BioTICLA - Biologie et thérapies innovantes des cancers localement agressifs

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Biologie et thérapies innovantes des cancers localement agressifs (BioTICLA)

From the

University of Caen

November 2010

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

Section des Unités de recherche

AERES report on the research unit:

Biologie et thérapies innovantes des cancers localement agressifs (BioTICLA)

From the

University of Caen

Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

November 2010

Research Unit

Name of the research unit: Biologie et thérapies innovantes des cancers localement agressifs (BioTICLA)

Requested label: UMR INSERM

N° in the case of renewal

Name of the director: Dr Laurent POULAIN

Members of the review committee

Committee chairman:

Mr Louis BUSCAIL, Paul Sabatier University Toulouse 3

Other committee members:

Ms Bettina COUDERC, Paul Sabatier University Toulouse 3

Ms Nathalie ANDRIEU-ABADIE, Paul Sabatier University Toulouse 3

Ms Marie-Claude JAURAND, University Paris 7

Mr Theodore ALEXANDROV, Zentrum für Technomathematik Universität, Bremen, Germany

Ms Dominique WACHSMANN, University of Strasbourg

Ms Ruth RIMOKH, University of Lyon

Observers

AERES scientific advisor:

Jean ROSENBAUM

University, School and Research Organization representatives

Mr Pierre DENISE, Vice President, University of Caen

Mr Khaled MEFLAH, Director, Centre François Baclesse

Mr Michel MATHIEU, Director, IFR ICORE

Mrs Catherine LABBÉ-JULLIE, INSERM representative

Report

1 • Introduction

- Date and execution of the visit:

The visit took place in Caen on November 3, 2010 in the comprehensive cancer center building, Centre François Baclesse. The site vist began at 8:30 am with a meeting of the committee with the AERES representative.

At 9 am, the group leader first briefly introduced the general strategy of the lab. This was followed by 4 short presentations by several scientists from the team until 11 am. The committee then split into 3 subgroups in order to meet separately the PhD students, the technicians, and the scientists. The committee then met University, INSERM and other local representatives during 30 minutes.

At 1 :30 pm, the committee met for debriefing and drafting the report. The visit ended at 3 :45 pm.

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

The BioTICLA project is based on the previous EA1772 (GRECAN: Groupe Régional d'Etudes sur le Cancer) in Caen. The lab is located on the premises of the Centre François BACLESSE with which it has strong relationships, CHU of Caen. The project of unit involves the fusion of the former BiocTICLA team with the HIQ (Histo-imagerie Quantitative) team. This latter team will give rise to an internal Technological team named MICA. Overall, the lab will use 700 square meters of lab space.

- Management team

The unit will be directed by the former responsible of the BoTICLA team. The director appears clearly as the leader of the unit.

- 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)	10	7
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)	10	9
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	5	5
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	7	6

2 • Overall appreciation on the research unit

- Summary

The BioTICLA and HIQ (Histo-imagerie quantitative) teams are joining their efforts to develop a project on ovarian cancer, a locally aggressive cancer which is characterized by a high rate of recurrence after first line chemotherapy, associated with chemoresistance acquisition. Condidering the high mortality rate of ovarian cancer due to the absence of curative treatment, new therapeutic strategies are urgently needed. One of the major goals of the study is to block the antiapoptotic effects of Bcl-xL and McL1 which are overexpressed in this tumor. The therapeutic strategy presented is based on the use of: i) siRNA technology (coupled to various synthetic vectors and transporters); ii) BH3-mimetic molecules, both being applied on ovarian cancer cell lines and animal models. The pharmacological approach is developped with an industrial group by testing the ABT-737 compound. Another major aspect of the project is to find a signature of chemoresistance of ovarian cancer using proteomics and miRNA expression studies. In addition, an in vivo approach investigated the use of PET (positron emission tomography) imaging in the evaluation of the response to treament in mice. The HIQ team evaluated more specifically the stroma reaction of ovarian cancer on histological sections.

- Strenghts and opportunities

The unit is highly integrated in a medical and scientific environment that would allow transfer from bench to the bedside. The unit is closely related (geographically, medically, scientifically anf functionnally) to the comprehensive cancer center (Centre F. Baclesse) and the University Hospital. The research is oriented “on” and “against” ovarian cancer with many opportunities such as: tumor bank, ascitis bank, good recruitment of ovarian cancer patients, several dynamic young MD/PhD researchers, financial support (especially from Low Normandy Region), and finally all the forces are concentrated on a single, severe and locally aggressive disease. The research team is closely associated with the management of clinical trials

- Weaknesses and threats

The MICA projects displays a low lisibility and integration within the other major scientific priorities of the unit. Moreover, there is a low number of full time permanent researchers involved in the miRNA project, which is however a highly competitive project. In general, the review committee found that the large number of projects contrasted with a rather low number of full time permanent researchers. No high-ranking publications were published or are currently in revision/press.

- Recommendations

The unit might focus its research on the miRNA and BH3 projects and must more clearly integrate the imaging process to the biological research program of the unit. The miRNA project would benefit from the recruitment of a full time researcher.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	7
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	10
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	87.5%
A4: Number of HDR granted during the past 4 years	2
A5: Number of PhD granted during the past 4 years	10

3 • Specific comments

- Appreciation on the results

- **"BH3 mimetic project"**: the use of BH3-mimetics to reverse the resistance of ovarian cancer cells to chemotherapy-induced apoptosis is an up-to-date and relevant project for the pathology. Moreover, it is reinforced by good partnerships (especially industry) and a clinical approach. This is a really integrated program with new and promising results.

- **Therapeutic siRNA project:** It is a long lasting project with a few publications and results for the in vitro approaches, but no consistent results with the in vivo applications. A good point is that the team joined a network for this project, however there is apparently no specific researcher to conduct this project.

- **miRNA project**

It is a very integrated and interesting project in the field of ovary cancer (linked to biological resources and clinical activity of the cancer center with a large patient recruitment). However, today this project is entering in a highly competitive area.

- Imaging and innovative treatments:

- **The « PET project"** is a useful and interesting aspect of this program with several publications and great potential.

- **The MICA project** involves many people, with a strong histological and clinical background, but there are very few publications and there is no clear proposal.

During the 4 past years, the different teams that plan to set up the BioTICLA unit produced 31 original papers (16 with IF <3 or not indexed, 11 with IF between 3 and 5 and 1 with IF betwen 5 and 10) and two patents. 28 out of these publications involve lab members as first and/or senior author. The best publications were in good but not top specialty journals (Int J Cancer, Carcinogenesis, Proteomics). 14 PhD have been graduated.

There is a good and stable partnership with industry, local institutions and clinical centers and laboratories.

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

The director of the unit gave 31 communications but few invited conferences (mainly national); there is no award.

There is a good potential for attractiveness and efforts. However, no foreign students and post docs were welcomed; this should be improved. There have been no visiting scientists but it is difficult to consider this item because this is a new project and a new unit.

There is a good funding (near 1 million euros over 4 years) from region Low Normandy, Ligue against Cancer, OSEO, Canceropole, ARC, General Council of Calvados, Caisse d'épargne ; good industrial links and financial partnership with industry. In the future, fundings for post-doc should be considered.

The unit has a good networking activity and participates to the Ligue consortium (CIT program), and has been involved in European FP7 and siRNA consortium.

- Appreciation on the management and the scientific strategy

The management of the team is good in terms of obtaining funding, collaborations and teaching. Each PhD student obtained a mean of 2 to 3 publications. Some of them acquired a position (MCU). There are good initiatives for scientific animation as well as to develop cutting edge and pre-clinical projects. Several actors participate to a good and effective relationship with the local scientific and clinical (CLCCC and CHU) institutions: host organization, platform, clinical study, structuration of local research and network for research against cancer,

- Appreciation on the scientific strategy and the project:

Taking into account the past difficulties on the in vivo approach, as well as the international competition, the committee recommends to slow down or reconsider the siRNA project.

Regarding the competition and the hot aspect of the miRNA program in ovarian cancer, the committee encourages the unit to put their forces in this project (especially in terms of researchers). It is very important to obtain a stable position for the scientist mainly in charge of this project.

`The MICA project: The weak background in image processing should be improved in order to stay within the international competition and it is thus recommended to link/share this project to an image processing team. The MICA projects should be more integrated within the scientific project on ovarian cancer.

The BH3 project represents a cutting edge and original project but it is recommended to develop a more fundamental and mechanistic research. A return to the bench would be interesting in this program especially if clinical results prove not to the expectancy.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
BIOLOGIE ET THÉRAPIES INNOVANTES DES CANCERS LOCALEMENT AGRESSIFS (BIOTICLA)	B	B	A	B	B

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**

Monsieur le Directeur
Section des Unités de Recherche
AERES

Caen, le 28 février 2011

V/Réf. : Evaluation - S2UR120001219 - Biologie et Thérapies Innovantes des Cancers Localement Agressifs (BioTICLA) - 0141408E

The BioTICLA team would like to thank the review committee for the quality of the preparation of the visit as well as for its helpful comments and recommendations. We agree with the overall conclusions of the committee, as well for the strengths as for the weaknesses pointed out by the committee. However, we would like either to give some complementary information or to clarify some items, particularly concerning the committee's recommendations.

1. Additional information concerning siRNA project

In agreement with the recommendation of the committee, we chose to reconsider the siRNA project. Indeed, we decided to work exclusively with industrial partners ready-to-go through clinical trials, if applicable with our Bcl-xL/Mcl-1 multi-targeted strategy. We will thus work this year in the context of an international collaboration with a US partner already involved in preclinical and clinical validation of siRNA strategies (MTA in preparation). This partnership is established with the support of the "Ligue Nationale Contre le Cancer", within the national Consortium "validation préclinique de siRNA d'intérêt pour le traitement des cancers", itself part of the CIT® program. We planned *in vivo* experiments aiming to confirm the interest of the proposed vectorization system to silence expression of the targeted gene, followed by the validation of anti-tumor effect of this multitargeted strategy. Metabolic imaging (FDG and/or FLT μPET) will be particularly useful to demonstrate such effects. Moreover, iodinated-siRNA imaging will also be performed in collaboration within the consortium to precise siRNA bio-distribution. These works will be placed, as previously, under the direct responsibility of the director of the Unit (this point is specified as the committee wrote "there is apparently no specific researcher to conduct this project"). A PhD student is currently working on this project and part of the technical staff also participates to this program. Moreover, a dedicated technician will be recruited in a few weeks for one year to allow a fast move on this project (financial support requested from LNCC). In case of successful experiments within the 18 next months, a collaborative early phase clinical trial will be proposed to this pharmaceutical partner. In case of unsuccessful experiments, the team will close this program, and will put its forces in the other projects of the Unit. However, we think that the "know-how" acquired during the last years in the field of preclinical evaluation of siRNA-based strategies as well as in the field of metabolic imaging would be highly valorised through this short-term project (at least for the first phase of its potential development), and that the taken risk is modest as compared to the possible increase of international visibility in case of success.

2. Reinforcement of the miRNA project

The committee recommends stabilising the position of "the scientist mainly in charge of this project". This is indeed the priority of the Unit in term of recruitment. We thus presented a high profile post-doc at Inserm (CSS7) and CNRS (30th section) competitive recruitment procedures to obtain a stable full-time research position. After two successive selections and auditions, he was successively classified by Inserm in 10th and 12th position without final selection. He will postulate once more this year, in the new context of the structuration of the Unit and of cancer research in Caen.

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It should be specified that CNRS detached a CR1 researcher to our Unit from two years, and that the activity of this researcher has been progressively dedicated to the miRNA project. A first article concerning his "miRNA activity" has been recently published (Breast Cancer and Research Treatment, 2011) and a second one has been submitted, as presented below. Moreover, we asked the University to support our Unit through the creation of an Assistant Professor (MCU) position dedicated to the project "predictive and therapeutic interfering RNA". We also hope to reinforce soon the staff working on this project, through the recruitment of a PhD student and/or post-doc (French or foreign) and of a dedicated technician thanks to the support of Low Normandy Region.
We also would like to inform the Committee that a publication concerning this project has just been submitted to Oncogene *(Targeting of Bcl-x_L by miR-491-5p or Mcl-1 by miR-193b induce apoptosis in a Bim-dependent manner in chemoresistant ovarian carcinoma cells. C. Denoyelle, B. Lambert, et al.).*

3. **Clarification about the activity of MICA project and its integration within the priorities of the Unit**

First of all, it should be mentioned that the integration of MICA activities in the scientific project of the Unit constitutes the objective of the next quadrennial plan; we agree that we would have to further clarify the proposal in this field, and to present more clearly the expected benefit of the fusion of the former BioTICLA and HIQ teams of GRECAN. Thus, we would like to re-express these points here.
ERT MICA declines its activity around two main activity domains, that concern (i): the design of algorithms adapted to the optimal treatment of virtual slides in oncology; (ii): the development of a quality control approach for image processing. The tools and developments proposed by ERT MICA can be used to allow convenient histological interpretations, thus being particularly interesting in the context of pre-clinical and clinical assessment of the response to treatment and/or for the design of predictive tools. They will be progressively applied to the specific themes of the Unit. First, this will soon be the case in the context of clinical trials currently under preparation (NaviCarbo study, PHRC 2010; AMICAT study...), as well as in the context of preclinical studies in progress (ABT/CARBO *ex vivo* study, siRNA *in vivo* etc.). Such common works have been previously realised between HIQ and BioTICLA internal teams of GRECAN, as attested by common publications (de Bouard et al. 2007, Aide et al. 2008 and 2009, Labiche et al. 2009).
Moreover, these tools could allow removing technological difficulties such as the ones that are met for automatic quantification of apoptotic cell death *in situ* or for apprehension of tissue heterogeneity for instance. These points will lead our team to specific common developments.
The other own projects of ERT MICA, some of them progressively converging towards ovarian pathology, will contribute to reinforce its experience in the field of algorithm design and quality control. All the possible points of convergence between ERT MICA and BioTICLA scientific priorities are now clearly identified. Our emerging Unit also identified the absolute necessity to merge imaging activities with its other scientific project and will work in this way to lead quickly to an integrated research.

Concerning the few number of publications of ERT MICA and corresponding Impact Factor: It should be specified that this point has been clearly identified as critical by our Unit, and the progression of the number of publication per researcher and per year is a priority. Thus, 5 papers are expected during the next year (2 of them are in press, the submission of 3 more papers is expected in 2011). Moreover, concerning the low impact factors, it should be specified that the best IF in the field of image analysis and processing is not over 3.

It could be also noticed that the University recently decided to reinforce the Imaging Core Facility of IFR146 ICORE which is placed under the responsibility and closely related to ERT MICA by the recruitment in 2011 of a Research Engineer. This will of course favourably impact on ERT MICA activity.

The Committee also recommends to ERT MICA to "develop its interaction with image processing teams". The ERT MICA presents multidisciplinary features, merging biologists, pathologists and image processing researchers. This multidisciplinary allowed the setting up of original solutions attested for instance by corresponding international patents. Moreover, agreeing with the necessity to reinforce and complements its own competences in image processing, ERT MICA developed several collaborations with national and international teams clearly identified as specialist in the field of image processing : (i) The Clinical Image Analysis Laboratory, Department of Biomedical Informatics of Ohio State University, USA (Dr Metin Gurcan); (ii) the Stereology and Electron Microscopy Research Laboratory, Department of Computer Science of Aarhus University, Denmark (Dr R. Nyengaard and Dr E. Jensen) and (iii) the "Ecole des Mines de Paris, Centre de Morphologie Mathématique de Fontainebleau et Centre de géostatistique" (Dr F. Meyer, Dr D. Jeulin and Dr C. Lantuéjoul). The two first collaborations are contractually formalized. These collaborations will be reinforced in the next quadrennial plan.

4. BH3-mimetic project

The committee wrote "The BH3 project represents a cutting edge and original project but it is recommended to develop a more fundamental and mechanistic research. A return to the bench would be interesting in this program especially if clinical results prove not to the expectancy."
These aspects have been briefly presented in the Unit project but are currently in development as active parts of the BH3-mimetic project. These fundamental works, presented below, could allow the design of new Mcl-1 inhibiting strategies, that constitutes a major challenge for the success of clinical applications of the multitargeted strategies developed by the Unit.

- Molecular mechanisms involved in the modulation of Mcl-1 expression in response to BH3-mimetics

The possible involvement of endoplasmic reticulum, calcium flux and subsequent activation/inactivation of signalling pathways in transcriptional and/or post-transcriptional control of Mcl-1 is under investigation. Moreover, the impact of such events on the expression of BH3-only proteins able to modulate the activity of Mcl-1 (Noxa, Puma, Bim...) is carefully investigated, as well as the modulation of partnerships of Bcl-x_L and Mcl-1 with other Blc-2 family members after exposure to BH3-mimetic molecules.

- Molecular mechanisms of Bcl-x_L/Mcl-1 cooperation

The mechanisms through which these two proteins specifically cooperate (other anti-apoptotic Bcl-2 family members being not involved) to protect ovarian cancer cells remain to be elucidated. Bax/Bak inactivation does not seem to impede cell death in response to Bcl-x_L/Mcl-1 multitargeted strategies (work in progress). We thus wonder about the possible involvement of concomitant sequestration of Bok by Mcl-1 and of BNIP3 by Bcl-x_L, these two proteins cooperating themselves to induce cell death. The results of this work could also impact on the development of such multitargeted strategies.

- Identification of pharmacological tools for Mcl-1 inhibition

Platinum derivatives that we currently use to directly (transcriptional regulation) or indirectly (BH3-only protein activation...) inhibit Mcl-1 show a lower efficiency than siRNA. Since siRNA are not (yet) applicable for clinical use, the design of other Mcl-1-targeting agents appears as a major challenge. In order to prepare future clinical trials with BH3-mimetics (post NaviCarbo trial), we will study the interest of various pharmacological agents, either currently in clinical use or specifically designed to

inhibit Mcl-1 activity (innovative drugs), to improve the efficiency of Mcl-1 inhibition to be associated to BH3-mimetics-based Bcl-x_L inhibiting strategies in a more potent, more specific and less toxic manner. A PhD student will be recruited in 2011 (half financial support obtained from ABBOTT, complementary support requested from Low Normandy Region).
This approach includes the study, in collaboration with the chemists of the "Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN)", of the interest of a new family of molecules as Mcl-1 inhibitors, some of them presenting exciting properties as showed by our preliminary results. Associated molecular modelling approach as well as protein-protein interaction studies are currently under development in our partner's laboratories. This multidisciplinary project is under expertise to obtain a three years financial support from Low Normandy Region (Emergence Project).

5. Overall in the progression in the publication rank

We would like to highlight the fact that a clear progression of the level of impact factors has been achieved by BioTICLA internal team of GRECAN from 2006 to 2010. Indeed, the mean impact factor was 3.656 in 2006 for 5 papers versus 4.957 in 2010 with 8 papers. We will strive to continue this progression during the next quadrennial plan.

6. Attractiveness

The committee mentioned: "There is a good potential for attractiveness and efforts. However, no foreign students and post docs were welcomed".
A Chinese surgeon has been welcome for 4 years for a PhD thesis before going back to China for a permanent position. During the past 4 years, the Unit welcomed 3 undergraduate foreign students (Spain, Denmark and Lithuania) for short training periods (3-6 months). Moreover, we are currently studying the possibility to obtain post-doctoral fellowship from Low Normandy Region to attract foreign researchers (miRNA project).

In summary, the construction of BioTICLA Unit in the next five years will integrate all the suggestions of the AERES committee members. Efforts will be concentrated on miRNA and BH3-mimetic projects, associated to a short term "valorise or close" approach concerning the siRNA project. Metabolic and histological imaging competences and activities will be integrated and focused on the scientific priorities of the Unit in the field of ovarian cancers therapeutic care, at the preclinical as well as clinical translational levels.
A reinforcement of the Unit is expected from the institutions, mainly for the interfering RNA projects. Transient recruitments (post-docs and technicians) will also be essential in the next years, as well as the planned reinforcement of the number of accredited research supervisor (HDR) and associated PhD students.
The Unit will also reinforce its position in the context of national networks for research against ovarian cancers (FEDEGYN, GINECO, GINOVA, and hopefully INCa-piloted workgroup). Associated to the very recent recognition by INCa of the early phase clinical trial activity of the Clinical Research Unit of the CLCC F. Baclesse, these elements should be favourable to the development by BioTICLA Unit of effective translational research, from bench to bedside...to bench.

La Présidente de l'Université
de Caen Basse-Normandie

Josette TRAVERT

Dr Laurent Poulain

Responsable de l'Unité : « Biologie et Thérapies Innovantes
des Cancers Localement Agressifs » (BioTICLA)
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Caen, 24 March 2011

Answer from BioTICLA Unit to the AERES Review Committee members (Date of the visit: 3 November 2010)

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2. Reinforcement of the miRNA project

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3. Clarification about the activity of MICA project and its integration within the priorities of the Unit

First of all, it should be mentioned that the integration of MICA activities in the scientific project of the Unit constitutes the objective of the next quadrennial plan; we agree that we would have to further clarify the proposal in this field, and to present more clearly the expected benefit of the fusion of the former BioTICLA and HIQ teams of GRECAN. Thus, we would like to re-express these points here.

ERT MICA declines its activity around two main activity domains, that concern (i): the design of algorithms adapted to the optimal treatment of virtual slides in oncology; (ii): the development of a quality control approach for image processing. The tools and developments proposed by ERT MICA can be used to allow convenient histological interpretations, thus being particularly interesting in the context of pre-clinical and clinical assessment of the response to treatment and/or for the design of predictive tools. They will be progressively applied to the specific themes of the Unit. First, this will soon be the case in the context of clinical trials currently under preparation (NaviCarbo study, PHRC 2010; AMICAT study…), as well as in the context of preclinical studies in progress (ABT/CARBO *ex vivo* study, siRNA *in vivo* etc.). Such common works have been previously realised between HIQ and BioTICLA internal teams of GRECAN, as attested by common publications (de Bouard et al. 2007, Aide et al. 2008 and 2009, Labiche et al. 2009).

Moreover, these tools could allow removing technological difficulties such as the ones that are met for automatic quantification of apoptotic cell death *in situ* or for apprehension of tissue heterogeneity for instance. These points will lead our team to specific common developments.

The other own projects of ERT MICA, some of them progressively converging towards ovarian pathology, will contribute to reinforce its experience in the field of algorithm design and quality control.

All the possible points of convergence between ERT MICA and BioTICLA scientific priorities are now clearly identified. Our emerging Unit also identified the absolute necessity to merge imaging activities with its other scientific project and will work in this way to lead quickly to an integrated research.

Concerning the few number of publications of ERT MICA and corresponding Impact Factor: It should be specified that this point has been clearly identified as critical by our Unit, and the progression of the number of publication per researcher and per year is a priority. Thus, 5 papers are expected during the next year (2 of

them are in press, the submission of 3 more papers is expected in 2011). Moreover, concerning the low impact factors, it should be specified that the best IF in the field of image analysis and processing is not over 3.

It could be also noticed that the University recently decided to reinforce the Imaging Core Facility of IFR146 ICORE which is placed under the responsibility and closely related to ERT MICA by the recruitment in 2011 of a Research Engineer. This will of course favourably impact on ERT MICA activity.

The Committee also recommends to ERT MICA to "develop its interaction with image processing teams".
The ERT MICA presents multidisciplinary features, merging biologists, pathologists and image processing researchers. This multidisciplinary allowed the setting up of original solutions attested for instance by corresponding international patents. Moreover, agreeing with the necessity to reinforce and complements its own competences in image processing, ERT MICA developed several collaborations with national and international teams clearly identified as specialist in the field of image processing : (i) The Clinical Image Analysis Laboratory, Department of Biomedical Informatics of Ohio State University, USA (Dr Metin Gurcan); (ii) the Stereology and Electron Microscopy Research Laboratory, Department of Computer Science of Aarhus University, Denmark (Dr R. Nyengaard and Dr E. Jensen) and (iii) the "Ecole des Mines de Paris, Centre de Morphologie Mathématique de Fontainebleau et Centre de géostatistique" (Dr F. Meyer, Dr D. Jeulin and Dr C. Lantuéjoul). The two first collaborations are contractually formalized. These collaborations will be reinforced in the next quadrennial plan.

4. BH3-mimetic project

The committee wrote "The BH3 project represents a cutting edge and original project but it is recommended to development a more fundamental and mechanistic research. A return to the bench would be interesting in this program especially if clinical results prove not to the expectancy."
These aspects have been briefly presented in the Unit project but are currently in development as active parts of the BH3-mimetic project. These fundamental works, presented below, could allow the design of new Mcl-1 inhibiting strategies, that constitutes a major challenge for the success of clinical applications of the multitargeted strategies developed by the Unit.

- Molecular mechanisms involved in the modulation of Mcl-1 expression in response to BH3-mimetics

The possible involvement of endoplasmic reticulum, calcium flux and subsequent activation/inactivation of signalling pathways in transcriptional and/or post-transcriptional control of Mcl-1 is under investigation. Moreover, the impact of such events on the expression of BH3-only proteins able to modulate the activity of Mcl-1 (Noxa, Puma, Bim…) is carefully investigated, as well as the modulation of partnerships of Bcl-x_L and Mcl-1 with other Blc-2 family members after exposure to BH3-mimetic molecules.

- Molecular mechanisms of Bcl-x_L/Mcl-1 cooperation

The mechanisms through which these two proteins specifically cooperate (other anti-apoptotic Bcl-2 family members being not involved) to protect ovarian cancer cells remain to be elucidated. Bax/Bak inactivation does not seem to impede cell death in response to Bcl-x_L/Mcl-1 multitargeted strategies (work in progress). We thus wonder about the possible involvement of concomitant sequestration of Bok by Mcl-1 and of BNIP3 by Bcl-x_L, these two proteins cooperating themselves to induce cell death. The results of this work could also impact on the development of such multitargeted strategies.

- Identification of pharmacological tools for Mcl-1 inhibition

Platinum derivatives that we currently use to directly (transcriptional regulation) or indirectly (BH3-only protein activation…) inhibit Mcl-1 show a lower efficiency than siRNA. Since siRNA are not (yet) applicable for clinical use, the design of other Mcl-1-targeting agents appears as a major challenge. In order to prepare future clinical trials with BH3-mimetics (post NaviCarbo trial), we will study the interest of various pharmacological

agents, either currently in clinical use or specifically designed to inhibit Mcl-1 activity (innovative drugs), to improve the efficiency of Mcl-1 inhibition to be associated to BH3-mimetics-based Bcl-x_L inhibiting strategies in a more potent, more specific and less toxic manner. A PhD student will be recruited in 2011 (half financial support obtained from ABBOTT, complementary support requested from Low Normandy Region).
This approach includes the study, in collaboration with the chemists of the "Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN)", of the interest of a new family of molecules as Mcl-1 inhibitors, some of them presenting exciting properties as showed by our preliminary results. Associated molecular modelling approach as well as protein-protein interaction studies are currently under development in our partner's laboratories. This multidisciplinary project is under expertise to obtain a three years financial support from Low Normandy Region (Emergence Project).

5. Overall in the progression in the publication rank

We would like to highlight the fact that a clear progression of the level of impact factors has been achieved by BioTICLA internal team of GRECAN from 2006 to 2010. Indeed, the mean impact factor was 3.656 in 2006 for 5 papers versus 4.957 in 2010 with 8 papers. We will strive to continue this progression during the next quadrennial plan.

6. Attractiveness

The committee mentioned: "There is a good potential for attractiveness and efforts. However, no foreign students and post docs were welcomed".
A Chinese surgeon has been welcome for 4 years for a PhD thesis before going back to China for a permanent position. During the past 4 years, the Unit welcomed 3 undergraduate foreign students (Spain, Denmark and Lithuania) for short training periods (3-6 months). Moreover, we are currently studying the possibility to obtain post-doctoral fellowship from Low Normandy Region to attract foreign researchers (miRNA project).

In summary, the construction of BioTICLA Unit in the next five years will integrate all the suggestions of the AERES committee members. Efforts will be concentrated on miRNA and BH3-mimetic projects, associated to a short term "valorise or close" approach concerning the siRNA project. Metabolic and histological imaging competences and activities will be integrated and focused on the scientific priorities of the Unit in the field of ovarian cancers therapeutic care, at the preclinical as well as clinical translational levels.
A reinforcement of the Unit is expected from the institutions, mainly for the interfering RNA projects. Transient recruitments (post-docs and technicians) will also be essential in the next years, as well as the planned reinforcement of the number of accredited research supervisor (HDR) and associated PhD students.
The Unit will also reinforce its position in the context of national networks for research against ovarian cancers (FEDEGYN, GINECO, GINOVA, and hopefully INCa-piloted workgroup). Associated to the very recent recognition by INCa of the early phase clinical trial activity of the Clinical Research Unit of the CLCC F. Baclesse, these elements should be favourable to the development by BioTICLA Unit of effective translational research, from bench to bedside…to bench.

Laurent POULAIN