EC2M - Early detection of colon cancer using microbiota

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Early detection of Colon Cancer (CRC) using Molecular and Microbial Markers

EC2M3

Under the supervision of the following institutions and research bodies:

Université Paris-Est Creteil Val de Marne - UPEC

December 2013

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr. Louis BUSCAIL, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee,the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

Unit name:	Early detection of Colon Cancer (CRC) using Molecular and Microbial Markers
Unit acronym:	EC2M3
Label requested:	EA
Present no.:	EA4393
Name of Director (2013-2014):	Mr Iradj SOBHANI
Name of Project Leader (2015-2019):	Mr Iradj SOBHANI

Expert committee members

Chair:	Mr Louis BUSCAIL, University of Toulouse 3
Experts:	Mr Etienne DORVAL, University of Tours (representative of CNU)
	Mr Guy LAUNOY, University of Low Normandy
	Mr Pierre LAURENT-PUIG, University Paris Descartes
	Mrs Janick SELVES, University of Toulouse 3

Scientific delegate representing the AERES:

Mr Jean GIRARD

Representative(s) of the unit's supervising institutions and bodies:

Mr Jorge BOCZKOWSKI, University Paris 12

Mr José COHEN, (Representative of Doctoral School of University Paris 12)

1 • Introduction

History and geographical location of the unit

The unit was submitted to an important restructuration: formerly named UPEC EA 4393 (Laboratory of Clinical Investigation) devoted to several specialities (gastroenterology, rheumatology, epidemiology…) and goals, the unit is now presented with renewed team's members and objectives. Only three members of the previous unit are part of the present EC2M3 project, which switches from the optimisation of colorectal cancer (CRC) screening to identification and validation of new colorectal cancer biomarkers covering all the fields of this disease: screening, diagnosis, prognosis and prediction of therapeutic response. The project is based on two major points: constitution of cohorts and bio banks at each step of the disease, and collaborations with units performing basic research, with particular emphasis on microbial –gene markers. The unit is localized on the site of Henri MONDOR hospital with three main locations: the University building (bench working), the Center for Clinical Investigation (Bio banking) and the Clinical Department of Gastroenterology (screening and follow up of patients, collection of clinical data).

Management team

The director of the unit is Pr Iradj SOBHANI. The formal organisation of the scientific project is based on four Work packages (WPs) as follows: 1-constitution of cohorts including colon cancer patients and control with normal colonoscopy individuals at various risk levels of colorectal cancer (CRC); 2- clinical trials in CRC patients; 3- bio banking collections and discovery of biomarkers; 4- validation of biomarkers. The head of each WP is in charge of evaluation of the projects per WP and makes reports for the directory management committee. The unit created a directory management committee that comprises the PI of each WP together with the director (IS), and which is in charge of strategic decisions (starting new projects, ending current projects, significant investments, organisation of financial distribution, communication).

AERES nomenclature : SVE1_LS7

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	8	8
N2: Permanent researchers from Institutions and similar positions		
N3: Other permanent staff (without research duties)		2
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	3	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	1	3
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	12	13

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	1
Theses defended	1	1
Postdoctoral students having spent at least 12 months in the unit*		
Number of Research Supervisor Qualifications (HDR) taken	1	2
Qualified research supervisors (with an HDR) or similar positions	3	3

2 • Overall assessment of the unit

This is a positive restructuration of the unit that aims at isolating and characterizing new molecular markers for the early diagnosis of CRC. The unit comprises MD/PhDs involved in different steps of the work-plan from patients to bench and hopefully from patients to patients with the discovery of novel biomarkers. The Public Hospitals of Paris and the University Paris 12 support the unit that is also integrated in one of the DHU of the site (Virus Immunity and Cancer) and participates to the formation of future teachers and scientific researchers. The strategy of the unit is based on established annotated collections (stool, serum, biopsies, tissues) from several important prospective cohorts of CRC patients at different stages of the natural history of the disease: screening in general population, screening in patients with positive blood stool test, patients with polyadenomas and with cancer or with advanced cancer. These collections and cohorts are intensively used for: 1) fruitful research on molecular, epigenetic and proteomic studies (published or submitted); 2) patents and licences on which a start-up has been created with integration of a researcher and a post doctoral fellow from the team; 3) important collaborations highly useful for the scientific part of the project (i.e. proteomics, microbiote); 4) numerous grants including several PHRC and prizes. The project plan to: 1) validate faecal markers (epigenetics markers) and serum markers (protein markers) discovered by the team on existing cohorts, still followed-up, and in biological fluids and tissues of CRC patients; 2) characterize a bacterial signature of CRC. The unit possesses background, biorepository, financial support and adequate scientific collaborations for handling successfully this project within the next five years.

Strengths and opportunities related to the context

Ability and amounts of funding; federation and management of the project; creation of a start-up and valorisation; clinical and scientific networking; the project on CRC biomarkers based on the quality of the clinical cohorts and the availability of certified annotated biobanks; original translational aspects on microbiote and CRC studies/projects.

The quality of the cohort opens windows for collaboration with industry (testing new markers and responses to treatments, especially biotherapy) and for clinical valorisation in the field of early diagnosis of CRC.

Weaknesses and threats related to the context

Lack of permanent personnel, especially technicians and full-time researchers.

Wide-ranging objectives in respect to the composition of the team in the competitive field of biomakers for CRC.

Low number of PhD students.

Recommendatinons

The strategy should be focused on markers for diagnosis, prognosis, or response to treatment, but not for screening. The microbiote project is an opportunity for the team, and scientific output linked to the biorepository backbone, the life of the unit should be organized and structured to accomodate the upcoming studies 1) “validation of biomarkers thanks to the biobanks and clinical data and follow up of patients” ; 2) “identification of new biomakers from the microbiote studies”. The bioinformatic and statistical aspects should be reinforced. Among the clinicial projects, the radiobiology project should be given a low priority/ abandonned.

3 • Detailed assessments

Assessment of scientific quality and outputs

The unit published 144 original clinical and scientific articles. Among them, 25 are directly related to the core translational research, part of which is published in good or very good journals such as: Cancer Res, Gut, J Biol Chem, Genome Res, J Clin Oncol, Gastroenterology, … Members of the team are co-inventor of 5 patents (3 international extensions, 1 in France and 2 in Europe). They gave 8 Invited lectures including 6 in International meetings. There is a fruitful continuum from clinical trial, clinical data collection, biobanking annotation towards scientific platform and bench. A clever and realistic strategy has been set up to pick up knowhow and help from outside through scientific collaborations and platforms.

Assessment of the unit's academic reputation and appeal

The unit has been able to develop National Networks on CRC screening and clinico-biological collections through several PHRCs, as well as International Networks including collaborations with recognized national and international organisms/centers (Pasteur institute, INRA, EMBL Heidelberg, Imperial College of London…) as well as with groups involved in clinical research on CRC (GERCOR…). Collaborations with INRA/Imperial College are running, and the unit is involved in an M2R with Pasteur Institute. The unit organized several meetings and received Prices and Awards: a study has been distinguished by the United European Gastrointestinal society during the UEGWeek, October 2011 in Stockholm.

Assessment of the unit's interaction with the social, economic and cultural environment

The unit has organized networks, collected materials and contributed to novel structures (particularly in the field of screening) for reducing delays from bed to bench. Researchers discovered in parallel new biomarkers for early diagnosis of CRC. They have obtained money from PHRC, but even more importantly from industry. Several cohorts have been established and corresponding biobanks certified; a formal International scientific convention has been signed between EMBL (Heidelberg Germany) and Public Hospitals of Paris, and projects for a new patent are in progress. The topic of research on biomarkers of CRC has been selected as a priority field by Medicen, and the group has been funded accordingly. The project Horizon 2020 from EEC is also supported by Public Hospitals of Paris for an upcoming submission of a large project. On the basis of the discovery of a new marker, a start-up has been created after being awarded fundings by national bio emergence competition (in 2009) and creation competition (in 2010). The start up (Profilome) has been funded for the promotion of faecal and blood tests. Researchers have also initiated collaborations important for the scientific issues of the team: INRA and Pasteur Institute for microbial studies, the proteomic platform of IPC in Marseille. Several interviews and public broadcast were given on molecular or microbial markers as well as on CRC screening.

Assessment of the unit's organisation and life

The managment of technicians basic researcher and clinicians is very good in implementing the unit strategy.

Assessment of the unit's involvement in training through research

Team members participate in (or are in charge of) numerous teaching activities: among the GERCOR group, teaching and coordination of Digestive Oncology Paris 05 University, DIU of GI cancerology, regional colon cancer screening training, European courses in clinical IBD and cancer, international bi annual courses in oncology. A thesis has been defended and another one will be defended within one or two years. The unit welcomes M1 and M2R students.

Assessment of the strategy and the five-year plan

The strengths of this project are based on building important clinical networks on CRC and constituting/managing several biobanks, with clinical and biological data originating from the unit's own projects or from clinical trials. The general aim is the identification of new biomarkers (for screening, diagnosis, prognosis, prediction of therapeutic response) using several approaches (proteomic, DNA analysis, methylation, microbial analyses ...). Although this topic is highly competitive, the strength and originality of the project are: 1) large annotated biobanks of CRC at different stages (screening, low and high risk, adenomas, carcinoma); 2) molecular markers already identified (FoxP3, IL17, Wif-1, ...) that can be validated on prospective cohorts still followed-up; 3) the microbial aspect of the research with pre-clinical and upcoming clinical studies on fecal microbiote with metagenomic and influence of chemotherapy; 4) the potential to valorize their results with industry and the associated start-up; 5) the ability to join and train young clinicians and future teachers of the medical school, which warrants a long lasting scientific strategy and leadership in this domain.

Conclusion

This unit shows the capacity to lead recognized and fruitful translational research projects in the field of CRC, to raise funds and to valorize its discoveries. The main issue is the identification of molecular markers for early diagnosis of CRC and among them, microbial markers. This latter part is original and should be supported. Knowledge, means and strategy of the unit warrant the success of the project.

4 • Conduct of the visit

Visit date: December 18th, 2013

Start: 10 h

End: 16 h

Visit site: Hospital Henri Mondor

Institution: University Paris 12

Address: 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil

Conduct or programme of visit:

09h30 - 09h45	**Accueil des participants**
09h45 - 10h00	**Réunion à huis-clos / comité d'experts + DS de l'AERES**
10h00 - 10h30	**Présentation générale et bilan du contrat en cours**
10h30 - 10h45	**Discussion**
10h45 - 12h15	**Projets scientifiques**
12h15 - 12h30	**Discussion générale**
12h30 - 13h00	**Réunion avec tutelles et ED / comité d'experts**
13h00 - 14h00	**Repas et discussion avec les chefs d'équipe**
14h00 - 15h00	**Rencontre doctorants / post-doctorants et ITA**
15h00-16h00	**Délibération à huis-clos / comité d'experts**

5 • Supervising bodies' general comments

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VAL DE MARNE

Réponse au rapport du comité d'experts AERES suite à l'évaluation EC2M

Ref: E2015-EV-0941111X-
S2PUR150008893 - Early detection of Colon Cancer using Microbiota - 0941111X

First of all, we would like to thank all the members of the evaluation committee for carefully evaluating our main results and projects. We have no additional comments to add except for the two following paragraphs.

page 5: Weaknesses and threats related to the context

"Lack of permanent personnel, especially technicians and full-time researchers."

Permanent technician: The University is aware of this situation and will offer our group the opportunity to apply for a technician position if the team is created. If we succeed, this position should stabilise technical assistance through the group.
Full time researcher: We have undertaken collaborations based on very promising fields on microbiota and megadata analyses with basic research actors. This is an opportunity to promote young researchers from our partners' team into full time translational researcher. For our campus this is also a huge opportunity to welcome them. This requires us to participate in the competition for the opening. We have identified a young post-doc who is ready to apply for an "Avenir" position, which might be a first step to a formal position.

"Wide-ranging objectives in respect to the composition of the team in the competitive field of biomarkers for CRC."

The EC2M3 team focused its research in the field of biomarkers. Wide ranging objectives mentioned here include outputs of our patents (two in genomics, one in microbiota and one incoming in proteomic markers). Because all these fields are very competitive, research on microbiota is the only focus of academic studies academic studies, whereas development on gene and proteomic markers are based on academic and Industry inter actions.

Low number of PhD students.

The rationale for formalising the team as an independent group is grounded in our wish to accept more PhD students, which could not be easily done beforehand because of priorities within the LIC team, harbouring a wide range of subgroups and themes. At the present time, two students, one in a master's degree and one PhD, are involved in the team. In 2015, we'll have three students (one master's, and 2 PhD), which is a realistic number regarding the number of staff licensed to direct them (three at the present time) rate. In case a full time researcher is recruited we may bring this up to 4 students (two masters and 2 PhD).

Page 6: Recommendations

The strategy should be focused on markers for diagnosis, prognosis, or response to treatment, but not for screening.

This point is not argued and it is unclear why our research should exclude screening. The weakness of screening programs in Europe and particularly in France is explained by the low rate of participation of doctors and citizens; this is at least partly explained by low acceptance of faecal occult blood tests by physicians (insufficient sensitivity) and no alternative tests offered to citizens (such as self-administered faecal testing). It seems to us that our research can contribute to validating a more acceptable (blood, possibly urine) test.

The microbiote project is an opportunity for the team, and scientific output linked to the biorepository backbone, the life of the unit should be organized and structured to accomodate the upcoming studies

We are currently organizing the team on this specific pathway by establishing a formal contract with APHP and industry actors for proteomic and genomic markers platform processing.

> ***1) "validation of biomarkers thanks to the biobanks and clinical data and follow up of patients" ;***

Validation of microbial markers through geographical determinants will be undertaken in a prospective international project (proposal submitted to Horizon2020). After results of this project are available, promotion with Industry companies can be undertaken.

> ***2) "identification of new biomakers from the microbiote studies". The bioinformatic and statistical aspects should be reinforced.***

We plan to apply for an "Avenir" programme for a post-doc involved in microbiology and statistics; furthermore bioinformatic and biostatistics are going to be more developed on the campus thanks to the recruitment of a Professor in bioinformatics and to collaborations with the AlgoB group (http://igm.univ-mlv.fr/AlgoB/?lang=w&cat=home), which is part of our campus and is specialized in developing algorithms for bioinformatics. The EC2M3 team will interact more fruitfully with this platform and put this in connection with two other platforms (INRA-FR and EMBL-DE).

Among the clinical projects, the radiobiology project should be given a low priority/ abandoned.

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We take this advice in consideration and will prioritize colon cancer trials that do not include radiotherapy.

March 7 2014

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