Biomarqueurs prédicteurs et nouvelles stratégies moléculaires en thérapeutique anticancéreuse

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Biomarqueurs et prédicteurs de nouvelles stratégies moléculaires en thérapeutiques anti-cancéreuses

University Paris 11

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University Paris 11

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2009

Evaluation report

The research unit :

Name of the research unit : Biomarqueurs et prédicteurs de nouvelles stratégies moléculaires en thérapeutiques anti-cancéreuses

Requested label : UMR_S INSERM

N° in case of renewal :

Head of the research unit : Mr. Fabrice ANDRE

University or school :

Université Paris 11

Other institutions and research organization:

INSERM

Institut Gustave Roussy

Date of the visit :

December 16, 2008

Members of the visiting committee

Chairman of the commitee :

Mr. Jacques ROBERT, Institut Bergonié Bordeaux

Other committee members :

Mr. Hervé BONNEFOI, Institut Bergonié, Bordeaux

Mr. Bohdan WASYLYK, University of Strasbourg

Mr. Lhoucine OUAFIK, University of Marseille

Mr. Christiano FERLINI, Laboratory of antineoplastic, Rome, Italie

Mr. Federico CAPUZZO, Instituto clinico humanitas, Milan, Italie

Mr. Tito FOJO, National cancer institute, Bethesda, USA

CNU, CoCNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) representatives :

Ms. Jane-Lise SAMUEL (INSERM)

No CNU representative was available on the day of the visit

Observers

AERES scientific representative:

Mr. Charles DUMONTET

University or school representative:

Mr. Dominique EMILIE, Université Paris 11

Research organization representative :

Ms. Chantale LASSERRE, INSERM

Evaluation report

1 • Short presentation of the research unit

The Unit has a total of 26 members including :

- 2 researchers with teaching duties, including 1 PU-PH and 1 MCU
- 1 full-time researcher (CR1 INSERM-
- 8 hospital practitioners [PH] devoting 20-30% of their time to the Unit); a total of 5 among them are habilitated to lead research programmes (HDR);
- 8 technicians and engineers, including 4 on short term contract
- 2 post-doctoral fellows
- 5 PhD students, including 4 MD

In the past 4 years, a total of 183 publications, communications, conferences or book chapters contain the name of at least one staff member, 60 of them being directly related to the translational research activity of the constituting groups. Lead (1st or last) positions are found in approximately 10 publications in major journals (N Engl J Med, J Clin Oncol, Lancet Oncol, Clin Cancer Res). A total of 4 patents have been registered.

2 • Preparation and execution of the visit

The visit took place on December 16th 2008, from 9.30 until 16.30.

The applicant director presented the past accomplishments of the various structures that have decided to merge for this application and the overall strategy of the Unit. This was followed by the scientific presentations of the three specific aims by the group leaders. After lunch, the different categories of personnel included in the project (students and post-docs, technicians and engineers, researchers) were interviewed by the Committee. A debate was then held with a representative of the scientific council of Université de Paris 11 and the two heads of research at Institut Gustave-Roussy (IGR). After the private meeting of the Committee, a rapid debriefing took place with the applicant director.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The participants of the application for this new INSERM Unit were previously inserted in different structures, all present on the site of IGR, and all of them had an activity in the field of translational cancer research: there were 4 organ oriented groups (breast, lung, colorectal and prostate) and 4 core facilities working globally for research at IGR. These groups have produced an impressive amount of work in the past four years with a total of 183 publications, communications, conferences and didactic reviews. It is difficult, however, to evaluate the personal contribution of every staff member of the Unit because of the collaborative aspect of most of the scientific production, both at the level of IGR and at the national and international levels. However, this also indicates an excellent insertion within the international scientific community.

The project of the Unit is devoted to the identification of molecular predictors of tumour response to treatment (Aim 1), to the subsequent validation of new targets for cancer treatment (Aim 2) and to more specific validation of biomarkers in blood (Aim 3). The overall objectives of the Unit are translational, i.e. they aim at providing strong new evidence for the clinical use of molecular markers of response, the ultimate goal being the individualisation of cancer treatments ("getting the right drug into the right patient"). Starting from these identifications, the possibility of precise interventions for circumventing resistance to specific agents can emerge, allowing the development of clinical trials for validating the concepts. The third objective appears less prominent than the two other ones and may appear more technically oriented than hypothesis-driven.

Across these 3 general objectives, there still remains the 4 major cancer localisations considered, originating from the 4 previous clinical groups. They appear of unequal importance, both in terms of the work already conducted and the achievements obtained. Whereas all the clinical research forces of IGR in breast and lung cancer are integrated in the project of the Unit, it seems that this is not the case for colorectal cancer and this might be a weakness of the project not to have attracted the leading force of IGR for this disease. On the contrary, the insertion of the clinical groups within a single research unit will enforce their interaction and cooperation and allow the development of target-oriented research rather than organ-oriented research.

Independently from the 4 clinical groups, the Unit will depend upon the core facilities existing at the IGR since 2006: molecular pathology, cytology and biopathology, cellular biology and immunology, centre for biological resources, in addition to those which were already present on site: functional genomics, biostatistics. Several members of these facilities are participants in this Project and this will clearly facilitate the interactions and cooperation between biologists and clinicians. However, as a consequence, they have other tasks to perform, both for other research groups of IGR, or for routine activities. Conversely several senior biologists of the IGR have not been attracted for the creation of the Unit and this might be a drawback if one considers that the need of basic science is high when it comes to molecular biology. Depending upon external services provided by shared core facilities might not be an ideal situation.

It thus appears that only one member of the Unit is a full-time researcher. All others are either clinical oncologists (with an important and productive activity in patient care – but this in turn allows patient accrual for the studies), or biologists/pathologists also involved in routine activities. The expectations of new recruitments for the Unit include a molecular pathologist, 1.5 FTE bio-informatician, and the hope of attracting new post-docs. One can wonder whether the attraction of full-time researchers at a high level in molecular biology would not be a priority for the Unit at a very short term.

The collaborations already engaged by the different clinical groups are impressive; they include academic collaborations with international institutions, participation in consortiums devoted to clinical research (national and international), pharmaceutical and biotechnology companies which can directly sponsor several projects. The international renown of all staff members of the Unit is to be acknowledged as well as their willingness to promote their projects through collaborative efforts.

4 • Specific appreciation team by team and/or project by project

Aim 1: "Discover molecular predictors of drug efficacy and candidate therapeutic targets"

The strategy developed by the groups is clear and adequate: (i) identify potential predictors; (ii) build a model; (iii) validate the predictor on large prospective studies. The important recruitment of IGR in the four tumour localisations allows to anticipate that this approach will be successful; this has already been the case for several "biomarkers" such as ERCC1 expression for cisplatin sensitivity in lung cancer. Four specific projects are to be performed using this strategy: (1) in lung cancer, pursue the identification of determinants of cisplatin efficiency at the level of DNA repair proteins using genomic approaches in addition to the immunohistochemical approach already developed; and extend the studies to other cisplatin-sensitive tumours such as ovarian cancer; (2) in prostate cancer, pursue the validation of the 244-gene signature of docetaxel sensitivity already elaborated, and extend the prospect to breast cancer which is a common target for docetaxel treatment; (3) in breast cancer, elaborate and validate a signature of endocrine therapy efficacy, starting from retrospective samples available in the tumour bank; (4) in colorectal cancer, elaborate a SNP signature of drug efficacy and/or toxicity (few details have been provided concerning the SNP array that will be used). For each project, the people or core facilities involved or required are clearly defined. There is no doubt that the research plans proposed will lead to the identification and validation of new markers that will impact routine cancer therapeutics, at least for some tumour localisations.

Aim 2: "Perform functional validation of candidate targets"

The strategy developed by the groups is situated downstream the results obtained at the previous step and aims, from identified targets, (i) at validating them by a siRNA approach in vitro; (ii) at exploring the activity of small molecules on in vitro models; (iii) at studying the antitumour effect of these molecules in mouse

models. Here again, several specific projects are presented following this strategy: (1) in lung cancer, modulation of ERCC1 expression by anticancer drugs (based upon the fact that ERCC1 is a determinant of cisplatin efficacy); (2) in breast cancer, develop strategies for FGFR1 receptor inhibition (based upon the fact

that FGFR1 is amplified in 10% breast tumours) and for alternative splicing inhibition (microarray studies have revealed the involvement of spliceosome assembly components in breast cancer). This approach appears as highly original and should be especially supported; (3) in prostate cancer, using RNA interference, identify potential targets for circumventing resistance to docetaxel at the level of BIRC proteins of the IAP family. The approaches developed using Aim 2 strategy are adequate; this research is more "risky" and is based on hypotheses that may or may not be verified; but they may lead to the discovery of new therapeutic tools.

Aim 3: "Validate molecular predictors in blood samples"

This aim appears less strategic for the Unit and could be considered as methodological rather than truly scientific. Circulating tumour cells are only a tool in this respect, which has not been validated for biomarker purposes and strongly depends upon the biotech companies developing these techniques. Although this technology has to be studied and the results it may provide validated according to strict rules, it appears difficult to consider this third component of the Project as a scientific goal, but rather as a potential core facility for the projects developed in the two other components of the Project.

5 • Appreciation of resources and of the life of the research unit

The Unit will benefit from appropriate location within IGR; the laboratory surface area is of about 400 m^2, with access to shared meeting room facilities of IGR. The existence of shared core facilities present on site will give an important positive advantage to the Unit for many types of studies: morphological, genomic, bio-informatic tools will be available close to the research laboratories.

The finances of the Unit already come from various complementary sources, including national and international academic grants, industrial contracts for several projects and private donations. This funding is expected to be maintained at an adequate level.
Scientific animation of research already exists in the Unit, with general "data meetings" every month, project meetings bimonthly for each project, management meetings every month and seminars organised on a regular basis.

Very positive insights have emerged from the young researchers (graduate students and post-docs) and from the supporting personnel (technicians and engineers). There is a clear common willingness to work together to the benefit of a consistent project. It should be mentioned that all the supporting personnel belongs to IGR and that no University or INSERM/CNRS personnel is part of the Unit. This might create problems if IGR would like (or be forced) to reorient their activities. It would be wise to take into account the specific research activities of this personnel for their evaluation and promotion inside the IGR career organisation.

6 • Recommendations and advice

– **Strong points** :

The past clinical structure of the groups working on biomarkers at IGR is being replaced by a thematic structure, which creates more interactions and conceptual approaches; this will benefit to the whole project.

The large clinical and biological databases that are retrospectively available, as well as the impressive potential clinical recruitment, constitute an invaluable basis for the work of the Unit. (3) The long-term view on cancer therapy that is carried by the applicant director is acknowledged by the scientific community and appears as a guarantee of the relevance of the future projects of the Unit.

— **What needs to be improved :**

The number of (good) projects appears to be incommensurate with the size of the Unit, especially when considering the small number of full-time researchers; the individual merits of the group leaders should be translated at the level of the group. (2) There may be some qualitative disproportion between the various projects, and for some of them, the Unit may appear less competitive than for others; some choices have to be made. (3) There is a need for developing the bio-informatic skills independently from the Biostatistics unit of IGR. (4) There is also a need for the recruitment of senior molecular biologist(s) able to create the tools that will be needed for the validation step required after the identification step; this step of validation should be developed inside the Unit and not through collaborations. (5) The projects may appear too independent from each other; a right step has been made (replacing clinical groups by global aims) but the effort should be maintained.

— **Recommendations :**

All the members of the committee agree that the proposed project is of very high value both in terms of the scientific content and of the expertise and skills of the proponents. This project appears as an excellent project which should be supported. There exist very few examples of units devoted to translational research with such high-level skills.

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

UNIVERSITÉ
PARIS-SUD 11

Le Président de l'Université Paris-Sud 11

à

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

Orsay, le 9 octobre 2009.

N/Réf. : 333/09/GCo/LM/LS

Objet : Rapport d'évaluation d'unité de recherche
N° S2100012411

Monsieur le Directeur,

Vous m'avez transmis le 12 juin dernier, le rapport d'évaluation de l'unité de recherche «Biomarqueurs prédicteurs et nouvelles stratégies moléculaires en thérapeutiques anticancéreuses», et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions.

Le directeur de l'unité n'a pas souhaité apporter de commentaires au rapport.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma sincère considération.

Guy COURRAZE
Président

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