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

Section des Unités de recherche

AERES report on the research unit

Genetics of cancer and of neuropsychiatric diseases

From the

University of Rouen

INSERM

November 2010

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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 : Genetics of cancer and of neuropsychiatric diseases

Requested label : UMR_S

N° in the case of renewal : UMR_S 614

Name of the director : M. Thierry FREBOURG

Members of the review committee

Committee chairman :

M Olivier DELATTRE, Institut Curie, Paris, France

Other committee members :

M Alex DUVAL, University of Paris, France

M Marc SANSON, University of Paris, France

M Ian TOMLINSON, Wellcome Trust Centre for Human Genetics, Oxford, UK

M Efthimios M. C. SKOULAKIS, Institute of Cellular and Developmental Biology, Vari, Greece

Ms Kerstin KUTSCHE, Institut für Humangenetik, Hamburg, Germany

Ms Valérie CORMIER-DAIRE, Université Paris Descartes, Paris, France (CSS INSERM)

M Michel GOOSSENS, Université Paris Est France (CNU)

Observers

AERES scientific advisor :

Jean ROSENBAUM

University, School and Research Organization representatives :

M Cafer OZKUL, University President

Ms Nicole ORANGE, University Vice-President

Ms Chantal LASSERRE, INSERM representative

M Hubert VAUDRY, Director of the IFR

Ms Virginie CHARMOY, local INSERM representative

M Bernard DAUMUR, Director of the hospital

M Pierre FREGER, Dean, Faculty of Medicine

M Pierre JOLY, Vide-dean, Research, Faculty of Medicine

Report

1 • Introduction

- Date and execution of the visit

The visit was organized on November 23rd 2010. After a general presentation of the unit, Thierry FREBOURG, Jean-Michel FLAMAN and Jean-Baptiste LATOUCHE presented the cancer genetics project then Thierry FREBOURG, Magalie LECOURTOIS and Alexanda MARTINS presented the neurogenetics projects. After meeting with the institutional representatives, the site committee splitted into three subgroups to meet with PhD students, engineers and technicians and researchers. The visit ended with a closed deliberation of this committee.

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

The new unit is a joint structure between INSERM and the University of Rouen and is in direct continuity with the previous unit. The clear scientific unifying criteria for the unit is human genetics with two groups, one on cancer genetics and the other on the genetic bases of neuropsychiatric diseases. The unit has a very strong structural role for biomedical research, both in Rouen and more widely in the region Normandie. It is expected to be a major partner in the forthcoming Institute for Research and Biomedical Innovation of Haute Normandie.

- Management team

Each group includes different projects that are conducted either by the group leaders themselves or by permanent scientists. In addition, each project includes clinician-scientists that enable a very tight link with the hospital. The director is assisted by a secretary. The whole laboratory appears as very united, using and exchanging on concepts and methodologies in genetics. Group and lab meetings are organized on a weekly basis.

- 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)	8	7
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)	6	8
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	7	
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	
N7: Number of staff members with a HDR or a similar grade	6	6

2 • Overall appreciation on the research unit

- Summary

The Unit is composed of two teams. Team n° 1 : Genetics of cancer headed by Thierry Frebourg develops a project on genetic basis of colorectal cancer, the Li and Fraumeni syndrome, immuno-therapy of colorectal cancer and responses to therapy in colorectal cancer. Team n° 2 : neurogenetics headed by Dominique Campion addresses topics on the genetic basis of dementia with a particular emphasis on Alzheimer disease, use of Drosophila to investigate mechanisms of neuronal cell death, SMA and splicing, CNV and mental retardation and psychosis. The unit has contributed to important developments and findings in the last four years. Of particular note are the development of ex vivo splicing assays that are used by both groups, the progress in understanding the molecular bases of Li-Fraumeni syndrome, hereditary colorectal cancer and Alzheimer disease, the search for causal CNVs in mental retardation and psychoses, the use of Drosophila as a model system to investigate neurodegenerative diseases.

- Strenghts

- Excellent integration in the medical community. In addition to the principal investigators of the project, a total of 12 physicians are partners of the unit and involved in the projects. They bring to the unit critical clinical expertise.

- Excellent expertise of the group leaders in human genetics, cancer and neurodegenerative disorders

- Strong interest of the unit in technological developments and valorization. Some tools developed by the unit are used by many French laboratories (QMPSF technique, Alamut software…).

- Specific interest in mutations generating splicing defects, which clearly constitutes an originality in the French genetic landscape.

- International visibility in studies of Li-Fraumeni syndrome and Alzheimer disease.

- Opportunities

- Leadership role in the planned Institute for Research and Biomedical Innovation of Haute Normandie.

- Well-organized continuum between research, molecular diagnostic and the clinics.

- Development of a strong partnership with the cancer genetics unit in Caen.

- Weaknesses

- Some projects do not have a sufficient critical mass, or the appropriate environment to be really competitive at the international level.

- Threats

- There is a risk of dispersion due to the number of projects

- The difficult choice between genetic projects, which require a strong investment in bioinformatics and a scaling up of the cohort of patients, and functional investigations of the identified mutations.

- Recommendations

- To scale up some genetic projects

- To encourage permanent scientists who are not group leaders to take the lead on some projects and consequently to publish as senior authors.

- To define a clear strategy for the creation of new groups, being either headed by scientists of the unit as emerging group leaders, or attracted from the outside.

- Question the follow-up of the immunotherapy and anti-EGFR sensitivity programs

- Put emphasis on the functional characterization of mutations suspected to alter splicing.

- Should Drosophila be the model system to be prioritized for functional analyses of variants, this team should be reinforced.

Consider electrophysiology as a complementary system.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	8
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	4
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	6
A5: Number of PhD granted during the past 4 years	9

3 • Specific comments

- Appreciation on the results

During the past 4-5 years the unit has contributed to important results.

Strong examples in the cancer genetics field are:

- The study of the genetic interaction between MDM2 and p53 in Li-Fraumeni syndrome.

- The update of the clinical criteria for Li-Fraumeni syndrome.

- The contribution of germline rearrangements to the spectrum of BRCA2 mutations.

- The relevance of KRAS mutations for the management of colorectal cancer patients.

- The characterization of BRCA1, BRCA2, MLH1, MSH2 unclassified variants for splicing effect.

- The role of p53 mutation to predict response of colorectal cancer to Cetuximab therapy.

Strong examples in the neurogenetics field :

- Identification of APP locus duplication in early onset Alzheimer disease which clearly constituted a major breakthrough in Alzheimer disease research. The princeps paper has been followed by a comprehensive characterization of the clinical and pathological features of APP-duplication linked Alzheimer disease.

- Association of a PRODH CNV with autism

- Identification of cytoskeleton proteins as potential modulators of Tau-induced neurodegeneration in Drosophila.

- The study and characterization of the genetic interaction between SMN1 and SMN2 variants.

In addition to these scientific contributions, it is important to mention that the unit has developed technological or bioinformatic tools (QMPCF, Alamut) that are widely used internally but also more broadly by the scientific community in France.

The unit seems to have a strong collaboration with a local bioinformatics group. The unit has recently applied to the EQUIPEX call with the aim to develop bioinformatics tools to be used for NGS analysis. If not granted it is not clear what will be the plan B for NGS analyses.

Importantly, the unit has also been directly involved in the creation of three start-ups.

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

The two group leaders have unambiguously national and international reputations. The visibility of the other PIs in the unit appears more limited.

No information is provided on awards.

The participation as invited speakers to international conferences is good on cancer predisposition (mainly Li-Fraumeni syndrome) and splicing.

The unit has been very successful in raising funds from national research agencies (INCa, ANR, charities).

The participation to international networks is more limited. In particular there is no participation to Europe-funded projects.

Most PhDs and post-docs of the unit come from the surrounding region meaning that the unit may have difficulties to recruit outside its neighborhood.

Socio-economic partnerships are excellent with the creation of three start ups.

The two group leaders are strongly involved in training activities

- Appreciation on the management and life of the research unit

Human genetics clearly constitutes the strong unifying link between both groups. All the technological developments are shared between the two groups. The unit has a very important structuring role for biomedical research in the hospital and reciprocally the hospital is clearly convinced that it must invest to support this unit.

The scientific life of the unit relies appropriately on weekly group meetings and lab meetings.

- Appreciation on the scientific strategy and the project

One can be very confident on the ability of the laboratory to generate new, important and useful results. The unit is facing very classical concerns to define its long term strategy. Indeed, almost by definition, genetic groups can hardly define a priori which genes will be revealed by their analyses and hence which assays will be required for functional follow-up analyses.

The neurogenetics group has clearly identified Drosophila as a model system to investigate the role of mutations. This appears to the committee as a sound option but to be really competitive, the Drosophila structure of the unit may need to be strengthened with additional staff.

Some projects (oligogenic determinism of colorectal cancer) require being scaled up, in particular through collaborations, to reach the appropriate statistical power.

The analysis of splice variants, both in cancer predisposing genes and in neurogenetic disorders, is an important strength and an original aspect of the unit. The present step is to investigate the mutations using both the splice assay that has been developed and the analysis of appropriate tissues from patients. It is not fully clear what will be undertaken following this important, yet descriptive step.

In light of the number of projects of the unit, some projects, like immunotherapy and response to therapy, appear less competitive and hence should be revisited.

4 • Appreciation team by team

Team: Neurogenetics

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2.5	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1.5	1.5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1.5	1.5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3.5	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	1.5	2

- Appreciation on the results

Overall the production of papers was quite good: they had 33 papers in international journals, with at least one member of the team as a first and/or last author. The Nature Genetics paper was a highlight and a breakthrough in the field of Alzheimer's disease (273 citations to date). The paper in Archives of General Psychiatry highlighted the genomic approaches to map genes involved in autism, schizophrenia, and mental retardation and will be significantly referenced for some time. However, the vast majority of the papers are coming from the team leader and more junior members of the team must be helped and encouraged to publish more.

The team has long-lasting, strong and stable interactions with neurologists of the hospital and this is a clear and highly productive advantage that differerentiates this team from others of similar focus and orientation.

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

It is a well recognized lab, the team has a good reputation and they have a good ability to attract money from national institutions (in particular a large grants from the Plan Alzheimer, the foundation Alzheimer and the AFM and other grants from ANR, Gis maladies rares or fondation de France). They are strongly encouraged to seek funding from abroad, within EU and outside.

With respect to attractiveness of the team, clearly the current staff is barely adequate for the number and scope of ongoing projects and there seems to be little recruitment to the team from outside Normandie and Paris. Notable exceptions to this pattern are the recruitment of a foreign scientist and recently of a foreign post-doc to the group of Dr Lecourtois. Additional effort to increase attractiveness to students, post-docs and potential faculty outside the current recruiting vicinity must be made.

The publication of collaborative papers indicates good participation to international scientific networks and it is puzzling how this is not translated to European Union and International funding efforts.

A strong activity of the team is their ability to translate their research into organized databases and then to clinically useful tools (e.g. the minigene assay).

- Appreciation on the scientific strategy and the project

Collectively, the scientific strategy is very well appreciated. The long-term projects are feasible, but a decision has to be made on whether the scale of the screening projects has to be increased or more extensive functional studies have to be implemented. For functional genetics it is clear that additional students/post-docs and even a new group will be necessary. This is exemplified by the Drosophila projects that will benefit greatly from increased personnel and even a new complementary analysis system, such as electrophysiology. With respect to the screening project, validation of their genetic results is necessary before moving to functional studies.

- Conclusion :

  - Summary

Overall, this is an internationally recognized group with promising future plans who will benefit greatly from being more extrovert with respect to international collaborations and successfully seeking EU or International funding. This will make an even greater impact of their work.

  - Strengths and opportunities

Strengths are the close association with the hospital, excellent national recognition and impact. There are strong opportunities to develop functional assays for their clinical findings that lead to even better international networking and recognition.

  - Weaknesses and threats

There are too many projects for too few people.

There is a question as to what follows after characterization of the sequence variants which affect splicing.

The formality and frame of their interaction with the bioinformatics group is not clear.

  - Recommendations

They should increase the personnel or focus resources and efforts to the most promising projects.

Team : Cancer Genetics

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5.5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2.5	2.5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3.5	3.5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3.5	
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	3.5	4

- Appreciation on the results

  - Relevance, Originality, Quality:

Highly relevant translational research, especially in testing of variants of unknown significance (VUS) in breast and colon cancer families.

Reference laboratory for Li-Fraumeni syndrome

The quality of work in molecular diagnostics is high

The project of biomarker of response to therapy was not presented. This is a highly competitive field and it is important for the team to assess whether the number of cases to be investigated will be appropriate to reach a sufficient statistical power.

Results of immunotherapy project based on CEA-based immunotherapy were recently published. They indicate that CEA may not be the appropriate target for immunotherapy. The new project that was presented was not fully convincing and need to be revisited.

An extreme originality is difficult to achieve in such a highly applied field

  - Impact:

The publications and other output are very good/good, taking into account the difficulty of publishing highest-impact manuscripts in the field of translational medicine (a total of 33 manuscripts with first or senior authorships from the group and 29 collaborative papers). Most publications are in good specialty journals (J Med Genet, Br J Cancer, Human Mutation) with a few in high-ranking journals such as J Clin Oncology or Gastroenterology.

  - Partnerships:

Locally strong collaborations with clinical departments vital to work of laboratory.

The cancer genetics group collaborates with most cancer genetics French groups, in particular in the fields of breast and colon.

Good national collaborations; strength of international collaborations less strong.

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

The participation in international conferences is acceptable.

There are few international students or Post-Docs which probably reflects a common problem outside major cities in France in recruiting high-level scientists at all levels.

The national fund-raising is good, with multiple staff successful (large grants from the INCa on the "translational research" call, numerous other grants from Fondation de France, Ligue Nationale Contre le Cancer, Cancéropole Nord Ouest). International funding is however very limited.

The participation in national networks is very good; more limited international participation.

The team has produced several results very useful for clinical diagnostic practice; they have very good socio-economic partnerships.

- Appreciation on the scientific strategy and the project

Important and useful information will undoubtedly emerge from the proposed work, but there are concerns about several aspects of the proposed projects.

Several projects lack clear plan for the future, often manifest as a choice between large-scale screens (e.g. NGS) or strengthening functional studies.

Some projects require greater ambition to build optimally on the sound basis that has been produced, e.g. a plan for following up the splice site changes either genetically or functionally.

The involvement of the full-time senior scientific staff will be critical in the success of individual projects, and these staff should be provided with the necessary resources to develop these.

Some projects need consideration as to their scientific viability in the current location, e.g. oligogenomics without larger sample sizes and clearer medium-term plan, immunotherapy.

The biomarker project was not presented and it is not clear whether this remains an aim.

- Conclusion :

This project has been very successful in areas such as assessment of VUSs and characterization of Li-Fraumeni syndrome. The future plans should build on these successes and the patient cohorts accrued. However, plans should be specified more clearly, with more focus where appropriate (for example, making decisions between large-scale screens in humans and smaller-scale functional analyses in model systems where appropriate.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
GÉNÉTIQUE DU CANCER ET DES MALADIES NEUROPSYCHIATRIQUES	**A**	**A+**	**A+**	**A+**	**A+**
NEUROGÉNÉTIQUE [FREBOURG-CAMPION]	A+	A+	Non noté	A+	A+
GÉNÉTIQUE DU CANCER [FREBOURG-FREBOURG]	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 ROUEN

Fait à Mont-Saint-Aignan
Le 11 avril 2011

Le Président

À

Monsieur Pierre Glorieux
Directeur de la section des unités
de recherche
Section 2 – AERES
20, Rue Vivienne
75002 Paris

Réf : S2UR120001255– Génétique du Cancer et des maladies neuropsychiatriques – 0761904G

Monsieur le Directeur,

Je vous prie de bien vouloir trouver ci-joint la réponse formulée par le directeur de l'U614-Génétique du Cancer et des maladies neuropsychiatriques.

Je profite de l'occasion pour souligner le bon déroulement de la visite du comité d'évaluation de l'AERES.

L'établissement soutient sans réserve cet excellent laboratoire et accompagne son développement.

Ainsi, une chaire mixte Université-Inserm a été créée pour cet Unité dans le cadre d'une politique de redéploiement des supports vacants : le concours de recrutement d'un maitre de conférences est ouvert pour pourvoir ce poste au 1er septembre 2011. J'ajoute que, par anticipation d'un départ à la retraite, un autre poste de maitre de conférences sera ouvert au concours en 2012.

Je vous prie de recevoir, Monsieur le Directeur, l'assurance de ma considération distinguée.

Cafer ÖZKUL

UNIVERSITÉ DE ROUEN

Comments on

The AERES report on the research unit
Genetics of cancer and of neuropsychiatric diseases
From the University of Rouen INSERM

April, 4 2011

We thank the review committee for the quality of the report and the constructive critical comments. Enclosed please find reply to questions, comments and additional information:

p 4, p5 and p8 : Questions on the perspectives in bioinformatics :
- Since the visit of the committee, we have learned that our project on NGS entitled " Creation of a Genomic Center for detection, interpretation of genetic variants and training to NGS data analysis" has not been selected in the context of the Grand-Emprunt Equipex call. Nevertheless, we got in december 2010 the plan B that we had prepared : **we obtained**, in the context of the **plan Etat – Region**, **a funding of 320.000 euros** and, **from La Fondation pour la Recherche Medicale**, **237.980 euros** in the context of a national call. Furthermore, we obtained from the Fondation pour la Recherche Medicale a **salary for an engineer in bioinformatics for 2 years**.
- We have increased our weekly collaborations with the department of bioinformatics of the university of Rouen (Computer Science Laboratory - Data Processing in Biology and Health team LITIS-EA 4108, Prof Thierry Lecroq,; Dr. Helène Dauchel) which, through the MSc Bioinformatics, has trained many engineers in bioinformatics working in France, Europe, Canada, USA. In particular, this narrow interaction has recently allowed **the development of the EVA (*Exome Variation Analyzer*) program** which considerably facilitates the filtering and analysis of data generated by NGS, and we are in the process of finishing, thanks to the EVA program, the analysis of 12 exomes from patients with autosomal form of Alzheimer disease without *PSEN* or *APP* mutations. Sophie Coutant, engineer in bioinformatics is now working full-time in the unit. Furthermore, we also benefit from the expertise of the local company Interactive Biosoftware (http://www.interactive-biosoftware.com/) which had developed, in close collaboration with out unit, the Alamut™ software for mutation interpretation in medical molecular genetics, widely used by molecular genetics laboratories in Europe, North America and Asia. **The combined expertise of the department of bioinformatics and the Interactive Biosoftware company creates an appropriate bioinformatics environment for the implementation and development of NGS planned before September 2011.**
- A **chaire d'excellence Inserm - University of Rouen** has been obtained and will be opened **in 2011** to recruit a PI in charge of NGS programs.

- p6 and p9: Appreciation on the quality of links with international partners :
Although we have developed several scientific and technological international collaborations over the last four years, as demonstrated by the publications, it is right that we have not

participated so far to Europe-funded projects. For the neurogenetics team, since the visit of the committee, we have learned that **our project SMA-Var will be founded by the SMA European consortium**. This will allow us to **recruit a post-doc** who has already been selected (Kathleen Mahias). For the cancer genetics team, considering the **2012 Health theme of FP7** (*I. Biotechnology, generic tools and medical technologies for human health; I.2 Detection, diagnosis and monitoring with a specific focus on personalised medicine applications*), **we have decided to prepare and submit a project entitled "Classification of unclassified variants detected in inherited forms of cancers",** which will be based on our expertise on splicing. Collaborators, who have been contacted and agreed, include Robert Hofstra (University of Groningen), Niels de Wind (Leiden University) and Lene Juel Rasmussen (University of Copenhagen).

p4 and p6 : Question on the anti-EGFR sensitivity and immunotherapy programs

- We are aware that, like for all small to medium size research laboratories, a risk is the dispersion due to the number of projects and one of our permanent concern is to focus our projects on topics on which we have a national and international position. Considering our local position in a university hospital, we also think that we have the responsibility to stimulate the translational research for the benefits of patients. The important advance in the treatment of metastatic colorectal cancer, thanks to the anti-EGFR monoclonal antibodies, and the need to identify predictive markers of therapeutic response, led us in 2006 to create, within the genetics team, a group entiled "Biomarkers - Biotherapies of colorectal cancer" and based on the complementarity expertise between digestive oncology, pathology and molecular genetics. Just after the original work published in 2006 by the team of Pierre Laurent-Puig (Inserm U775 HEGP, Paris), we were the first group to show that *KRAS* mutation results into resistance to anti-EGFR. Our first paper on the topic (*Di Fiore et al., Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy. British Journal of Cancer 2007*) has now reached **257 citations** and our published data were then confirmed by numerous publications which led to restrict the use of anti-EGFR to patients without *KRAS* mutations. Another article on the impact of *TP53* mutations (*Oden-Gangloff et al., British Journal of Cancer 2009)* was **highlighted in Nature Reviews Clinical Oncology 2009**. Therefore, we think that our work initiated since 2006 enabled us to have a quick positioning on this subject at the international level and the medical repercussions of this work were consequent, our team having actively contributed to the development in France of *KRAS* genotyping.
- We have the wish to develop, in our fields of expertise, programs of therapeutic interest. In this context, we integrated in our unit an immunotherapy program under the direction of Jean-Baptiste Latouche who had developed, at the Memorial Sloan-Kettering Cancer Centre in New York, the artificial antigen presenting cells (AAPC) technology currently used in clinics within this Insititute. Our specific aim is to apply this technology to the RER colorectal cancers associated with the Lynch syndrome. After the implantation of this technology within our unit and the first application focused on CEA, this team has now finished to construct AAPC presenting the specific TGFβRII frameshift epitopes associated with RER+ colorectal and **the results recently obtained clearly demonstrate that it is possible to expand, thanks to these AAPC, specific cytotoxic T Lymphocytes from Lynch patients with germline *MMR* mutations**.
- Therefore, we think that these programs are of potential interest and our laboratory might achieve in the future significant contributions in these fields. We also understand the constructive recommendation of the AERES committee to restrict our programs for the next years. Therefore, following the recommendations, we are going to explore both in the context of the local federative structure "the **Institute for Biomedical Research and Innovation of**

Haute-Normandie", which has positively been evaluated by the AERES and which integrates a biotherapy research unit, and **the North-Western Canceropole** (Lille- Rouen-Caen), which has also been positively evaluated by the AERES, the possibility of development of these programs in other research structures.

New formally accepted publications (original articles) since the evaluation of the unit:
(The names of the members of the unit are in bold)

- Houlle S, Charbonnier F, Houivet E**, Tinat J, Buisine MP, Caron O,** Benichou J, **Baert-Desurmont S, Frebourg T**. Evaluation of Lynch syndrome modifier genes in 748 MMR mutation carriers. EUROPEAN JOURNAL OF HUMAN GENETICS 2011 Mar 16. [Epub ahead of print] (5-years Impact factor: 3.8)
- **Lamy A**, Blanchard F, Le Pessot F, Bossut J, Fiant E, **Di Fiore F, Sesboüé R, Frebourg T, Sabourin J-C**. Metastatic colorectal cancer KRAS genotyping in routine practice: results and pitfalls. MODERN PATHOLOGY, 2011 in press (IF : 4.5)
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