Génomique fonctionnelle des tumeurs solides

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Functional Genomics of Solid Tumors

Of University Paris 5

March 2009

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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 : Functional Genomics of Solid Tumors

Requested label : UMR_S INSERM

N° in case of renewal : UMR_S 674

Head of the research unit : Ms. J. Zucman-Rossi

University or school :

University Paris 5

Other institutions and research organization:

INSERM

Date of the visit :

March 6th 2009

Members of the visiting committee

Chairman of the commitee :

M. Claude SARDET, CNRS, IGMM UMR 5535, Montpellier

Other committee members :

M. Philippe MERLE, INSERM U871, CHU Lyon

M.Jean-François DUFOUR, Klinische pharmakologie, Berne, Switzerland

M. A. KANE, Brown University, pathology and medicine laboratory, Providence, USA

M.Massimo LEVRERO, Sapienza University of Rome, Italy

M. Eamonn MAHER, Medical genetics, University of Birmingham, UK

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

M. Philippe MONTCOURRIER, CSS, INSERM

M. Bernard DUCOMMUN, CNU

Observers

AERES scientific representative:

M. Charles DUMONTET

University or school representative:

M. Bruno VARET, Université Paris 5

Mme Marie-Claude LABASTIE , Université Paris 5

Research organization representatives :

Ms. Chantal LASSERE, INSERM

Ms. Danielle MURCIANO, INCA

Evaluation report

1 • Short presentation of the research unit

— Number of lab members: 20 including

- o 2 researchers
- o 4 researchers with teaching duties: 3 PU-PH, 1MCU
- o 1 PH
- o 3 post-doctoral fellows
- o 5 PhD students, all with a fellowship
- o 6 engineers and technicians: 2 IE, 1 TS, and 3AI on short term contracts

— Number of HDR : 5, 4 of them being PhD student advisors

— Number of students who have obtained their PhD during the past 4 years: 5

— Number of lab members who have been granted a PEDR : 0

— Number of "publishing" lab members : 6 out of 6

2 • Preparation and execution of the visit

The present unit is composed of two teams: the team working on neurofibromatosis (NF) tumors and development was not evaluated here since the team leader recently moved to California to create a new lab One should regret that France lost this bright scientist with unique expertises in animal models. The remaining team members working on meothelioma chose to merge with the other team to, collectively, present a new project. They will be joined by clinicians from the HEGP and from Necker hospital working on Renal Cancer.

The review took place at the present site of implantation of the unit (St-Louis Hospital). Oral presentations of the research program were made by senior and junior scientists, as well as by clinicians, participating in the new project. These presentations have described the highlights of the past three years achievements of the three groups and outlined the ongoing and future research directions of the new unit.

The review group met the students / post-doc, the technical staff and the representative of the Paris 5 University, Inserm and INCA.

All members of the review group were present from the beginning to the end of this visit and have returned independently their argumented comments to the chairman.

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

The research unit is currently located at Centre Hayem/ Hopital St-Louis/Paris7. It was composed of two teams working on various cellular, molecular, developmental and genetic aspects of neurofibromatosis (NF, team 1), mesothelioma and of liver cancers (team 2), respectively. In 2007, the leader of team 1 moved to California to develop his projects on NF and was replaced by the current project leader as head of this unit. Team 1 members working on mesothelioma choose to merge with team 2 to, collectively, present a new « one team » project.

Overall, this unit appears as a highly interactive team of basic and clinical researchers whose goal is to identify new diagnostic and prognostic molecular markers of liver cancer and mesothelioma using genomic profiling as well as functional studies. They do so by driving collaborative networks throughout France to use very valuable tumor banks with complete clinical and pathological correlations.

Their attempt to work closely with internationally-recognized pathologists and epidemiologists is a major strength and unique in genomic approaches to solid tumors. Recent progress in the genomic analysis of these solid tumors has been most successful for liver tumors, with slower progress for malignant mesothelioma. Notably, the liver tumor team has achieved significant progress during the last four years in identifying novel candidate tumor suppressors and oncogenes and by developing a new molecular classification for hepatic adenomas with significant implications for targeted therapy. Collectively, scientists and clinicians involved in this project have an outstanding publication record, a long list of invitations to the best international scientific meetings, and overall have recently greatly contributed to the development of research on cancers (see section 4 below for details). This places this unit in excellent position to increase in size during the next four years and to apply the same successfull strategy to other types of tumors, starting with mesothlioma. In addition, a group of clinicians from the HEGP and from Necker working on Renal Cancer, is willing to join the unit as soon as possible to benefit from its genomic profiling expertise, and is therefore considered as being part of the new project. The combination of the currently available genomics expertise and the clinical trials expertise in kidney cancer provides great potential for translational studies to identify molecular markers for prognostication and choice of therapy.

In general, the evolution of this team to include closer collaboration with active clinical researchers and to further improve interactions between basic and translational researchers is a major strength and is essential for achieving their future goals.

In summary, this project will include three sub-groups which envision the same line of research on cancers of various origins. The successfull strategy used by the project leader in liver tumors will be used as a matrix for future studies on mesothelioma and renal cancers. To fulfill these collective and ambitious scientific objectives, the unit wishes to move to an other campus offering a better context for projects targeting solid tumors and aiming to combine genetic, bioinformatic and biological approaches. Additional space and resources would allow them to grow and recruit younger scientists to build a critical mass of basic cancer researchers. Accordingly, they are currently responding to a 2009 call made by Institut Cochin/University Paris 5 to attract additional research units working on cancer on the Cochin campus. Undoubtedly, the technological platforms and interdisciplinary laboratories present in this prestigious Institute fit perfectly with the scientific objectives of this project and should enable this team to incorporate a more functional approach into their genomic analyses. The University representative confirmed that the university actively supports this operation, notably, through the creation of a full professor position (PU-PH) proposed to the project leader. Overall, this appears to the review committee as an excellent scientific operation for both parts.

4 • Specific appreciation team by team

This team will includes three sub-groups that vision the following lines of research :

Liver Tumors:

This group has been outstandingly successful in using genetic approaches to the classification of hepatic tumours. Their work has provided the rare combination of both important insights into the basic biology of neoplastic processes and clinically-relevant molecular markers for the prognostic stratification and diagnostic classification of benign hepatic tumours. This work is clearly outstanding and has changed in a few years the way one looks at benign and malignant liver cancers. This work also led to the identification of mutations in novel signaling pathways involved in tumorigenesis. This work have been published widely in the most competitive and prestigious peer-reviewed journals (Nature, Hepatology, J Hepatology, Gut, Cancer Research) and the group is the driving force in many excellent ongoing collaborative networks. Their future projects are along the same line and will try to bring further functional and translational validations of the importance of these pathways in cancer, while they tackle other sub-types of liver cancers. This project is scientifically excellent and timely since it is clear that the incidence of liver cancers is increasing and it has been recently shown that targeted therapies interfering with signalling pathways improves the survival of patients with liver carcinomas. Nevertheless, on the genomic aspect of this program, the review group encourages this unit to pay more attention to how newer technologies (e.g. second generation sequencing) might be utilised for the proposed studies.

Collectively, this group appears well organised, harmonious and attractive, i.e. in a good position to recruit new scientists and clinicians around its thematic and to foster new fruitful collaborations. Indeed, the committee estimates that there is an urgent need to attract additional scientists with permanent and non-permanent positions to fully exploit the numerous and exciting opportunities presented, as well as to perpetuate their very valuable expertises in the long term. Notably, a biostatistician / bioinformatician would be a great asset to the unit.

Mesothelioma :

The incidence of mesothlioma is rapidly increasing in France and although it is considered as newsworthy, too few groups are working in this field. Noteworthy, this is one of the rare labs in France that has made several important contributions in this field : i/ They have established key collaborations throughout France that led to the constitution of a very valuable tumor bank with complete clinical and pathological correlations. This attempt to work closely with internationally-recognized pathologists and epidemiologists is a major strength and unique in genomic approaches to malignant mesothelioma. Their project is now at the stage to utilise this very valuable ressource to apply a similar approach to that employed by the liver group to define the transcriptional profile and genome copy number characteristics of mesothelioma. Although they were careful not to overinterpret preliminary and unpublished data, there were hints during the on-site visit that this strategy has already provided novel information. The visiting committee strongly encourages this group to pursue its efforts in this direction since it is anticipated that any novel information on the pathways altered in mesothelioma should give the group visibility in the arena of cancer biology and should open urgently needed new directions for biological, classification and clinical studies on this cancer. ii/ They also established one of the rare animal models that develop mesothelioma. Some aspects of this project (complex KO models) are suffering from the departure of team 1, and although advances have been made with these animals it might become difficult to go further in this direction since the headcount devoted to this topic appears at present too restricted to develop this type of long-term project in a competitive way. The review group encourages the team to freeze/slow down temporarily its studies on such models while waiting for additional information on signaling pathways altered in mesothelioma.

Since the very competent scientific leader of this group is due to retire during the next mandate of the unit, this project is clearly and urgently in need of a younger scientist who could offer long-term leadership on the experimental aspects of this project and "bridge the gap" between the clinicians and the technical and non-permanent staff.

Renal cancers :

A group of clinicians from the HEGP and from Necker working on Renal Cancer is willing to join this unit. The leader of this group has experience of both clinical and laboratory based research on prostate and Renal cancers. As a clinical investigator he has been prolific with several publications in the highest impact factor journals describing the results of clinical trials (N Engl J Med, J Clin Oncol, Clin Cancer Res). These achievements attest to his ability to organize patient recruitment and specimen procurement. A very large number of kidney cancer (RCC) samples from patients treated with anti-angiogenic agents are currently available for analysis and a large prospective collection has been initiated. There is here an excellent opportunity to use similar approaches to those adopted for the liver tumor studies in order to identify prognostic markers of response to angiogenic therapies for advanced RCC. This is a very important clinical question and accurate biomarkers for the identification of patients likely to respond to treatment with very expensive therapies would be a major advance. The review group strongly support this project as it estimates that it is timely and represents an important strategic opportunity for the future unit, the combined expertises placing this team in good position, worldwide, to contribute unique results to translational research on RCC. Our only concern about this project is that the planned headcount of scientists devoted to this topic appears too limited to develop rapidly in a competitive way. A strong and immediate effort of the unit to recruit high-quality, young scientists to work on this project is necessary.

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

There are no causes for concern in the current direction and management of the personnel and resources. Most participants to this project have an excellent track record in attracting competitive private and public external fundings. The principal investigator of the Unit is to be congratulated.

She is an energetic and imaginative leader, and a productive scientist, who has the support of team members at all levels and gets the most out of her staff. This unit appears well organised, harmonious and seems to work in a pleasant friendly atmosphere. The training and support for graduate students and postdoctoral fellows is excellent. In summary, the project leader has all the leadership qualities and she and her co-applicants appear to be keen to work together and develop and expand this new unit. The arrival of a group working on renal cell cancer is a very positive step that should reinforce the translational research expertise and clinical visibility of the unit.

However, concerning future projects, the effort to recruit high-quality, young scientists to this team to expand their capacity for the proposed experimental studies must be intensified and accelerated or there will be a risk to lose this momentum and leadership in genomics of solid tumors. This will require additional support from the « tutelle » (INSERM/University/INCA) to obtain additional lab-space, scientific staff (MCU ?) and financial resources, possibly through its installation within a larger research center such as Cochin Institute.

6 • Recommendations and advice

Strong points:

Overall, this is an excellent, timely and forward looking application from a team that is in the best worldwide position to contribute unique results to the field of solid tumors. As so, this project justifies funding and full support from participating institutions.

Weak points:

The number of full time researchers is low when considering the number of ambitious projects planned.

Recommendations:

The committee recommends to identify space and resources as soon as possible to move this research team close to a larger research center with modern core research facilities and platforms, and broader biological expertises.

The committee recommends to appoint several permanent and non-permanent younger scientists that would "bridge the gap" between the well-established applicants, the clinicians and the remaining staff, i.e. develop a strategy to sustain interactions of the physician-scientists working on these research projects. This point is urgent for the mesothelioma and RCC projects that have great potential but will require stronger investment in manpower (scientists) to fully achieve the opportunities presented. A permanent biostatistician / bioinformatician would be a great asset to most parts of this project. Inserm/University/Inca should provide additional support on this question.

On the technological/genomic aspects of this program, the review group encourages this unit to pay more attention to how newer technologies (e.g. second generation sequencing) might be used for the proposed studies.

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 DESCARTES

Le Président
Axel KAHN

Paris, le 7 avril 2009

DRED 09/n° 145

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité « **UMR-S674 Génomique fonctionnelle des tumeurs solides** » rattachée à mon établissement.

L'Université s'est déjà préoccupée de la localisation de cette équipe dans un centre de recherche (Cochin). Si l'équipe préfère une autre localisation, elle devra s'assurer d'y trouver les plateformes dont elle a besoin.
Concernant la Biostatistique/Bioinformatique, l'équipe, une fois transférée à Paris Descartes, aura accès au service commun de Biostatistique/Bioinformatique dont le développement est une priorité de l'Université pour le contrat quadriennal 2010-2013.

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

Le Président de l'Université

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UNIVERSITÉ
PARIS DESCARTES

DIVISION DE LA RECHERCHE
ET DES ECOLES DOCTORALES

Paris, le 7 avril 2009

UMR-S 674 Génomique fonctionnelle des tumeurs solides

Retour sur le rapport du comité AERES – Observations de portée générale

Pas d'observations.