma biomarkers such as ligands and soluble forms of tyrosine kinase receptors (VEGF, sVEGFR, cKIT, etc...). The team could investigate their predictive value in the clinical study conducted with VEGF-interacting antiangiogenic compounds. Interactions with team 1 should be reinforced.

Team E3: Physical agents: use for diagnostic and therapeutic targeting,

Team leader: Mrs Françoise MORNEX

- Team staff or staff allocated to the project (according to the dossier submitted to AERES):

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	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)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	3
N7: Number of staff members with a HDR or a similar grade	5	5

- Assessment of work produced and scientific quality:

The project on glioblastoma treatment with hadrontherapy is original and highly promising, especially since it includes treatment of cancer stem cells. It is a leading team for excellence and good practice in radiation therapy. Extremely important is the reactivity of the team towards the improvement of new industrial developments of new devices for radiotherapy. Without any doubt the work on the procedures used with the new radiotherapy machines is essential and very awarding.The team takes thus into account future sequellae and quality of life of the patients. The team studies short and long term effects. On these research lines there are strong international collaborations. It is the leading team for Hadron therapy in the framework of the project ETOILE and is involved in international collaborations on this. The outcome of the work concerns the better and more efficient handling of new radiation devices. Of course, it has to be kept in mind that the team is mainly involved in clinical research and relatively little in fundamental research. Thus, the main results are not scientific advances but optimized conditions of clinical and therapeutic outcomes.

– Quantity and quality of publications, papers, theses and other work:

100 publications are listed but their scientific value is difficult to assess since they mostly concern advances in clinical research. The team should consider publications on particular and more specific topics and on the topics where they are leaders. This will increase their impact factor.

2 University PhD thesis were defended in the last 4 years, 3 are in progress. These 5 theses are mainly related to clinical topics and their scientific value is difficult to evaluate.

- Quality and solidity of contractual relations over time:

Several national and international collaborations (hospices civils de Lyon, Centre anticancéreux Montpellier, Oscar Lambret Center of Lille, Bruxelles university).

- Assessment of the influence, appeal and integration of the team or the project in its environment:

  - Number and reputation of the prizes and distinctions awarded to the members of the team or to the participants in the project, including invitations to international events:

There is no information on this point.

  - Ability to recruit top-level researchers, post-doctoral and other students, especially foreigners:

There is a certain ability to attract research students, however, this activity is not yet very much developed.

  - Ability to obtain external financing, to respond to or launch calls for tenders and to participate in the activities of competitiveness clusters:

This team is very active in terms of external financing. An important financial support was obtained from INCA and different PHRC, and ARC and LNCC contracts for a total of 750000 euros were obtained during the last 4 years.

  - Participation in international or national programmes, existence of important collaborations with foreign teams:

This team is active at the national level, but no international program seems to be developed.

- Assessment of the strategy, governance and life of the team or project:

  - Relevance of its organisation, quality of its governance and internal and external communication:

The organization of the team is adequate. The team interacts with other French centers. One might regret the lack of international collaboration. Research students are well trained and regularly supervised by their PhD director within the team (weekly presentation). They are encouraged to present their results in national and international meetings. This team sometimes receives invited researchers. A good interaction with team 4 (with a common M2 student) is noted.

  - Relevance of initiatives aimed at scientific coordination and the emergence and taking of risks:

No major risks are taken.

  - Involvement of the members in teaching activities and in organising research in the region:

Many team members are strongly involved in teaching activities and in the organisation of the research at local level.

- Project assessment:
  - Existence, relevance and feasibility of a medium- or long-term scientific project:

The long term scientific project is developed along 4 axis:

- The first one is the conformal therapy for hepatocellular carcinoma and the organ mobility and the dosimetric impact. An extension to lung tumours will be developed. Clinical studies in urologic and kidney cancerology will be made in collaboration with different hospitals (HCL, Lille, Nancy). Association between Stimuvax® or targeted therapies and radiotherapy will complete this work.

- The second one relates to digestive cancerology and the therapeutic targeting. A phase III clinical trial on cryotherapy and radio-frequency is in progress and will be analyzed from 2011.

- The third one will be devoted to the development of a therapeutic targeting in nuclear medicine, using either classical PET tracer (PET FDG in lymphomas, pseudo myxomas, thoracic cancers) or others such as FLT/F-DOPA, F-choline. Conventional scintigraphy and vectorization therapy (Zevalin, MIBG I131 and topotecan), translational research with ETOILE (hadrontherapy) and the use of Tc99-annexin V will also be studied.

- The last deals with the optimization of surgery practises on endocrinal cancers. For this, the best therapeutic strategy will be defined by creating a national network with a multicentric study.

All of these subjects are of high relevance and this work could strongly participate to the improvement of many aspects of the treatment of cancer. There is a lot of potential for this team for the next years, with a positive dynamics in the team including a high number of young motivated surgeons (5 PhD, 2 Masters 2), well supervised by seniors researcher and surgeons.

The project on the synergy between Hadrontherapy and chemotherapy is interesting and needs to be further explored.

  - Existence and relevance of a resource allocation policy:

This team has clearly defined industrial collaborations and is able to collect different financial supports.

  - Originality and risk-taking:

A large part of the project is dedicated to the future Hadrontherapy. Obviously, it is highly dependent on the launching of the project ETOILE.

- Conclusion:
  - Opinion:

The glioma project is very original with hadrontherapy, especially when combined with the promising stem cell treatment (collaboration with team 4). The team is obviously a leader for excellence and good practice in radiation therapy. Indeed, work on the new therapy radiation devices and practical guidelines is of great importance, as industrial guidelines are clearly not sufficient. The importance of this activity is seen by strong international collaborations. The team shows excellent dynamic concerning short and long term effects of radiation therapy including the quality of life of treated patients. It is noticeable that the team is strongly involved in university teaching.

  - Strengths and opportunities:

This dynamic team has strong involvement in clinical research and high potential, and it is open to new approaches. The radiotherapy devices are rapidly changing. There development is essential for efficient therapy, however, the new machines have to be well controlled and mastered. This is one of the aims and main strengths of the team.

– Weaknesses and threats:

The project highly depends on the launching of the ETOILE project.

– Recommendations:

The interactions with the other teams could be more developed.

The question arises of whether and how the scientific side of the work can be further developed.

The (scientific) publication level should be improved. Publications are encouraged on topics where the team members are leaders. This is likely to improve the team's visibility.

Team E4: Cellular and Molecular Radiobiology

Team leader: C. RODRIGUEZ-LAFRASSE

- Team staff or staff allocated to the project (according to the dossier submitted to AERES):

	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)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade	4	5

- Assessment of work produced and scientific quality:

The team has been built recently with fundamental researchers in cellular and molecular radiobiology, as the team leader (from an INSERM Unit) joined the Unit in 2007. The team has been constituted with 3 Senior scientists with HDRs, 2 postdocs, 4 PhD students, and 3 technicians. Notably the research team has been reinforced by the arrival of a group from INSERM, Grenoble, which is an important complement. The team has been already very active, and develops new exciting research projects using innovating and original approaches. The main axes of research concern tumour responses to photon and carbon irradiation, i.e. molecular mechanisms underlying resistance, and development of radiosensitizing therapies. In the last years, the team has achieved significant scientific advances on mechanisms implicated in radiation-induced tumour responses and radioresistance, including the role of a ceramide-dependent but p53-independent apoptotic pathway, the implication of energy metabolism and glutathion-antioxidant cellular defenses, and the important role of the Hsp27 anti-apoptotic and tumorigenic protein. The team has also developed original and promising approaches to characterize the role of cancer stem cells in radioresistance of glioblastoma to exposures of carbon ions, and to develop radiosensitization (deposition of a patent). Related themes are experimental assessment of a simulation model for treatments with carbon Hadrontherapy. and prediction of tumor responses using modelisation and molecular biomarkers. Studies of the radiosensitivity of normal tissues include prediction of acute reactions to therapeutic doses and the risk of radiation-induced cancers at diagnostic doses.

– Quantity and quality of publications, papers, theses and other work:

The team has published 18 papers centered on the main research line in good or very good peer-reviewed journals during the last 4 years. More than half of them are signed in last position by the PI. This scientific production is excellent with an increasing index of citations. However, many papers are in very good speciality journals such as Int J Radiat Oncol Biol Phys, and it should be possible to publish in more general journals. Strategy of publication should more ambitious, in line with the excellent results obtained.

One Ph.D. thesis has been defended since 2007. The team has organised the International Congress of Radiobiology (CIRFA) in September 2009.

– Quality and solidity of contractual relations over time:

The team has benefitted permanently from solid national, regional and international financial support due to contracts with GSI, Darmstadt, Germany (EURONS 2005-2007), Project Emergence-Cible 2006-2007 (collaboration), Groupement de Coopération Sanitaire ETOILE 2008, Ligue Contre le Cancer, Comité de l'Ain, Programme Rhônealpin de Recherches en Hadronthérapie (PRRH) ETOILE) and many industrial (Pharma Mar, Spain; Eyrytech Pharma, France; EDF) and national partners (INCa 2009 et 2008-2011, GRRAAL; Cancéropôle CLARA 2009 et 2010, projet LANTHARAD 2010; ARC 2010-2011 and la Ligue contre le Cancer, comité de la Drôme 2010; HEMI-Break NR, PRAXITELE CNES).

- Assessment of the influence, appeal and integration of the team or the project in its environment:

Quite unique is the positioning of the team in France in fundamental research work on Hadrontherapy and tumor treatments, mechanisms of radioresistance, and individual sensitivity of normal tissues to radiation. Furthermore, there are multiple interactions and established collaborations with other national (INSERM, Dijon; GANIL, France; EA Clermont-Ferrand, CEA Grenoble) and international research centers (GSI , Darmstadt and Heidelberg in Germany, Karolinska Institute, Stockholm, Sweden, with NIRS, CHIBA, Japan and Toronto, Canada).

– Number and reputation of the prizes and distinctions awarded to the members of the team or to the participants in the project, including invitations to international events:

Members of the team were distinguished by several prizes and distinctions Académie des Sciences (Prix Peyré 2009), Fondation Rhône Alpes Futur prix: Fontaine R.A. 2008),

– Ability to recruit top-level researchers, post-doctoral and other students, especially foreigners:

The team has been able to recruit good researchers, post-doctoral and students, as well as foreigners, with regular recruitment of master and Ph.D. students, and a post-doctoral fellow.

– Ability to obtain external financing, to respond to or launch calls for tenders and to participate in the activities of competitiveness clusters:

The team is very much engaged in several national and international projects, and it is very reactive in responding to opportunities and to launch calls (see above). The team was able to obtain external financing for a total of 390000 Euros over the last four years, which shows an excellent capacity to raise its own funds.

– Participation in international or national programmes, existence of important collaborations with foreign teams:

As mentioned above, the team takes an active part in several national and international research programmes, including ENLIGHT (EUROPEAN NETWORK for LIGHT ION HADRON THERAPY) and ULICE (Union for Light Ion Centres in Europe) as well as in contracts with GSI, Darmstadt, Germany, Groupement de Coopération Sanitaire ETOILE, Programme Rhônealpin de Recherches en Hadronthérapie (PRRH) ETOILE, NIRS, Chiba Japan), Pharma Mar, Spain; Eyrytech Pharma, France; EDF, France;) and with INCa-INSERM, GRRAAL; Cancéropôle CLARA, projet LANTHARAD; HEMI-Break NR, PRAXITELE CNES.

– Valuation of research and socio-economic or cultural relations:

The research was validated with two patents, PCT US 60/893086 in Canada, one in France.

- Assessment of the strategy, governance and life of the team or project:

– Relevance of its organisation, quality of its governance and internal and external communication:

The team is well organized with regular group meetings, organisation of internal and external seminars and participation in meetings organised by the Unit. It is thus well integrated in the unit and communicates with the other teams (see numerous collaborations). The recent arrival of researchers from Grenoble (a total of 9 people) doubling the number of active researchers gives rise to a problem of lab space that has to be solved in order to stabilize the team at least for the four forthcoming years.

The project ETOILE may ask for new arrangements for researchers directly working with ETOILE (this may involve a future move to forthcoming ETOILE laboratories) and those continuing active collaboration (which may stay with the present laboratory). Because of numerous collaborations, the national and international communication is excellent. It is to be noted that the team head has been responsible for the organisation of the 9eme COLLOQUE FRANCOPHONE de RADIOBIOLOGIE in Annecy, France in September 2009. Furthermore, the research on Hadron therapy and Heavy ion research strengthens important links to other research labs in the field of therapeutic applications (GSI, Darmstadt, Karolinska Institute, Sweden, NIR, Chiba, Japan) as well as fundamental (CEA, Grenoble, GANIL, Caen, INSERM, Clermont Ferrand, INSERM, Dijon) and space research (CNES, Paris).

– Relevance of initiatives aimed at scientific coordination and the emergence and taking of risks:

The project responds to strong societal needs to improve antitumour treatments with radio- and Hadron-therapy a well as combined treatments, and to avoid treatment sequellae by assessing individual sensitivity. The molecular and mechanistic approaches chosen are highly relevant to these issues. The team is taking a positive option in the forthcoming construction of the Hadrontherapy platform ETOILE in Lyon. The research project can be expected to have solid impact not only on the comprehension of molecular mechanisms of radioresistance, but also on the patients' follow-up with new molecular biomarkers) and on the mechanisms of individual sensitivities and normal tissue response to low-dose radiation. In this context, the use of animal models will be of great importance as well as modelling of radiation and therapy responses in collaboration with team 2.

– Involvement of the members in teaching activities and in organising research in the region:

Many team members have teaching activities and are involved in the organisation of the research at local level. The head of the team is responsible for the University Diploma in Radiobiology and Radioprotection (UCBL) and the Radiobiology module of the Master 2 in Medical Physics University Lyon 1. The research-lecturers participate in the 1st and 2nd cycles of medical studies, masters 1 and 2. The master and Ph.D. students in the laboratory belong to 6 different master courses (Cancerology, Genetic and pathology, Biochemistry, Physiology, Complex Systems, Pharmacology and therapeutic innovation) showing the wide range of disciplines covered by this fundamental research laboratory.

- Project assessment:
  - Existence, relevance and feasibility of a medium- or long-term scientific project:

The research project is wide ranging, interdisciplinary and integrative. The three subprojects (molecular mechanisms of resistance, radiosensitizing antitumour therapies and tissue and tumour response prediction) are highly relevant for the actual progress of scientific knowledge and for new therapeutic treatment modalities. The project includes a variety of models and targets as well as different technical and methodological approaches. Given the originality of the technologies used (Hadron therapy, combined radio-chemotherapy) it should be possible to stay well in focus on the main research objectives. The different research lines concerning use of peptidic aptamers against the tumorigenic protein Hsp27, the impact of energy metabolism and antioxidant status, the responses of radioresistant and radiosensitive tumour and normal tissue cell lines, targeting of tissue stem cells and detection of molecular signatures, mixed exposure modalities (radio- plus chemotherapy) as well as the models used (HNSSC, glioblastoma, etc) are highly relevant in the interational context of radiation research. The research line on specific tissue and individual radiation sensitivity should have also an impact on current radiation protection issues (biological effectiveness of different radiation qualities and the effects of moderate and low radiation doses as well as diagnostic exposures). The project on individual sensitivity to low dose radiation as well as the detection of BRCA1/2 positive women during mammographie is of great interest and needs to be pursued. The collaboration with team 3 on the synergy between hardrontherapy with chemotherapy should be pursued as well.

  - Originality and risk-taking:

Projects on the involvement of telomers, the association between hadrontherapy and drugs, and analysis of individual radiation sensitivity in radiotherapy patients using biopsies of the skin and new biomarkers are very original. As such the proposed research lines have high potential with no major risk taken in exploring rather specific aspects of cell, tissue, tumour and individual sensitivity (a hot issue in radiation therapy follow up and radiation protection) after exposures to defined radiation modalities (photon and Hadrontherapy) and even mixed exposures. The research outcome will be relevant for scientific progress, clinical treatment modalities and maybe even for radioprotection on earth and in space.

- Conclusion:
  - Opinion:

Team 4 has gathered a decent number of qualified reseachers (5), master students (2), PhD students (4), post-doctoral fellows (2) and technical and administrative staff to take up the challenge of working in a coordinated and synergistic manner on a wide-ranging, original research project. Progress is expected in the mechanistic and molecular understanding of cell, tissue and tumour sensitivity in individual patients, development of radiosensitizing therapies and prediction of tumour responses. All research lines are supported by collaborative interactions on the national or international level and by a solid network of financing opportunities. The team is well situated in the word-wide competition for new anti-tumour modalities and benefits from the Unit's infrastructure and many inter-team collaborations within the Unit. Setting up original molecular and mechanistic approaches (biomarkers, individual profiling, tumour radio-and chemosensitization) plays an important and integrative role in the unit and substantially contributes to develop new treatment modalities. Moreover, it is important for further development of radiobiological sciences and new individually matched antitumour therapies. The work on targeted sensitization of tumours by Hadrontherapy is likely to be decisive for the future development of the ETOILE project, since beside selecting the most effective treatment it may also involve the follow-up of patients.

  - Strengths and opportunities:

One of the main strengths of the team is to combine molecular and biochemical approaches with toxicological and histopathogical approaches, using animal models and clinical research available in the unit. Interactions with the other teams, particularly with team 2 for the modeling process are sound and feasible.

Collaborative (national and international) efforts will allow to take profit of additional competences.

– Weaknesses and threats:

Because of the multiplicity of parameters in radiation biology, there is a slight danger of getting dispersed by initiating too many research lines at the same time. The important goal of setting up an effective Hadrontherapy in Lyon should be one of the federating research lines matching nicely with the improvement of radio- and chemotherapeutic treatment modalities and the emphass on tissue and individual sensitivity. In the long run, when the ETOILE project is fully built up, it may be useful to seed a new research unit directly attached to the ETOILE building with researchers already prepared for that in the present team and research unit.

– Recommendations:

1. Concerning the scientific production, care should be taken to increase the number of publications and their impact by publishing in more general journals.

2. The work on cancer stem cells radiosensitivity together with gene expression profiling, and the involvement of energy metabolism in radioresistance merits to be strengthened.

3. Participation to international congresses, participation in European or other international competitive calls, and possibly, the exchange of students and researchers should be favoured in order to increase visibility.

4. Effort should be put on prioritization of research objectives and focus on truly original scientific questions to avoid dispersion (see work on retinoic acid, or impact of radiotherapy on telomeres). The project ETOILE is one of these.

5. Considering the density of researchers, students and technical staff, there is a need for increased laboratory space to facilitate experimental work.

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

Team 1: Chirurgical targeting and peritoneal carcinomatosis

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

Team 2: Modelisation of tumor biology

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

Team 3: Physical agents: use for diagnostic and therapeutic targeting

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

Team 4: Cellular and Molecular Radiobiology

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

Université Claude Bernard Lyon 1

Le Président
Lionel Collet

Villeurbanne, le 16 Avril 2010

M. Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne

75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité de recherche :

«Ciblage thérapeutique en oncologie» rattachée à mon établissement.

Ce rapport n'appelle pas de commentaire particulier de la part de l'université.

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

Le Président de l'Université

Lionel Collet

Université Claude Bernard Lyon 1

We read with attention the AERES report on the unit « Therapeutic targeting in oncology – EA 3738 » and do thank the members of the expert committee for the constructive comments they made.
Of course, and according to the comments, we will move from a national network toward a European one (and it was also the INCA recommendation when starting the project); we also will reinforced the research on biology of peritoneal rare tumors, thanks to the strong connection we built with Pr. Jacques Samarut's team.
Regarding teams 3 and 4, the unit director will go on enlarging the relationships between these two teams, underlining the strong involvement of members in the ETOILE project.
At least, we did appreciate the recommendation for an annual one day intensive brain storming meeting on common projects within the whole unit.

Once again, all the unit members join me to thank the members of the committee.

Corrections :
Page 2 : the expert committee also met Pr.Lionel COLLET, Lyon University president.
Page 5 (in the "recommendations for the unit director") : the expert committee proposed to build a European center for lymphomas. As far as lymphomas are concerned, it is a very different disease with no junction with peritoneal tumors and very different ways of treatment. More than this, there is already on the same universitary location, a European Institute for lymphomas. Probably, the correction could be "to build a European center of Peritoneal tumors…" which is also the recommendation from INCA.
Page 20 : in the Table, N1 is only "3 in the past" and not "7" and N7 is only "4 in the past" and not "9".

Lyon, 15 April 2010

François Noël Gilly