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

Section des Unités de recherche

AERES report on the research unit

CRO2 - Centre de Recherches en Oncologie biologique et Onco-pharmacologie

From the

Université de la Méditerranée

Université de Provence

INSERM

January 2011

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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 : Centre de Recherches en Oncologie biologique et Onco-pharmacologie

Requested label: UMR_S INSERM

N° in the case of renewal: 911

Name of the director: M. Dominique LOMBARDO

Members of the review committee

Committee chairman

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Other committee members

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Ms. Marie-Josèphe LEROY-ZAMIA, INSERM

Report

1 • Introduction

- Date and execution of the visit

The visit took place on January 28, 2011 in Marseille. It began at 8:45 am with a general introduction by the director. Then, every team leader(s) presented the activities of his team. The committee met separately with the students, technicians and scientists, then convened for drafting the report. The visit ended at 5:30 pm.

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

The UMR 911 Inserm was created in January 2008 on the "Campus santé" of La Timone Hospital, Marseille. This unit resulted from the gathering of from 3 already existing CNRS/Inserm structures. This unit depends from 2 Universities, Université de la Mediterranée and Université de Provence. The laboratory rooms are distributed in 2 distinct buildings located in the same area of the campus. During this first period, the unit was composed of 5 teams.
Team 1: "cytosquelette microtubulaire et progression tumorale". This team was focused on the alterations of the dynamic of microtubule cytoskeleton and their repercussions on microtubules regulation in tumour proliferation and endothelial cells migration
Team 2: "Molécules d'adhérence et invasion tumorale". This team worked on cell to cell and cell/matrix interactions mediated by integrins in tumour progression and metastasis diffusion.
Team 3: "Médiateurs intercellulaires et progression tumorale". The project was based on an immunotherapy strategy targeted to an abnormal enzymatic glycoform (BDSL) expressed in pancreatic tumours. The thrombogenic role of circulating BDSL was also addressed.
Team 4: "angiogenèse, invasivité et microenvironnement tumoral". This team was focused on the study of the effects of adrenomedullin in tumour aggressiveness in glioblastomas, and on the effect of this molecule on tumour vasculature.
Team 5 was directed by Erwan LORRET, and was working on AIDS and HIV.

The new unit project results from a profound reorganization of the previous one.
Team 2 does not exist anymore as it was before. This new team 2 results from the splitting of the previous team 1. It is directed by two senior scientists, both belonging to the previous team 1. It also incorporates staff belonging to the previous team 2. The new team 2 develops a new project, with no overlaps with previous team 2. It has however relations with team 1 projects, concerning the biology of microtubules in cancer.
Team 5, which was out of the scope of the CRO2, does not participate to the new project. Teams 3 and 4 remain globally organized as they were in the previous project.

- Management team

The management team is composed of the director of the unit and of the Director and codirectors of the 4 teams. It also contains representatives of the different staff categories.

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	38	40
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	8	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	6
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	34	36
N5: Number 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)	17	
N7: Number of staff members with a HDR or a similar grade	28	29

2 • Overall appreciation on the research unit

- Summary

The global project is mainly focused on the study and treatment of different solid tumours (pancreas, gliomas, colon…) and the biological consequences of the development of these tumours (i.e. thrombosis). Tumour microenvironment is also considered, mainly by teams 2 (redox environment) and 4 (circulating cells, angiogenesis). Pharmacological aspects such as identification of new targets (i.e. identification of microtubule target agents, team 1) are developed. Transfer to industry is also developed through different projects. For example, antibodies directed against specific glycoforms of enzymes expressed in pancreatic tumours are being developed by team 3.

The project is strongly clinically oriented, with a high representation of clinicians (PU-PH and MCU-PH) in the 4 teams. The unit has an important transfer activity, pursued by these clinicians. This enables the laboratory to have access to useful patient's tissue collections.
The unit is also strongly implanted in the university, and includes many University teachers/researchers.

Finally the unit has developed different technical platforms (proteomic, biological resources, imaging, cell sorting), which function autonomously. These platforms have dedicated staff members and access to specific funding

- Strengths and opportunities

The unit relies on robust research projects which are developed since several years and which have generated results continuously associated to a constant and robust paper production. Interestingly, since the different initial structures have gathered to form one unit, the level of impact factor of published papers has significantly increased, showing a benefit effect of this new organization.

The unit includes pathologists having their clinical activity at La Timone Hospital, enabling the constitution of patient tissue collection (establishment of platforms for clinical transfer) and facilitating the development of clinical trials. Close relationships with the hospital also facilitate the recruitment of clinicians interested in research projects. The unit also actively participates to the "canceropole" and to the local CIC (Centre for Clinical investigation).
In parallel, many researchers have teaching responsibilities in 2 universities, favouring the attraction of students (master and PhD).

Apart from the different teams, the unit contains several technological/transfer platforms which are well organized and operational. These platforms rely on specific funding.

The unit also has the capacity to raise funds, from competitive structures (European projects, ANR programs), from local organizations or from the industry.

- Weaknesses and threats

The main weakness of the unit is the low number of researchers exclusively dedicated to research activities (Inserm, CNRS). Most of them have clinical and/or teaching responsibilities.

Most researchers, clinicians, post docs and PhD students have been recruited locally, at the Hospital or the University.

Even if researchers from the different teams have published common publications, communication between the different teams is not clearly shown (except for teams 1 and 2).

- Recommendations

The unit should increase national and international visibility to attract young and senior scientists fully dedicated to research activities

Scientific interactions between the teams should be enforced.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	40
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	6
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	7
A5: Number of PhD granted during the past 4 years	37

3 • Specific comments

- ## Appreciation on the results

The unit has produced results in different domains related to cancer. In general, these results are relevant and original, and most of them are published in journals of intermediate rank (4 to 6). Some papers however reach higher impact factors (J Clin Oncol: IF 17,15; J Clin Invest 16,6; J Exp Med: 15,2; Brain: 9,6….). The unit has also produced 6 patents.

Most team leaders are invited in international conferences. The unit also produces a number of theses and HDR which is the average (22 theses, 6 HDR during the period). Team leaders have also established strong partnership with different teams abroad (Europe, USA, Australia, Japan…).

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

The team leaders have been invited in conferences (more than 30 invitations during the period), they have organized several congresses. They have a good capacity of rising funds. The current budget includes funds from 20 grants, reaching a total of 440 K€. Several members are involved in international networks, such as FPP7 European networks. The unit has strong relations with private pharmaceutical companies.

- ## Appreciation on the management and life of the research unit

The management of the unit is well organized. Strategic decisions are jointly taken by all team leaders and associate team leaders, the platform managers, the representative of each staff category.

Staff from the unit appeared being satisfied from their conditions of work.

- ## Appreciation on the scientific strategy and the project

Most projects are the logical extension of previous work, and rely on the long lasting experience of the team leaders and senior scientists. These projects have proved their validity, and they regularly produce results and publications. In addition to these robust projects, cutting edge, but more risky project are also pursued.

Before 2008, the different members of the unit were distributed in different structures. Creation of Inserm U911 had resulted in a concentration of resources, and in a tentative to focus the projects and favour interactions. This has resulted in an increased quality of the scientific production, which underlines the positive effect of this reorganization. In the new projects, the restructuration effort is pursued forward. This increases the homogeneity of the structure, and probably, its attractivity in the future.

4 • Appreciation team by team and/or project by project projet

- TEAM 1: Communications microtubules-mitochondries: Implications en oncopharmacologie. Diane BRAGUER

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	12	5
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)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	9	3
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)	16	
N7: Number of staff members with a HDR or a similar grade	6	4

- Appreciation on the results

Team 1 main expertise concerns the study of cellular tumorigenicity from a pharmacological point of view with a particular interest for the biology of microtubules and mitochondria. For this purpose team 1 has developed **strong collaborations** with pharmaceuticals **companies developing new compounds** as well as tight interaction with **hospital** providing **human pathologic samples**.

Team 1 has published a large number of papers (55) during the last 4 years, with 14 papers in which the authors are at the first and/or last position. In the last 5 years, team 1 has published 10 papers with an IF > 5, **4 papers with an IF > 10** (like JCO). They also wrote an invited review in Nature Reviews Clinical Oncology. Team 1 has many **publications in collaboration** including co-publications with other CRO2 teams.

Team 1 has established **collaborations with private pharmaceuticals companies** and with the national and international **communities working on microtubules/mitochondria**. This ability is clearly visible through the participation of the team to several European programs. Team1 is composed of teachers and physicians reflecting the **beneficial interaction** of the team with the **university** and the **hospital** located at the same site. In that context, we can underline that 5 PhD theses have been defended in the previous 4-years.

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

During the last 4 years, the group leader and team members have participated to national and international meetings, with several invitations as **invited speakers.** Additionally team leader and members have organized **successful scientific national and international meetings** (St Raphael Inserm meeting on microtubules and cancer for example).

The ability to recruit high levels scientists, post-docs and students, and more particularly from abroad needs to be improved but it is true for all CRO2 teams and the Director of the CRO2 himself agreed.

The team has acquired a clear visibility, illustrated by various fruitful collaborations with national and international laboratories. In addition, the collaboration with the other CRO2 teams of the unit is good. team leader and other team members have got various and numerous external financial resources from ANR, INCa, Cancerôpole PACA, PHRC, ARC....showing the dynamic of their group and positive evaluation by national funders. Additionally and importantly one can note **the participation of team leader in both the 6th and 7th PCRD** which clearly reflect the recognition of team skills by the European scientific community and this consistently over the years, **testifying the strength of the team**.

- Appreciation on the scientific strategy and the project

The program originates at least in part by the study of MTA (microtubule target agents) which are a major class of anti cancerous molecules. MTA have been shown to directly act on microtubule dynamic though the microtubule + end binding protein (+TIP) EB1 promoting an inhibition of migration and of angiogenesis. But MTA also act as cytotoxic elements inducing apoptosis through BCL2 dependant mechanisms in mitochondria.
Part of the proposed program will analyze the **Bim molecule** which seems to be at the **interface of microtubule and mitochondria networks**. The genic regulation of Bim and it functional regulations (shuttling between MT and mitochondria) will be studied by biochemical and cell biology techniques in cancerous cell lines after or not application of MTA agents; Bim being evaluate as a potential predictive biomarker.
Another part of the proposal will focus on **EB1** which is removed from microtubules by MTA agents. EB1 contribution to apoptosis and/or cell migration will be evaluated in term of quantities of EB (down or up regulations), in terms of the nature of its C-terminal amino acid (tyrosine) and in terms of phosphorylation level.

In its translational approach the team will investigate some aspects of **metronomic chemotherapy**. Based on the observation that cancerous cells can develop a dependency for the therapeutic drug, they will investigate mechanistic aspects of the 4DE therapy (drug-driven-dependency-deprivation Effect). In the context where cancer is consider as a chronic disease they will apply protocols where cancerous cells will be exposed and withdrawn from drugs to obtain sensitive, resistant and dependent cells lines. Using these three types of cell lines they will analyze **in vitro and in vivo the sensitivity to the 4DE.**
Overall, all this team has accumulated experience in the field, has a good potential and is well known among the experts. The topic about the relations between microtubules and cancer is developed in a limited number of teams, and is thus original. It is expected with these solid bases that this **program** should **develop without major difficulties**

- Conclusion :
    - Summary

The main research topic of the team has been re-focused and will concern the study during tumour progression, of the crosstalk between microtubules (MT) and mitochondria including pharmacological investigations. This approach is **original** and should give interesting data but should also propose alternative targets and protocols useful in cancer therapies.

The thematic focus on MT/mitochondria relationship is a positive element.

    - Strengths and opportunities

Strong local interaction with university
Collaboration with hospital providing tumour samples and clinical outcomes
Collaboration with pharmaceuticals companies providing new active molecules useful to understand basic biological questions

    - Weaknesses and threats

Post doc and permanent researcher recruitment is suboptimal.

    - Recommendations

The team should stay focussed on the topic of oncopharmacology targeted against the cytoskeleton, which constitutes its real specificity

- TEAM 2: Micro-environnement redox, cytosquelette et progression tumorale. Hervé Kovacic, Vincent PEYROT

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		14
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		7
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade		7

Team 2 is a **new team** created by the split of one single initial team (team 1), which has been led by D. Braguer during 4 years and positively evaluated by the previous committee. This split is associated with the reassignment of permanent researchers, technicians and students.

- Appreciation on the results

The creation of this new team2 has emerged as the **logical continuation** of the previous organization of the unit. Reallocation of staff or financial resources does not seem to cause problems, situation that reflects the already established **scientific independence** of the team 2 with respect to team1.

In the past, the two team 2-group leaders and their co-workers have investigated the role of Nox1 on tumour cell and highlighted an integrin-dependent mechanism, which modulates tumour cell migration. They have shown that Nox1, through a redox-dependent effect, controls the switch between random *versus* directional tumour cell migration by inhibiting RhoA and increasing the availability of α2β1 Integrin at the surface of the cells. Moreover, they have established that the redox status of colon tumour cells underlines antagonisms of action of some chemotherapeutic drugs. For the **first time**, these data demonstrate the cross-talk between **Nox1**, oxidative stress and an **integrin-dependent** mechanism of tumour cell migration. Moreover, results of this team provide new clues for the role of redox potential on **antagonistic effects of some chemotherapeutic agents**, well known to increase endogenous reactive oxygen species (ROS) levels.

The domains of research of the new team 2 include quite competitive fields. Nevertheless, Team leaders have published a **high number of papers** during the last years in journals examined by external peer reviewers (altogether 30 publications, plus 16 in collaboration). More precisely, in last 4 years, when considering only publications as **last author**, one of the team leaders has published 4 papers (mean IF = 5, including Mol Cell Biol, Int J Cancer) and the other 4 papers (IF=3, including Biochemistry, J Med Chem). The scientific production of researchers from the same team, with team leaders as **penultimate authors** (6 papers, including J Biol Chem, FASEB J, Mol Biol Cell, Biochemistry)) is also **satisfying** and shows that permanent researchers in team 2 can develop their own independent research projects. Furthermore, this team has many publications in **collaboration**, demonstrating its ability to interact on its various themes. Thus, although these publications do not reach very high impact factors, the general track record of team 2 is **high in number** and exhibits a **positive global scientific input**.

One obvious observation concerning team 2 is the high number of associated teachers and, in lower proportion, physicians. This high rate of recruitment of professors reflects the **beneficial interaction** of the team with the university, located at the same site. Team 2, composed of a high number of MCU and PU, is highly involved in teaching in various different fields related to onco-biology. This function is of **high importance**, especially in the site of location of the CRO2. In that context, from both team1 and new team 2, **10 PhD theses** have been defended and **2 post-doc formed** in the previous 4-years mandate.

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

During the last 4 years, the 2 group leaders have participated to national and international meetings, with **4 invitations as invited speakers** listed in the final draft of previous mandate. Since this team is newly created, the **international visibility** of its leaders and researchers may be best measured in the next evaluation of the CRO2.

As indicated by the Director of the CRO2 himself, the number of students and post-docs is generally low in this structure, especially when considering the high proportion of teachers or researchers in each team. This observation is true for team2, especially for recruitments from abroad. However, since team2 is a newly created team, international recognition and associated recruitment will be more appropriately evaluated when the team2 will exist for some years.

The group leaders have obtained **various and numerous external financial resources** from ANR, INCa, Cancerôpole PACA, PHRC, PICS, ARC....showing the **dynamic of their group** and **positive evaluation of funders**. In that context, they participate to ongoing **LABEX** applications. However, although the group leaders obtained contracts as participants, further showing their recognized expertise on their fields of investigation, they have not been referred to as promoters (as PI) of any listed contract.

The new team 2 has established collaborations with 4 international teams and has been integrated into several national contracts. This underlines beneficial interaction with national and international teams and confirms the nascent international visibility of the team.
Ongoing applications from team2 have been filed in collaboration with two pharmaceutical companies.

- Appreciation on the scientific strategy and the project

Team2 research projects plan to define the role of the NADPH oxidase 1 (Nox1) and subsequent oxidative stress on tumour development and acquisition of resistance to treatment. Projects are mostly based on colon adenocarcinomas since Nox1 expression is detected in the healthy tissue and highly increased in the corresponding tumours. Based on previous activities of the team, two complementary themes will be developed: (1) the role of Nox1 in metastatic spread (2) the therapeutic and predictive potential of redox signalling in cancer. In theme 1, few axes will been considered including the role of Nox1 in integrin-switch, the transition between mesenchymal to amoeboid migration type and the impact of microtubules on Nox1 signalling. In theme 2, the antagonism between oxaliplatine and cetuximab will be investigated, and the potential regulation of this antagonism by Nox-1-derived reactive oxygen species. Since no correlation was observed between Nox1 expression and any clinical parameters (either from already published data by other teams or from the expression data available in CRO2), the potential link between Nox1 activity, the metastatic spread and the anticancer therapy efficiency will be further investigated. Many studies have already established the role of overproduction of ROS by Nox as a risk factor in cancer development. Indeed, H2O2 produced by Nox proteins promotes tumour angiogenesis and globally alter stromal properties such as myofibroblast or macrophage recruitment. It has been shown that Nox proteins also increase growth and survival of cancer cells. Results from Team2 also demonstrate that Nox1 overexpression and subsequent stress modulates tumour cell migration. The first theme is thus in agreement with the general observations made worldwide on the pro-tumorigenic functions of Nox1.

In that context, the second theme appears the most innovative and thus the most interesting one. Although being also a bit risky, this theme will bring innovative outcomes on ROS-mediated effects on chemo-sensitivity. Interestingly, these research programs will be developed in close collaboration with the hospital located nearby, with free-access to human samples from patients with a precise clinical follow up and potentially in collaboration with private companies. The committee thus recommends focusing to this second promising theme, by considering data as whole and performing multi-parametric studies.

Each group leader or each permanent researcher is involved in funding requests. Money is then distributed according to the initial demands and respective participation in the projects.

As discussed above, the second theme of research based on redox control of chemotherapy is of particular interest. The proportion of human (total ETP in team 2= 6,5 + 3,6, when considering both researchers and technicians) and financial resources devoted to this project are consistent with its realization.

- Conclusion:

  - Summary

Newly created team

Interesting projects on redox signalling and chemosensitivity

  - Strengths and opportunities

Strong local interaction with university and essential function of the 2 team leaders and permanent-associated researchers in teaching

Expertise in Nox1-dependent pathways and redox-signalling

High number of publications

Collaboration with hospital providing tumour samples and clinical outcomes

  - Weaknesses and threats

International visibility is low

  - Recommendations

To focus on the second axis of research projects and to develop ongoing applications with private companies

- TEAM 3: Progression tumorale et immunothérapie expérimentale. Dominique Lombardo et Jean-Paul BERNARD

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	11
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6	5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	5	10

- Appreciation on the results

The Team #3 develops an excellent and original research on pancreatic adenocarcinomas focusing on the oncofetal glycoforms of bile salt-dependent lipase (BSDL) and on the relationship between pancreas cancer, thrombosis state and metastases formation. This research is developed in a closed collaboration with the clinicians of the Timone hospital.

The team develops a strategy for the immunotherapy of pancreatic cancers that targets the pathological BSDL glycoforms recognized by the mAb 16D10. The laboratory has recently demonstrated that this antibody is able to induce pancreatic cancer cell death through the mitochondrial apoptosis pathways. The humanization of 16D10 mAb allows now to consider its utilization in targeted immunotherapy. In parallel, the team has recently shown that the BSDL J28 glyco-epitope can be presented to naive T-lymphocytes by the CMH II of DC. This epitope also induces a partial maturation of iDC and activate the response of naive CD4+ T-lymphocytes. The J28 glycopeptide is currently produced in the laboratory in the perspective of mouse anti-tumoral vaccination trials. That research field involves French and European academic collaborations as well as collaboration with a private company (Innate-Pharma) for the humanization of 16D10 mAb, with strong perspectives of clinical application at mid-term.

The study of the relationship between pancreatic tumours-derived microparticles and thrombus formation constitutes a highly original and promising field of research of the team. Previous works have shown that circulating BSDL can play a role in thrombus formation. The laboratory was able to show that BSDL is associated with the microparticles liberated in the blood flow by the pancreatic tumour cells and that microparticles target thrombosis sites by specific interactions between PSGL-1 and the P-selectin expressed by both vascular endothelium and platelets. The presence of BSDL in the microparticles could therefore explain the higher risk of thrombus formation for the patients.

The team has produced 30 scientific publications during the four last years with a continuous increase in the impact factor, including first class publications such as J. Clin. Invest., J. Exp. Med., Cancer Res., Blood, J. Immunol., J. Hepatol., Ann. Neurol., Am. J. Pathol. They have published 13 papers in which authors from the team are in first and/or last positions. This includes most of the first class publications. They have also published 8 scientific papers in collaboration, including papers in Ann. Oncol., Nat. Genet., Cancer Res., and about 90 clinical-type associated publications.

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

The different members of Team have given 15 invited lectures. The funding of the team is based on 2 ANR contracts (ANR Emergence et Maturation et ANR Jeune Chercheur), on several industrial contracts (Actelion Ltd, InnatePharma, Novartis Pharma) and a subvention from ARC. Four patents have been deposed on the 16D10 mAb. Four students are currently preparing their PhD thesis in the Team. Moreover, the team recently received the reinforcement of several MCF and PU-PH in the new organization chart.

- Appreciation on the scientific strategy and the project

The research program of the team is strongly refocused on the anti-tumoral vaccination pancreas cancer, trusting fundamental results accumulated during past years on the expression of BSDL glycoforms. The team possesses the expertise, the tools and the background required to successfully develop the research project and gains of equipment facilities and positive environment. The development of anti-glycopeptides antibodies (16D10 and J28) as an alternative for the diagnosis and pancreas cancer treatment seems promising and could result in therapeutic applications. In the same time, the relationship thrombosis/metastasis is clearly demonstrated in pancreas cancer and the demonstration of the role of BSDL in thrombus formation constitutes a promising and original field of research. The project *thrombosis and pancreas cancer* should be therefore examined thoroughly and supported. In parallel, the team recently received the reinforcement of a new research group on the role of cadherin-integrin relationship in the mechanism of tumoral invasion allowing to positively considering the development and success of the project.

- Conclusion :

  - Summary

The goal of the team is to identify new original therapeutic targets for pancreas cancer treatment, to obtain new insights for a better understanding of thrombosis states associated to pancreas cancer and to identify new therapeutic approaches to inhibit metastases formation. The team has a good notoriety in its research field and its work should result in new therapeutic and diagnostic approaches.

  - Strengths and opportunities

The team possesses the background, the expertise, the equipment and the tools required for the development of the research project. The hypotheses are clear and previous works convincing. The focusing of research project on pancreas cancer is a positive point. The scientific environment is of a good level, the close relationship with the hospital and the participation of clinicians favour the clinical development of translational researches, allowing to predict a positive future for this project. In parallel, the team gains of the acquisition by the CRO2 of innovative equipments allowing new experimental approaches in living animal. The team also recently received the reinforcement of a new research group on the role of cadherin-integrin relationship in the mechanism of tumoral invasion.

  - Weaknesses and threats

The project is highly focused on two mAbs that leave only limited alternatives in case of difficulty in the development of these antibodies. In parallel, the lack of information on the structure of the epitope recognized by the 16D10 mAb remains a critical point that should be rapidly solved.

  - Recommendations

- Continue and reinforce the collaboration with the hospital for rapid clinical outcomes with 16D10 mAb.
- Develop and support the project *thrombosis and pancreas* cancer.

- TEAM 4 Angiogenèse, invasivité et micro-environnement. L'Houcine OUAFIK and Dominique FIGARELLA-BRANGER
- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	11	16
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)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	12,8	12,8
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)	6	
N7: Number of staff members with a HDR or a similar grade	7	

- Appreciation on the results

This team has been very active in two main axes of research: cellular and molecular characterization of brain tumours (glioma, glioblastoma - GBM) and the functional characterization of the role of adrenomedullin in cancer.

The GBM projects generated important insights into the cellular basis of GBM and the identification of prognostic and predictive molecular markers. Gene expression profiling revealed genes distinctive for invasion and angiogenesis of potential prognostic and therapeutic value, which is a rewarding result confirming the originality of the approach.

The adrenomedullin (AM) project addressed the role of AM in tumour cells (glial, colorectal, renal tumours) and tumour-associated vasculature (tumour angiogenesis). The main result emerging from these studies is that ADM promotes tumour progression and angiogenesis through auto/paracrine mechanisms. Notably, treatment of tumour-bearing mice with an anti-AM antibody causes the disruption of tumoral vessels and the inhibition of tumour growth. This observation opens the way to possible therapeutic applications, and has been protected by a granted patent. Both projects are highly translational, and of high clinical impact.

This team has produced 129 publications in the past funding period, 55 of which were originated from the own lab (first-last authorships). This corresponds to one publication per person per year, all personnel included. Twelve team-own publications were issued from basic-experimental research, and in all of them, authors from the team were at first and/or last position These include several publications in Oncogene (IF 7.1), one in Brain (IF 9.6) and others in good journals such as FASEB, Int J Cancer. They also published 16 papers from translational-clinical research activities among which 12 have authors from the team occupying first position Several of these articles are in very good journals such as Brain or Cancer. Many papers from collaborative work have been published, among which publications in some of the most prestigious journals, such as The New Engl J Med, Nat Med, Genes Dev, PNAS, Blood, Oncogene, FASEB J, Brain, Cancer Res, Clin Cancer Res, J Clin Oncol). In short, the publication record is very strong.

Several book chapters and didactic articles were published.
Seven doctoral theses were defended during the past period.
Members of the team gave many external national and international communications: 26 invited or selected presentations at national or international conferences, including in the US; 66 other oral and 24 poster presentations.

In short, the productivity and international visibility of the team are very good.

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

Several members of the team consistently gave external communications throughout the past funding period: 26 invited or selected presentations at national or international conferences, including in the US.

This team recruited 5 postdocs and 5 students from Universities and Institutes in France.

This team obtained 1.329 Million € in competitive funding, including from INCa, PROCAN (Canceropole), STIC-CCRB-IBIs, and from collaborations with industry.

The team is collaborating with over 20 investigators nationally and 9 internationally. This important number of external collaborations is well reflected in the large number of collaborative publications (57), many of them in high impact journals (e.g. NEJM, Nat. Med, Genes and Dev, Blood).
This team obtained one national priority patent and extended one patent to international coverage (therapeutic use of antibodies). It was also involved in two competitive poles: Eurobiomed (with the company CLL Pharma) and Cancéropôle PACA.

- Appreciation on the scientific strategy and the project

This team proposes to develop two main projects along the two axis of the previous phase and built on previous achievements.

In the glioblastoma (GBM) project, the team addresses 3 important questions: what determines the different biological-pathological-clinical characteristics of GBM growing in different regions of the brain; do these differences have therapeutic implications and does tumour hypoxia contribute to maintain GBM stem cells?

This is a very original, highly relevant and ambitious project at the cutting edge in GBM research. It is highly transdisciplinary and involves the use of human tumour material, in vitro cell and molecular biology experiments, functional genomic analyses and in vivo animal experiments.

The adrenomedullin (AM) project aims at investigating the molecular regulation of AM expression and its role in tumour angiogenesis in particular in the recruitment of pro-angiogenic bone marrow-derived cells, in the modulation of endothelial cell interactions, and in the promotion of angio/vasculogenesis in GBM recurring after radiotherapy. The investigation of the AM/AM-receptor axis as therapeutic target is further pursued.

This project is a logical extension of previous work, now implicating emerging fields of research (BMDC in angiogenesis, tumour escape after radiotherapy). The translational work (i.e. development of anti-AM antibodies as therapeutic strategy) is promising.

The GBM project requires important functional genomics studies to be conducted in collaboration with other groups at the PACA, which whom collaborations already exist. Also, innovative cell culture and in vivo techniques needs to be implemented.

A main asset for this project is the availability of a well characterized tissue bank for brain tumours.

Based on specific expertise and previous achievements, the project is feasible, provided the new expertises and techniques required are transferred efficiently into the team. This may be achieved by recruiting postdocs with relevant experience in the field.

The AM project is also highly interesting and ambitious and addresses several complex aspects of tumour biology and therapy (regrowth after treatments). The field is highly competitive and it will be important to focus on precise questions and to possibly establish novel external collaborations for selected questions.

Although the team seems quite well supported locally, it is important that the local leadership commit for resources. In particular support for high performance in vivo and in vitro imaging equipments and animal facilities is needed. The team may also benefit from a strong University policy to attract foreign students and post-docs.

- **Conclusion :**

  - **Summary**

The team has performed well in the past period, with important results documented in many publications in good impact factor journals and in collaborative work, publications in high impact journals (e.g. NEJM, NetMed, Genes, Cancer Res, Genes and Dev, Blood).

The team also has well established collaborations and competences in translational studies. One patent has been secured on the AM project.

The team has been able to attract significant funding.

The proposed projects are highly relevant to human cancer, ambitious and innovative, with the potential to generate results of great clinical significance for prognosis, therapy prediction and new treatment of cancer, in particular GBM.

  - **trengths and opportunities**

The team has a positive track record and stability over time.

It has significant internal competencies and well-established networks, including with functional genomics groups.

A well annotated tissue bank is available.

Some investigators are internationally recognized figures in their field, which will facilitate contacts for the proposed projects.

  - **Weaknesses and threats**

The projects are in highly competitive fields, and several high-profile groups are working on similar or related questions.

The likely necessary collaboration with pharma industry to develop the anti-AM Ab (or related tools) for therapeutic purposes can be hardly controlled by the team and may represent a potential threat to the development of a drug.

Difficulty to attract foreign students and postdocs may limit the acquisition of expertise for the rapid establishment of novel techniques.

  - **Recommendations**

For the new AM projects focus initially on specifc questions to rapidly position the group in the field

Attract junior scientists, possibly from abroad, to strengthen expertises for the new projects.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
CRO2 - CENTRE DE RECHERCHES EN ONCOLOGIE BIOLOGIQUE ET ONCO-PHARMACOLOGIE	**A**	**A**	**A+**	**A**	**A**
COMMUNICATIONS MICROTUBULES-MITOCHONDRIES : IMPLICATIONS EN ONCOPHARMACOLOGIE [LOMBARDO-BRAGUER]	A	A	Non noté	A	A
MICROEENVIRONNEMENT REDOX, CYTOSQUELETTE ET PROGRESSION TUMORALE [LOMBARDO-KOVACIC-PEYROT]	A	B	Non noté	A	A
PROGRESSION TUMORALE ET IMMUNOTHÉRAPIE EXPÉRIMENTALE [LOMBARDO-LOMBARDO-BERNARD]	A+	A+	Non noté	A	A+
ANGIOGENÈSE, INVASIVITÉ ET MICROENVIRONNEMENT TUMORAL [LOMBARDO-OUAFIK-FIGARELLA]	A	A	Non noté	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

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

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

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

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

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

UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Objet : Réponse au rapport d'évaluation - **S2UR120001651 - CRO2 - Centre de Recherches en Oncologie biologique et Onco-pharmacologie - 0131843H** - de l'unité CRO2 - Centre de Recherches en Oncologie biologique et Onco-pharmacologie

Observations d'Aix-Marseille Université

First of all we would like to address ours special thanks to the experts for their involvement in the evaluation of our structure and for their suggestions and comments. They will be useful to the future of the CRO2. To answer the report, we would be pleased to add some lighting to expert committee.

Four main points have been raised by the expert committee:

1- The first one concerns the low number of full-time researchers. This is likely due to your privileged links with two Universities (Univ Med and Univ Provence, both being part of Aix-Marseille University) which provide us with many positions as assistant-professor. During the last years 6 assistant-professors have been recruited all coming from outside laboratories.

Christophe Dubois, PhD in Basel (Switzerland), post doc in Basel (Switzerland) and Harvard Med School (Harvard, USA).

Sylvie Monferan PhD Toulouse, post-doc in Toulouse.

Gilles Breuzard PhD Reims post-doc in Orleans.

Alessandra Pagano PhD in Geneve (Switzerland), post-doc in Marseille.

Ludovic Leloup PhD in Bordeaux, post-doc Pitsburg Univ (USA).

Marie-Anne Estève PhD in Marseille recruited after a 6-month stay in a pharmaceutical company developing new microtubule interfering agent.

2 – The second point concerns the"endemic" recruitment. As already said (see point 1) many people recruited recently at the CRO2 come from outside laboratories and not from our lab.

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Tél. : +33 (0)4 91 39 65 00 . Fax : +33 (0)4 91 31 31 36 . www.univmed.fr

3 – Concerning the need for increased visibility, we noted some sentences in the report, these are as follows :

Specific comments (point 3) "most team leaders are invited in international conferences"

Team 1 page 8 "The team has acquired a clear visibility" "Additionally and importantly one can note the participation of team leader in both the 6th and 7th PCRD which clearly reflect the recognition of team skills by the European scientific community and this consistently over the years"

Team 2 page 10 "During the last 4 years the 2 group leaders have participated to national and international meetings..... Since this team is newly created the international visibility ... may be best measured in the next evaluation" Further on "the new team 2 has established collaborations with 4 international teams and has been integrated in several national contracts. This underlines beneficial interaction with.... and confirms the nascent international visibility of the team".

Team 3 page 13 "the team has a good notoriety in its research field"

Team 4 page 14 "and international visibility of the team "are" very good"

So the unit believes it is in the right way to acquire a very good visibility.

Specific comment on team 1 :

Since 2007, Team 1 has continuously a post-doctoral researcher who is funded on several grants: Alessandra Pagano coming from Geneva University was founded by a 6th PCRD project and then by the "Pole of competitivity" Eurobiomed project (Syn 2001) for 2,5 years. Currently, Raphael Berges is a post doc coming from Angers University who is funded on a contract with a pharmaceutical company (1 year). In 2012, a new postdoctoral researcher will be recruited for the ANR Lasernanobio project.

Concerning the recruitment of researchers, Eddy Pasquier will candidate as a full-time position researcher to INSERM.

Specific comment on team 2 :

1-The reviewer emphasizes that the members of the team have published a high number of papers during the last four years (125). From that publications, 20 are authored by the 4 new assistant-professor recruited from abroad since 2008 to reinforce the team. This confirms the attractivity of the team and the full local support for this new team 2 structuration.

2-This new team 2 has been structured to use the molecular and cellular fundamental findings as a pipeline for characterizing new anticancer compounds and provide rational for translational studies.

Specific comment on team 3 :

1: Note that the funding of the team is not limited to 2 ANR contracts, on several industrial contracts and a subvention from ARC, it also actively participate in an FT7 European 2011-2014 project (EndoTOFPET-US, CE N° 256984).

2: It is right that two mAbs leave only limited alternatives to treat PDAC. However we have some 100 mAbs, 10 have been selected for their very high reactivity with the target and 2 antibodies were finally selected. So the team has some spare material. Also nothing works efficiently with PDAC so we hope that these 2 antibodies will be OK. Note that Innate Pharma stop the program for many reasons (in part economical ones) and that discussion with "Roche" drived us to a work-plan and to the licencing of these antibodies to develop full human antibodies and to their use in human clinic. Therefore in collaboration with Roche Pharmaceutical (Basel, Switzerland) team will produce a human IgG 16D1-like. A work plan has been established and once this IgG 16D10-like available we will turn out to pre-clinical and clinical studies, of course after checking for this IgG 16D10-like properties (specificity, activity, pharmacology...). Noteworthy the J28 antigen that we are able to produce by engineering is able to induce the activation of naïve lymphocyte T to evoke a CD4+ and CD8+ response opening the way to an active immunotherapy of pancreactic adenocarcinome (Franceschi et al., J. Immunol. 2011, 186:4067-77).

3: A short post doctoral stay of Helge Reader (from the University of Bergen, Norway) in the lab gave a collaborative publication in Nature Genetics.

En accord avec les deux autres établissements d'Aix-Marseille

Le Président
de l'Université de la Méditerranée

Yvon BERLAND

Le Vice-président du Conseil Scientifique
de l'Université de la Méditerranée

Pierre CHIAPPETTA

UMR-911

Directeur : Dr. Dominique LOMBARDO

Answer to the AERES report concerning the CRO2 UMR 911 INSERM/Université de la Méditerranée.

First of all we would like to address ours special thanks to the experts for their involvement in the evaluation of our structure and for their suggestions and comments. They will be useful to the future of the CRO2. To answer the report, we would be pleased to add some lighting to expert committee.

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Ludovic Leloup PhD in Bordeaux, post-doc Pitsburg Univ (USA).
Marie-Anne Estève PhD in Marseille recruited after a 6-month stay in a pharmaceutical company developing new microtubule interfering agent.

However, some post-doctoral people present at the unity or the lab students doing a post-doc abroad could be in a near future in position for an eventual presentation at the INSERM to grant a full-time position researcher.
These are:
Raphael Berges coming from Angers University.
Céline Tiffon coming from Nice University.
Mohamed Ben Sgaier from the Institut Supérieur de Biotechnologie de Monastir (Tunisia).
Carine Jiguet-Jiglaire from INRA - Laboratoire de génétique cellulaire. Toulouse.

Also we have many students doing a post-doc abroad, these are:
Estelle Delamarre (IPSEN, Paris, France)
Amine Sadok (Institute for Cancer Research, London, UK)
Salma Taboubi (Barts Cancer Center, London, UK)
Eddy Pasquier (Sydney, children's cancer institute of Australia)
Grace Thomas (Harvard Med School, Harvard, USA)
Jennifer Watkins (Dana Farber Institute, Boston, USA)

Fabienne Brenet, (Weill Cornell Medical College, New York, USA)
Aurélie Tchoghandjian, (Frankfurter Stiftung für Krebskranke Kinder, Frankfurt/Main, Germany)

They could fuel the pipe for future recruitment at the INSERM, also. Note that the recruitment policy of Aix-Marseille University is to recruit young researchers preferably from outside (i.e. not having done their PhD at Aix-Marseille University) to favor mobility. This is clearly illustrated by the recruitments done these last years at the CRO2 (see point 1).

2 – The second point concerns our “endemic” recruitment. As already said (see point 1) many people recruited recently at the CRO2 come from outside laboratories and not from our lab.

3 – Concerning in-between-team collaboration, the CRO2 is only three years old with the gathering of pre-existing structures, working all in oncology but on different cell compartments, on different biological processes and several organs. This difference in models does not favor in first instance relationship between teams. Since the fusion and the lab reorganization we have managed collaborations around large thema such as angiogenesis, drug/antibodies, death mechanisms….Such implementation in collaborative works necessitate time and we are in the right way as collaborations already took place between. These collaborations such as that on Glioma (leader D. Figarella-Branger) were granted by INCa and associate 3 teams of the CRO2. Collaborations between teams will also be effective in the frame of the SIRIC proposal “PACA-Ouest”. Furthermore some other collaborations will specifically take place between and for examples teams3 and 4 agreed to collaborate on adrenomedullin and pancreatic cancer, and teams 1 and 4 on EB1 and glioblastoma.

4 – Concerning the need for increased visibility, I noted some sentences in the report, these are as follow:

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In addition, post doctoral researchers coming from abroad join our team for few months to perform specific experiments. For example, Sela Pouha coming from Kavallaris lab (Sydney Children cancer institute of Australia) for microtubule dynamics (manuscript in preparation), and Alissia from Ferlini team (Danbury Hospital, Connecticut) for Bim project.

Concerning the recruitment of researchers, we plan to present Eddy Pasquier as a full-time position researcher to INSERM. He his a post-doctoral student in Kavallaris' lab in Sydney (Children cancer institute of Australia). He his currently developing new animal models with tumor cells isolated from patients for studying drug resistance. These models should be very useful for CRO2. Due to their strong collaboration, Diane Braguer and Maria Kavallaris act together to allow Eddy recrutement in France.

Specific comment on team 2 :

1-The reviewer emphasize that the members of the team has published a high number of papers during the last four years (125). From that publications, 20 are authored by the 4 new assistant-professor recruited from abroad since 2008 to reinforce the team. This confirms the attractivity of the team and the full local support for this new team 2 structuration.

2-We structured this new team 2 to use the molecular and cellular fundamental findings as a pipeline for ***characterizing new anticancer compounds*** and provide rational for ***translational studies***.

-The characterization of new anticancer compounds results mainly from collaboration with chemists. The reviewer mentions that the resulting publications do not reach very high impact factor. These publications are considered as very good in their field of chemistry and chemical-biology. The quality of such research is also highlighted by the recent deposit of a patent on a new anticancer compound.

-We feel that the participation of the clinicians to the team's2 project was underrated in the report. We would like to emphasize that the translational study which represent one of the mentioned strength of our project was initiated four year ago by collaborative effort between team 2 leaders and the digestive oncology department of CHU la Timone (headed by Jean-François Seitz). Since then several clinicians were involved in Master and PhD program developed in the team of the redox control of chemotherapy. These clinicians participate to numerous international clinical studies on chemotherapy efficiency and more

than 50 publications with some in top-ranking journals (N Engl J Med; J. Clin. Oncol; Clin Cancer Res;…). Thus, beside providing colorectal tumour samples, clinical outcomes and international visibility, the clinicians from the digestive oncology department are totally integrated to the team. In the team, clinicians should find the fundamental support to test their hypothesis on the role of the redox control of chemotherapies in order to define new strategies to fight cancer.

Specific comment on team 3 :

1: Note that the funding of the team is not limited to 2 ANR contracts, on several industrial contracts and a subvention from ARC, we also actively participate in an FT7 European 2011-2014 project (EndoTOFPET-US, CE N° 256984).

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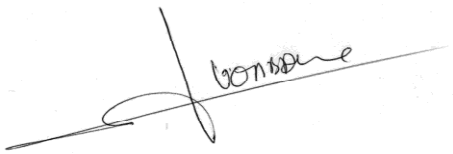
3: A short post doctoral stay of Helge Reader (from the University of Bergen, Norway) in our lab gave a collaborative publication in Nature Genetics.

Specific comment on team 4:

No specific comment.



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