Mécanismes de la tumorigenèse et thérapies ciblées

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Mechanisms of Tumorigenesis and Targeted Therapies

M3T

Under the supervision of the following institutionsand research bodies:

Université Lille 1 – Sciences et Technologies – USTL

Centre National de la Recherche Scientifique - CNRS

Université Lille 2 – Droit et Santé

January 2014

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. Alain PUISIEUX, 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:	Mechanisms of Tumorigenesis and Targeted Therapies
Unit acronym:	M3T
Label requested:	UMR
Present no.:	UMR 8161
Name of Director (2013-2014):	Mr Yvan DE LAUNOIT
Name of Project Leader (2015-2019):	Mr Yvan DE LAUNOIT

Expert committee members

Chair: Mr Alain PUISIEUX , Université de Lyon

Experts:

Mr Stéphane ANSIEAU, Université de Lyon

Ms Agnès BERNET, Université de Lyon (representative of CNU)

Mr Oliver BISCHOF, Institut Pasteur, Paris

Mr Vincent CASTRONOVO, Université de Liège, Belgique

Mr Christophe CAUX , Université de Lyon

Mr. Patrice DUBREUIL, Université Aix-Marseille

Mr Jean-Jacques FEIGE, Université de Grenoble

Mr Olivier FERON, Université Catholique de Louvain, Bruxelles, Belgique

Ms Urszula HIBNER, Université de Montpellier (representative of CoNRS)

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Ms Fanny MANN, Université Aix-Marseille

Scientific delegate representing the AERES:

Mr Daniel OLIVE

Representatives of the unit's supervising institutions and bodies:

Mr Alain EYCHENE , CNRS

Mr Patrick BERCHE, Institut Pasteur de Lille

Mr Philippe ROLLET, Université Lille 1 – Sciences et Technologies – UM1

Mr Bernard SABLONNIERE (representative of ED n° 446)

1 • Introduction

History and geographical location of the unit

The Institute of Biology in Lille (IBL) was created by the CNRS on the Institut Pasteur campus in 1996. Between 2006 and 2009, several IBL teams merged into a research unit, UMR 8161, under the direction of Mr Yvan DE LAUNOIT. The unit's scientific theme is the biology of cancer. In addition to the UMR 8161, the IBL building hosts two other units: UMR 8191 (Génétique des Maladies métaboliques) and UMR 8204 (Immunité et infection), both of which also have lab space elsewhere on the campus, and a team of administrators who are responsible for the logistics of IBL (GDS 3366, composed of 19 people under the responsibility of Mr Yvan DE LAUNOIT). Three technological platforms and two spin-off biotech companies are also located in the building. The UMR 8161 laboratories occupy about 2 700 m^2 of the total 12 000 m^2 and are located on the 3rd and 5th floors.

In 2010, the unit was destabilized by the departure of one of the group leaders, following a request from the CNRS to head the Institute of Interdisciplinary Research in Lille. This expert group of structural biologists had recently arrived at the IBL with an ambitious project, evaluated as excellent by the previous AERES experts committee, within the team led by Mr Yvan DE LAUNOIT. As a consequence of their leaving for the IRI, the team of the director had to profoundly re-structure their scientific project.

In the period under evaluation, the unit was composed of 6 teams:

1. Initiation of epithelial cancer (ICE), dir. Ms Corinne ABBADIE;

2. Functional studies of tumor suppressor gene HIC1 (HIC), dir. Mr Dominique LEPRINCE;

3. Angiogenesis, endothelium activation and cancer (Vaisseaux), dir. Mr Fabrice SONCIN;

4. Cancer biology and chemistry (CBC), dir. Mr Oleg MELNYK;

5. Signaling-apoptosis and cancer (Signal), dir. Mr David TULASNE;

6. Virus-cancer and transcription (VCT), dir Mr Yvan DE LAUNOIT;

The first five team leaders propose projects not necessitating major reorganisation of their groups, with the exception of team 5 that has recently been enriched by the arrival of a small group that has just completed their ATIP/Avenir programme (Mr Fabrice LEJEUNE). Importantly, team 6 has split into two thematically distinct groups: Ms Nadira DELHEM leads the programme "Immunoregulation of virus-induced cancers" (IRCV) and Ms Martine DUTERQUE-COQUILLAUD the one entitled "Ets proteins and associated diseases" (ETS).

The unit has a long-standing involvement in the Canceropole Nord-Ouest and is one of the pillars of the recently created SIRIC ONCOLille project. Their medium-term ambition is to move to the hospital/Université Lille 2 campus, already hosting the main forces of the cancer research in Lille. While the experts committee acknowledges that moving laboratories, not to mention constructing the new building that would be necessary to accommodate the incoming teams, would be costly, the logic behind uniting all cancer research on the same campus in the vicinity of the hospital and the Cancer Center Oscar Lambert sounds.

In the period under evaluation, 11 researchers left the unit and 7 full time scientists or scientists with teaching duties joined the unit. The translational research has been strengthened by the arrival of 5 clinicians. Staff members are detailed in the following “unit Workforce Table”. Noticeably, the unit benefits from an unusually high ratio of technical/research staff.

The level of institutional funding of the unit is low, gradually decreasing from 561k€ in 2009 to 306 k€ in 2013, although significant support for acquisition of equipment from the Université Lille 1 is to be noted (MALDI-TOF-TOF in 2012: 100 k€). External grants were constant between 2009 and 2012, but significantly improved in 2013 (1 125 k€).

Management team

The current director is Mr Yvan DE LAUNOIT (DR1, CNRS) and his directorship will be renewed for this 5-year contract. Mr Yvan DE LAUNOIT is highly experienced in the management of a laboratory and has a charismatic leadership. Nevertheless, the management of the unit is complicated by the fact that Mr Yvan DE LAUNOIT, who heads the team of 19 administrators within the IBL, is also responsible for the administration, but not the scientific policy,

of the entire IBL. While the experts committee has not met the other two units housed in the institute, the personnel of UMR 8161 unanimously praised Mr Yvan DE LAUNOIT 's directorship.

The life of the unit is organised and implemented by the board of the laboratory (Conseil de laboratoire), headed by the director and meeting twice a year, and the board of team leaders, meeting 8 times a year. Both scientific and general matters are discussed with all personnel twice a year at a retreat that takes place at a location in Lille, outside of the institute. The experts committee recognizes the high level of satisfaction of scientists, students and technical staff in regard to the unit's management, but feels nevertheless that more frequent scientific exchanges involving the whole unit might lead to a higher level of common projects as well as of internal collaborations.

AERES nomenclature

SVE1_LS3 Biologie cellulaire, Biologie du développement animal

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4	4
N2: Permanent researchers from Institutions and similar positions	16	16
N3: Other permanent staff (without research duties)	37	37
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	4
N6: Other contractual staff (without research duties)	3	1
TOTAL N1 to N6	**66**	**63**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	13	
Theses defended	31	
Postdoctoral students having spent at least 12 months in the unit*	10	
Number of Research Supervisor Qualifications (HDR) taken	6	
Qualified research supervisors (with an HDR) or similar positions	17	20

2 • Assessment of the unit

Strengths and opportunities related to the context:

- interdisciplinary expertise in chemistry and biology;

- a charismatic director, strongly involved in the development and the organization of cancer research in Lille;

- creation of 2 start-up companies (Innobiochips and XProchem; both spin-offs from Mr Oleg MELNYK's team);

- 11 patents filed since 2008;

- high number of technical staff;

- the research topic on MET receptor shared by two teams of the unit;

- localization of the unit on the Pasteur Institute Campus allowing access to technological platforms (animal facility);

- creation of the ONCOLille SIRIC program focusing on two themes (tumor resistance and tumor dormancy), for which the unit was, and remains, a major driving force;

- involvement of the teams in the Canceropole Nord-Ouest program. Mr Yvan DE LAUNOIT is a member of the scientific committee of the Canceropole and co-director of the axis 1;

- strong support from the CNRS (technical and administrative positions) and significant support from the Université Lille 1 (funding equipment, opening university positions for IBL scientists), although the recurring financial support from the university appears very moderate;

- the objective to merge cancer research teams in Lille and to strengthen the links with clinical teams is strongly supported by local authorities (Université Lille 1, Université Lille 2, Institut Pasteur);

- involvement of the teaching researchers and researchers in M1 and M2R programs.

Weaknesses and threats related to the context:

- insufficient scientific ambition of some scientific programs (lack of in vivo approaches), which may be partly due to the small size of some teams of the unit;

- insufficient publications in high-quality journals (IF > 10);

- with the exception of Ms Nadira DELHEM's team, the interactions of the teams with clinical departments could be strengthened. The newly created ONCOLille SIRIC should aid this necessary development;

- in respect to scientific presentations and discussions, weekly team meetings are reported for all teams, however, twice yearly exchanges involving the whole unit are not sufficient;

- decrease of the institutional support (CNRS, Université Lille). 2009-2013: 540 K€ to 306 K€;

- relatively low level of funding, although the success level for external grants was very significantly improved in 2013; lack of grants from international organisms;

- while the number of PhD students is reasonable, it would clearly be beneficial to recruit more post-docs. This can only be achieved by improved funding of the teams;

- no direct involvement in LabEx programs.

Recommendations:

- strengthen interactions with clinical departments;

- develop in vivo approaches (animal models; human samples);

- strengthen scientific meetings and networking to increase interactions between the different teams;

- initiate a strategy:

- to increase the attractiveness of the UMR 8161 to permanent researchers and post-docs (international calls to attract new researchers; ATIP/AVENIR, etc);
- to increase the overall scientific ambition of the teams;
- to motivate team leaders to apply for international grants and to participate in international networks.

3 • Detailed assessments

Assessment of scientific quality and outputs

The UMR 8161 was created in January 2006 with the ambition to associate research teams with chemical, physical and biological expertise and to develop interdisciplinary research programs. Although the CNRS decided 4 years ago to move the biostructuralist team to another unit, the UMR 8161 has retained this ambition and has developed a strategy based on the wish to strengthen interactions between biologists and chemists. Nowadays, this ambition is mainly demonstrated through the research program on the tyrosine kinase MET receptor aiming to decipher cellular functions of this oncoprotein and to identify new agonist and antagonist molecules in targeted cancer therapy. This program involves two teams of the unit, headed respectively by Mr Oleg MELNYK and by Mr David TULASNE. Although there are no common publications yet on this theme, the collaboration between these two teams is a stepping stone of the "Resistance program" of the newly created SIRIC ('Comprehensive Cancer Center') of Lille (ONCOLille) as well as the axis 1 of the Canceropole Nord Ouest.

Other research projects of the UMR 8161 include the role of ETS proteins, and associated fusion gene products, in bone metastasis in prostate cancers (Ms Martine DUTERQUE-COQUILLAUD team); the characterization of pre-tumoral emergence from senescent keratinocytes (Ms Corinne ABBADIE team); the characterization of HIC1 function and regulators (Mr Dominique LEPRINCE team); the analysis of the role of Eglf7 in normal and tumor blood vessel development (Mr Fabrice SONCIN team) and the characterization of immunological events occurring in neoplasms associated with HCV and EBV infections (Ms Nadira DELHEM team). Although each team shows both national and international collaborations, the number of strong scientific interactions between the teams of the unit appears to be limited. With a very few exceptions, there is also a lack of collaborations with teams from other units located at the IBL.

Overall, these projects are conducted by teams of small size, with a good level of scientific productivity but very few top quality publications. During the past 5 years, members of the UMR 8161 have generated more than 250 original papers (source: Web of Science) including 173 publications originating from studies performed by the teams in the frame of the present contract. Although a significant number of these manuscripts has been published in good general and specialist journals [Blood (IF 9.9), Cell Death Diff (IF 8.8), EMBO J (IF 8.3), Chem Sci (IF 8.3), Nucleic Acids Res (IF 8.0), Cancer Res (IF: 7.9), Oncogene (IF 6.4), Mol Biol Cell (IF 5.8), Am J Pathol (IF 5.5), Mol Cell Biol (IF 5.5), FASEB J (IF 5.3 etc.], the number of top quality journals is very limited [Angewandte Chem (IF13.6); Mr Oleg MELNYK team] for a unit of this size.

Assessment of the Unit's academic reputation and appeal

During the 5-year contract, five team leaders of the UMR 8161 attended international conferences as invited speakers. Among many scientific and steering responsibilities, the director of the unit, Mr Yvan DE LAUNOIT, is a member of the CN2 scientific committee of ARC, president of the scientific committee of Ligue National contre le Cancer, and a member of the scientific committee of the Canceropole Nord-Ouest and the SIRIC ONCOLille. He is also the Coordinator of the Biology platform of the SIRIC ONCOLille, and is director of the GDS 3366 which corresponds to logistics, administration and informatics of the IBL building (3 research units: UMR 8161, UMR 8199, UMR 8204). In contrast, the overall participation of team leaders in the scientific committees of french and foreign agencies/charities and in the scientific councils of centers/Institutes remains limited.

Overall, teams of the UMR 8161 have a national recognition in their respective fields of expertise but most of them suffer from a lack of international visibility. This weakness is illustrated by the relatively moderate number of invitations to give seminars at international conferences, the lack of leadership of international consortia as well as the very low number of international grants obtained by the teams of the unit.

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

Mr Oleg MELNYK has created two start-ups (Innobiochips in 2008 and Xprochem in 2012) and has received the "Trophée de l'Innovation INPI 2013". InnoBioChips has been the laureate of "Concours Emergence 2008" and "Création Développement 2010" and Xprochem has been the laureate of "Concours National d'aides à la création d'entreprises 2012" and of "Concours Emergence 2012". These achievements are fully in keeping with the ambition of the unit to develop multidisciplinarity, translational research and knowledge transfer.

Although 4 additional teams of the unit (Mr Fabrice SONCIN, Mr David TULASNE, Ms Nadira DELHEM, Ms Martine DUTERQUE-COQUILLAUD) have filed patents during the 5-year contract (total number of patents of the unit: 11), the involvement of these teams in the social and economic environment is moderate, with a number of partnerships with private companies which could significantly be strengthened (referenced industrial contracts since 2008: Mr Fabrice SONCIN team; Mr David TULASNE team).

Several team leaders and members of the unit have participated in public events and general information programs in France such as the "Fêtes de la Science" and "Apprentis chercheurs".

Assessment of the Unit's organisation and life

The encounters of the experts committee with staff members of the unit (engineers - technicians - adminstrative; staff scientists; students and post-docs) highlighted a very friendly and positive atmosphere with good working conditions. Members of the unit appear to strongly appreciate the management and the overall organization of the unit. The decision-making body of the unit is the board of team leaders (meetings 8 times a year) that includes the director and the group leaders. A written report following each board of team leaders meeting destined to be transmitted to the whole unit could be useful to improve the efficiency of the transmission of some pieces of information.

The board of the laboratory, that includes elected representatives, meets twice a year. An additional effort to have some input into the agenda for these meetings would add a new dimension to the role played by the committee, which sometimes appears to be limited to a communication role. However, generally, the organisation of the unit seems to be working at the administrative, financial and logistical levels, and is highly appreciated by the members of the unit.

As previously mentioned, scientific meeting are organized once a week by each of the teams. Scientific meetings gathering all the members of the Unit are only organized twice a year (two day-long meetings) outside the IBL, generally on the campus of Université Lille 1. The experts committee suggests increasing the frequency of unit scientific meetings in order to improve the overall scientific communication, which is a critical factor to strengthen interactions between the teams. In particular, the experts committee considers that the director needs to make sure that the current development of the Chemistry team, located on a separate floor to the rest of the teams, does not become entirely independent, but is instead used to benefit the entire unit.

A strong suggestion of the experts committee is that the Internal Procedures (Réglement Intérieur) of the unit should be written, describing and formalizing the governance as well as the functional organization and internal rules of the unit.

Assessment of the unit's involvement in training through research

Two professors (including a team leader: Ms Corinne ABBADIE) and 4 assistant-professors (MCU; including a team leader: Ms Nadira DELHEM) are affiliated with the UMR 8161. All team leaders and teaching researchers of the unit are implicated in L1-3 and M1-M2 programs of Université Lille 1 and Université Lille 2. Mr Oleg MELNYK and one of his collaborators are involved in international training programs. Ms Corinne ABBADIE was in charge of the Master "Biologie et Biotechnologies" from 2008 to 2012 and is now deputy director of "UFR - Biologie" Université Lille 1 in charge of education. One of the team associates is now director of the Master 1 "Biologie et Biotechnologies" and head of the "Genetique et Microbiology" research program in this Master. Ms Martine DUTERQUE-COQUILLAUD is in charge of the "Génétique et Microbiologie" research program of the M2R Univ Lille 1 and Lille 2. One team associate is director of the Master (M1-M2) "Génomique et Protéomique" Université Lille 1. Finally, Ms Nadira DELHEM has created a new « Tremplin - Réussite » Lille 1, undergraduate degree.

31 PhD students successfully defended their thesis during the 5-year contract, which is an indicator of the good quality of the tutoring of the students in the unit, and 6 researchers defended an HDR.

Assessment of the strategy and the five-year plan

Within the unit, the most significant change consists of the splitting of the former team entitled "Virus–Cancer–Transcription" and headed in the frame of the previous contract by Mr Yvan DE LAUNOIT, into two different teams, headed respectively by Ms Nadira DELHEM and Ms Martine DUTERQUE-COQUILLAUD (Mr Yvan DE LAUNOIT is a member of the latter team). This change appears to be a logical and natural evolution as the former team was composed of two relatively independent groups. Overall, the scientific programs presented by the 7 teams of the unit

are continuations of current projects giving rise to timely projects. Nevertheless, some of them are restricted to in vitro and mechanistic studies, weakening their overall ambition and their competitiveness at the international level.

The global strategy of the unit is to actively participate in the structuring of the SFR Cancer Lille teams, with the ultimate goal to gather cancer research teams (n=12; 5 units) to a single building on the campus of CHRU/COL (COL: Centre Oscar Lambret). This ambitious objective, supported by local authorities (Université Lille 1, Université Lille 2 and Institut Pasteur) relies upon three important achievements:

- the creation of the Canceropole Nord-Ouest in 2003;

- the "Contrat de Plan État Région" (CPER) between 2000 and 2007 that clearly defined Cancer Research as one of the four biomedical priorities in Lille and its region;

- the creation of the SIRIC ONCOLille in 2012 which relies upon 6 UMR and 4 EA of Lille from 3 campuses in partnership with the Université Lille 1, Université Lille 2, CNRS and INSERM.

The experts committee strongly supports this project in order to develop scientific interactions between teams involved in cancer research, to increase their visibility and their attractiveness and to strengthen the interface with the clinical teams of CHRU and Centre Oscar Lambret. This latter point is critical to develop ambitious translational research based on basic projects of the present UMR.

However, with the estimated completion of this project scheduled for 5-8 years time, the experts committee considers that it is essential to specify the unit's strategy for the next 5 years, in order to:

- reinforce the existing teams. So far, 1 associate professor (MCU) position has been obtained to increase the team of Mr Dominique LEPRINCE, currently consisting of only a single permanent researcher. Whilst this is a step in the right direction, it is important to anticipate recruiting on a wider scale (recruitment by EPST and the university of young researchers both internal and external) considering the small size of most of the current teams;

- attract young researchers with high potential. It may be possible to hire 1 or 2 ATIP/AVENIR teams in the next contract. A strategy for identifying candidates and their research themes needs to be defined;

- reinforce the interactions between the teams in the unit;

- encourage the researchers of the unit to raise their input in international networks and to apply for international grants;

- raise the general ambition of research projects developed within the unit, which should thus result in an increase in the number of publications with high impact factors.

4 • Team-by-team analysis

Team 1: Initiation of epithelial cancer

Name of team leader: Ms Corinne ABBADIE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	2	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5**	**5**

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

• Detailed assessments

Assessment of scientific quality and outputs

Given the heavy teaching implications, the publication output of the team is good. Nevertheless, the medium impact, with most last author publications in peer-review journals with IF between 3-8,5 (total 22 publications, of which 6 as last author including 2x Cancer Res., PLOS One). The group focuses on the identification of mechanisms, including ER-stress, oxidative stress and DNA damage among others, that appear to be drivers for senescence induction in human keratinocytes. More recently, the group has demonstrated a link between single-strand DNA breaks (SSBs), senescence escape and malignant transformation, which seems to be specific for these cells. The relevance of these original and interesting findings awaits an in-depth mechanistic analysis and an in vivo validation/confirmation to be published in high-impact journals. In particular, the consequences of SSB accumulation as a means for

senescence escape need to be established in the future. The work produced so far is of very good quality and interest but there is a lack of incisiveness to publish in high-impact journals.

Assessment of the unit's academic reputation and appeal

The appeal of the group is principally limited to regional PhD students and MCs (a renewal of the "Chaire d'Excellence" is expected for October 2015) and no national or international postgraduate student has been recruited. The team leader is a member of the Editorial Board of "Apoptosis" since 1996 and ad hoc recruited for peer-review (Apoptosis, FASEB or J Cell Physiol) and national grant proposals (LNCC, INCa). She is also a member of the scientific committee of "École Doctorale BioSe" at the Université de Lorraine and currently a member of the CoNRS section 21. She was a member of the CNU 65th section (2007-2011). Beyond this, the team leader and her group are nationally and internationally only mildly recognizable. There is also too few international collaborations and integration in trans-national grants (eg EU, binational) with leaders in the field and this is clearly tied to the team's reduced visibility.

Assessment of the unit's organisation and life

The project consists of three convergent axes autonomously developed by three senior researchers according to their expertise and overall coordinated/integrated by the team leader. The work is supported by technicians and PhD students who are closely supervised and followed by senior scientists. The internal flow of information is well-structured and students attend regularly institutional seminars from external scientists. Unfortunately, the attendance of scientists and PhD students at international meetings is on average every 2-3 yeras due to the tight funding situation, which is rather low and impacts on the team's visibility and keeping up-to-date.

Assessment of the unit's involvement in training through research

This is clearly a major strength of the group. The group leader is highly involved in helping the career development of students and permanent staff working with her. The team is a real training lab, given its make-up. In total, 7 M1, 5 M2 and 2 L3 students were trained. PhD students are well-instructed and guided throughout their theses and generally leave the lab with a very good publication record. All permanent personnel are heavily involved in the university curriculum, particularly at the M1 and M2 level and thus have a very good feel for training responsibilities.

Assessment of the strategy and the five-year plan

In the next 5 years, all projects will remain centered on how senescence impacts on cell transformation in normal keratinocytes. They will investigate both cell-autonomous and cell non-autonomous mechanisms and the relationships between the two. The first part of the project on in vitro description of senescence induction/escape corresponds to the proven group expertise and will undoubtedly lead to interesting findings. However, the projects described often remain poorly defined and incompletely thought-through. In particular, in vitro experiments required to address the outcome of SSBs, the markers needed to be analyzed by IHC on human samples, and the in vivo experiments, are insufficiently described. In the second part of the project, a new line of investigation will be initiated looking at secondary sarcomas occurring in irradiated field. It is hypothesized that SSBs are at the heart of this cancer. The final project envisions using a senescence reporter and eliminator mouse and dog models to explore whether or not the elimination of senescent cells impacts on the formation of secondary sarcomas after irradiation. Considering the small size of the team, the wide spectrum of proposed projects is slightly concerning, therefore it is essential to prioritize projects in the near future, given the effective group size. Moreover, the projects as proposed, though having very good potential, lack a certain incisiveness and depth; no high risk avenues are taken and the innovative character of research is not brought to its full fruition.

Conclusion

- **Strengths and opportunities:**

- expertise in senescence;

- proximity to clinical samples to test SSB hypothesis for senescence escape - the combined expertise of the three researchers should help to achieve this goal;

- the inclusion into the SIRIC program may aid in attracting cancer grant related funding (eg INCa) that would facilitate the recruitment of postdoctoral students.

- **Weaknesses and threats:**

- a relative lack of national and international visibility;

- research too focused on mechanistic analyses;

- innovative vision and novelty lacking;

- no major grants aside from regional LNCC-ARC;

- no appeal to postdoctoral students.

- **Recommendations:**

- networking must be increased by visiting international meetings and exposing research;

- national-international collaborations must be forged to enter bigger grant proposals;

- recruitment of postdoctoral students;

- the research plan would benefit from prioritization of projects.

Team 2 : Functional studies of tumor supressor gene HIC 1

Name of team leader: Mr Dominique LEPRINCE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	2
N3: Other permanent staff (without research duties)	1	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**3**	**5**

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

- ## Detailed assessments

Assessment of scientific quality and outputs

The PI is a leader in the HIC1 field with 33 of the total 195 publications coming from his lab. Most manuscripts have been published in journals with an IF of 5-9 (mostly JBC, with 14 last author publications and 5 collaborations). The output is surprisingly good given the funding situation and size of the team. The scientific activities of this small team have been centered on one particular transcriptional repressor, HIC1 (Hypermethylated in Cancer 1), a tumor suppressor gene inactivated through promoter methylation. In total, the research mainly focuses on the resolution of mechanisms concerning the role of post-translational modifications in HIC1 function upon the regulation of HIC1 control pathways. The biochemical and functional analysis of these modifications is of excellent quality, but the pertinence in the context of cancer therapeutics is minor. This latter point has prevented the integration of the team into the OncoLILLE programs. No high risk avenues are taken and innovative character of research is missing at times

(ie., lack of attempts to integrate state-of-art technologies). Overall, the scientific quality of the projects is very good but their ambition likely suffers from the very small size of the team.

Assessment of the unit's academic reputation and appeal

The unit has a good visiblity/expertise in the field. The overall appeal of the unit is principally limited to PhD students and no national or international postgraduate student has been integrated. This is mainly due to the very narrow research focus. Several national or international collaborations gave rise to a number of good publications in the HIC1 field. The team leader is a member of the scientific committee of "Septentrion" (Ligue Nationale contre le Cancer, Lille) and the scientific committee Life Sciences & Health (SVS-1) (FNRS, Brussels) from 2012. He is also an ad hoc peer reviewer for several national grant agencies and peer-review journals (Nucleic Acids Research, Oncogene, Cancer Research, Molecular and Cellular, Biology, Plos One, Molecular Cancer Research). There is no involvement in international programs and national collaborative grant programs. The team leader has consistently obtained national grants from 2008 to 2013 (ARC, FRM, Ligue contre le cancer, ARC).

Assessment of the unit's involvement in training through research

The team leader is highly involved in training, 3 Master (M2) students from 2008 to 2013, 2 postdocs were trained and 2 PhDs students went to Harvard Med School as Postdocs. He organized two master courses in 2008 and 2009.

Assessment of the strategy and the five-year plan

The strategy of the unit is consistent with its history in continuing to decipher the functional consequences of HIC inactivation during the early steps of tumorigenesis. This analysis is focused on the identification of target genes using a genome-wide ChiPseq approach and the the role HIC1 plays in the DNA-Damage response. Unfortunately, the team will only continue to study repression mechanisms and no endeavours beyond this are planned. The view could be more original and innovative. A permanent-researcher will be recruited in the next year by the Université Lille 1 and this will help to widen the scope of the laboratory.

Conclusion

- **Strengths and opportunities:**

- excellent expertise in chromatin biology and specifically HIC1;

- proximity to clinical samples and SIRIC/ONCOLille could constitute an entry point to extend research into the cancer biology field and may thus open funding possibilities if the work on HIC1 turns more towards therapeutic and innovative applications in the cancer field.

- **Weaknesses and threats:**

- the team is very small but this weakness will be somewhat improved by the recruitment of an assistant professor (MCU) in the months/year to come;

- the international visibility is very limited and the research too focused on single mechanistic details. A global perspective would strengthen the scientific program;

- no major grants aside from regional LNCC, ARC, FMR that would help to widen the scope.

- **Recommendations:**

- the work carried out by the team represents 17 % of all the work conducted on HIC worldwide, and thus this expertise must be conserved. However, networking must be increased to expose research and attempts to develop translational research should be considered to integrate the newly created ONCOlille SIRIC;

- national or international collaborations must be forged to enter bigger grant proposals;

- the recruitment of a permanent position to this small team will probably lead to the development of more ambitious perspectives.

Team 3: Angiogenesis, endothelium activation and cancer

Name of team leader: Mr Fabrice SONCIN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	2	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5**	**4**

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

- Detailed assessments

Assessment of scientific quality and outputs

The team leader is a recognized expert in the angiogenesis field. In 2003, the team discovered VE-statin/egfl7 as a specific marker of endothelial cells and has since pioneered the understanding of the biological functions of this protein. Interestingly, the team has shown that egfl7 plays a key role in the maturation phase of physiological angiogenesis by contributing to elastin deposition in the basement membrane of endothelial cells, thereby inducing vascular quiescence. The team also reported an original function of egfl7 in tumorigenesis. In this context, egfl7 promotes tumor escape from immune control by repressing the endothelial expression of lymphocyte/endothelial cell adhesion molecules (ICAM-1, VCAM-1, E-selectin), thereby controlling the infiltration of immune cells into the tumors. These observations have brought up a new concept of oncogenic activation of the tumor endothelium. The team has published several seminal papers about the biology of egfl7 (*Am J Pathol*, *EMBO J*, *Plos One*, *Cancer Res*). It has also participated in 6 other publications resulting from collaborative works with French and/or European teams, including

2 *Plos One*, 2 *Int J Oncol* and 1 *Stem Cells*. It is worth mentionning that Genentech is currently developing monoclonal antibodies against egfl7 for their future use in human cancer therapy.

Assessment of the unit's academic reputation and appeal

The team has an excellent academic reputation. The team leader was President of the French Angiogenesis Society from 2007 till 2011 and was a co-organizer of the 2012 Meeting of this Society that was held in Monaco. He is a member of the scientific committee (CN3) of the Association pour la Recherche sur le Cancer since 2009 and a member of the Editorial Board of two journals: *Experimental Hematology and Oncology* and *International Journal of Chronic Diseases*. He is also a member of the SANOFI Board of Experts on colorectal cancer. Another team member was invited as a speaker at the Gordon Conference on elastin in 2009 and at the 2014 Meeting of the French Angiogenesis Society. She won the 2013 Research Award on "Angiogenèse et Tumeurs" given by Roche Laboratories. The team was supported by the Ligue Nationale contre le Cancer as an "Equipe Labellisée" from 2008 till 2010 (60 k€/yr).

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

The team has patented the clinical applications of egfl7 in cancer therapy but CNRS abandoned the defence of this patent (since then, Genentech is developing drugs in this same field). The team received financial support from ROCHE (90 k€/2 yrs) to develop an egfl7 KO mouse and academic support from ARC, FRM Ligue contre le Cancer, Cancéropole Nord-Ouest (a total of 120 k€) and coordinated two INCa PL Bio programs (2008-2011 and 2013-2017, total: 830 k€). The team leader is a consultant for SANOFI in its board of experts on colorectal cancer.

Assessment of the unit's involvement in training through research

The team trained 3 PhD and 3 M2 students over the last 5-yr period. Virginie Mattot obtained her HDR in 2012. The team leader is teaching (about 12h/yr in total) in the M1, M2 courses at Université Lille 1, Université Lille 2 and at the School of Medecine Xavier Bichat (Paris). 1 post-doc was trained for 5 years on INCa and Fondation de France funds.

Assessment of the strategy and the five-year plan

The plan for the next five years is to follow up the analysis of the biological functions of egfl7, and to widen the focus of the team towards a larger number of endothelial genes and micro-RNAs that might contribute to endothelial cell activation (as defined by up-regulation of leucocyte adhesion molecules). A clean knock-out of egfl7 that does not affect the expression of miR 126 (a miR encoded by intron 7 of the egfl7 gene) has just been generated in C57-Bl6 mice which will allow the analysis of the phenotypic alterations of the physiological and tumoral vasculature using appropriate models. This should allow a better understanding of the respective in vivo functions of egfl7 and miR 126 as the results generated from the previous knock-outs were confusing. For the second goal, high-throughput screening approaches will be set up to find new genes or micro-RNAs that control endothelium activation. The project appears feasible as an assay has already been optimized in 384-well plates and since a new robot dedicated to microscopy image analysis has just been acquired by IBL. The candidate genes/micro-RNAs will then be studied in detail in the context of breast, colon and lung cancers.

Overall, the project appears original, competitive and well-balanced between further development of the pioneering work on egfl7 biology and a novel program aimed at discovering new genes/micro-RNAs of interest in endothelial biology. The excellent previous achievements of the team strongly support the feasibility of the project. The task force may need to be increased once the results of the HTS begin to come out.

Conclusion

- **Strengths and opportunities:**

- original project;

- good balance between follow-up of previous research on egfl7 and new developments using HTS;

- strong expertise and scientific reputation in angiogenesis;

- strong academic and industrial funding.

- **Weaknesses and threats:**

- small team: 2 researchers;

- a large number of genes/micro RNAs of interest are likely to be identified by HTS. This will require the elaboration of a strategy for choosing the most interesting ones to be studied *in vivo*. It may also require an increase in the task force of the team at this stage;

- relatively little interaction with other teams of the unit.

- **Recommendations:**

- keep developing research on egfl7 in order to maintain the academic reputation of the team while the more risky new high-throughput approaches are developed;

- increase the size of the team by recruiting a young researcher/associate professor;

- strengthen interactions with other teams of the unit, and further develop collaborations with clinical teams.

Team 4: Cancer Biology and Chemistry

Name of team leader: Mr Oleg MELNYK

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	1
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	7	6
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)	1	
TOTAL N1 to N6	**15**	**10**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	3

- Detailed assessments

Assessment of scientific quality and outputs

This team is composed of scientists of different expertise (chemists and biologists) whose activity is clearly pluri-disciplinary, working in the field of chemical biology. Its activity is focused on the mechanisms of activation of the Met tyrosine kinase receptor by the co-development of chemical and biological approaches. The originality lies in the emergence of projects at the interface between the two disciplines and in the development of a methodological breakthrough (SEA chemistry).

The group has a regular and excellent quality publication record: 57 publications, 32 of which are last author papers (interestingly, 23 publications are from the proteomic platform which is supervised by a technician). Most of the publications of the group are published in specialist chemistry journals. The IF of class A chemistry journals have an average of 5 and many of the papers published by the team are in this range or higher (6 *Org Lett* for

example, IF 6.1). One has been published in the best journal in chemistry (*Angewande Chemie International edition* (IF 13.5)) and another in *Chemical Science Edge* (IF 8.3). The remaining publications are the result of collaborative works.

The team leader is involved in many national and international expertise committees and he is the co-founder of two start-ups (*Innobiochips* and *XProchem*). Oleg Melnik is also involved in many industrial science-to-business marketing actions (6 patents declared and 3 exclusive licences) and he has successful collaborations with various pharmaceutical companies.

This team has followed 3 main axes of research: the first is the development of a strategy for total protein synthesis using the SEA native peptide ligation, with the aim of synthetizing a protein in its totality for therapeutic usage. This strategy is based on the chemical reaction of a Sulfanyl Ethyl Amido group with an N-terminal Cysteine residue. The team leader is a pioneer in this peptide ligation approach. The second axis of research (supervised by a junior scientist who recently obtained a CNRS position at the CR1 level) explores the structure-activity relationship of protein subdomains by using a ligand/receptor (HGF/c-Met) model. This pair of proteins is involved in cancer induction and is also implicated in chemotherapy resistance. The last axis of research, developed by a senior scientist who is leaving the team at end of 2014, is focused on HGF/c-Met regulation by non-coding RNAs.

Assessment of the unit's academic reputation and appeal

There is a real visibility of the team at the national level in the field of chemistry but the international dimension is less visible. One of the weaknesses of the team, especially regarding its size, is the weak involvement in international collaborative projects (remarked on by the team leader). Nevertheless, many invited reviews have been written by the different members of the team revealing its unquestionable reputation in the field.

Many different funding sources have been obtained by the team leader but all of them were at the local or national levels. Presently, the team is not involved in any European networks.

This team obtained many grants as the coordinator (ANR emergence, ANR blanche, OSEO, Jinnove, PICS, INCa, Ligue régionale) or as a partner (ANR, MEDICEN, CPER Cancer Project and SIRIC).

The team leader has been invited to speak at numerous scientific meetings. The team also has contributed widely at conferences (10 for the team leader) over the past 5 years.

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

Mr Oleg MELNYK has created two start-ups (*Innobiochips* in 2008 and *Xprochem* in 2012) and has received the "Trophée de l'Innovation INPI 2013". *InnoBioChips* has been the laureate of "Concours Emergence 2008" and "Création Développement 2010" and *Xprochem* has been the laureate of "Concours National d'aides à la création d'entreprises 2012" and of "Concours Emergence 2012". Notably, students are involved with the 2 start-up companies. Oleg Melnik is also implicated in many industrial science-to-business marketing actions (6 patents declared and 3 exclusive licences) and he has successful collaborations with various pharmaceutical companies Endotis Pharma; Imabiotech project). He is involved in several valorisation projects (Coordination ANR emergence; Projet Jinnove; OSEO project). Outstanding activity.

Assessment of the unit's involvement in training through research

There are many contributions to the teaching duties, mainly by the team leader and a young MCU, who has recently joined the team. The senior scientist, who is leaving the team at the end of 2014, is director of a master at Université Lille 1.

The contribution to PhD programs is satisfactory, but not excellent, with 4 PhD in regards to the number of permanent senior positions present in the team. The same weakness is shown through the very low number of post-doc positions present at the time of the report. However, 7 left the team between 2009 and 2013.

The low number of PhD students seems connected to the difficulty of student recruitment within the Doctoral School of Biology to which the team belongs. Indeed, to date, in spite of the presence of suitable students and projects, the school has not attributed any thesis grant to the team. The new doctoral school director has now made a commitment to carefully follow the evaluations of the interdisciplinary projects.

The team is hosting many short term internships: BTS (1), Licence Pro (2), M1 (2), Master (7) and special international fellows (7).

Assessment of the strategy and the five-year plan

The proposed project, largely based on the work of the previous years, aims to characterize Met activation by HGF. This project is split into four parts:

- the first is to better understand, to optimize and to automatize the ligation chemistry for protein synthesis.

- the second is continuing to evaluate the role of each subdomain of HGF in the activation of c-Met (using chemically synthetized HGF). These two parts are directly managed by the team leader;

- the third part will be supervised by a junior scientist who will study the role of hypoxia in c-Met signalling, and, particularly, the role of the heparanase enzymatic activity in regards to c-Met activation;

- the final part, supervised by a senior scientist, concerns the isolation and characterization of normal and tumoral prostate epithelial stem cells.

The strategy around the HGF/c-Met activation is now well integrated in this multidisciplinary project. It is a very innovative and original project with a lot of preliminary and already published data. It also benefits from the expertise and the proximity of team 5 at IBL and also from an active collaboration with a bio-structuralist team in Italy. The project relating to prostate stem cells should be considered more as a supplementary project. However, it should rapidly be integrated into the main work of the team in order to benefit from its various scientific, human and financial support.

Conclusion

- **Strengths and opportunities:**

- the work of the team leader is widely known and recognized in its field. It shows impressive mutidisciplinarity;

- very innovative projects;

- high number of technicians;

- high number of publications with some published in journals of high impact factors in chemistry;

- important links with industrial partners;

- outstanding involvement in valorisation (creation of start-ups; patents and licencing).

- **Weaknesses and threats:**

- the research plan of one of the recently recruited member is unclear and seems to be uncoupled from the rest of the team focus;

- low student and post-doc attractiveness. Post-docs need to be recruited particularly regarding the high level of funding obtained.

- **Recommendations:**

- intensification of collaboration with other teams, such as team 5;

- more clearly define the subprojects of a scientist who recently joined the team. Currently, the prostate epithelial stem cells project seems to not be closely integrated with the rest of the proposal and lacks the vision for further “in house” development.

Team 5: Signaling, Apoptosis and Cancer

Name of team leader: Mr David TULASNE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)	3	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	1	
TOTAL N1 to N6	**10**	**8**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	4

- Detailed assessments

Assessment of scientific quality and outputs

The team leader has a real and recognised expertise in the regulation of Receptor Tyrosine Kinases (RTKs) and has made significant contributions in this domain. Over the last 5 years, the team has demonstrated that one of the fragments of the c-Met receptor generated by the proteolytic caspase cleavage of its C-terminal kinase domain (p40) leads to apoptosis amplification, a hallmark of dependence receptor, and that this phenomenon was mitochondrial-dependent. They also studied transcription factors (Ets1, NS1) and kinase (LOK). In each of these programs, they showed that caspase cleavage strongly modifies the function of caspase targets. This team is also interested in the impact of the Met amplification on cellular transformation. They demonstrated that transcription factors of the PEA family (ETV1, 4 & 5) could play an important role in Met-dependent effects such as cell invasion and resistance to targeted therapy. This work on Met was extended by a High-Throughput sequencing program, in collaboration with

clinicians from Canceropole Nord-Ouest, in colorectal cancer and associated metastasis through seeking mutations in different kinases.

A recently arrived junior scientist (previous equipe AVENIR) focuses on the inhibition of Nonsense-Mediated mRNA Decay (NMD) and activation of premature termination codon (PTC) readthrough, by developing a small chemical compound screening system. The goal of this strategy is to develop new therapeutic approaches for genetic diseases caused by nonsense mutations. They identified a compound (amlexanox) which is able to induce incorporation of an aminoacid instead of the nonsense codon.

The publication record of the team is good but not abundant (20, of which 12 are first or last author) and not in top ranking journals (except for the three collaborative studies). The best publications were in 2008 in *Cell Death and Differentiation* (IF 8.8) and in *Oncogene* in 2009 (IF 6.3). The other publications are in journals with an IF between 4 and 6. The team leader has good and long-term collaborations. Two collaborations have recently resulted in publications, or manuscripts still in revision, in top rank journals (*Mol Cell* and *Dev Cell* as a co-authorship). A CR1 from IPL of the team was also involved in a *Science* paper in 2008.

Assessment of the unit's academic reputation and appeal

The team has a certain visibility at the national and international levels, as shown by 8 invited conference presentations and lectures for the team leader. The team leader is also involved in some national and international (Belgium) expertise committees for evaluation and grant proposals.

The team seems to be attractive, since new people has recently joined the team including clinicians and pathologists (2) with good publication records, as well as a young investigator following an “equipe avenir” period. All these people will bring new expertise necessary for the development of the proposed project.

Whilst many different funding sources have been obtained by the team leader, all of them were at the local or national levels. Presently the team is not involved in European networks. They obtained many individual grants: ARC, three different “Ligue régionale contre le Cancer”, AFM and Fondation “maladies rares”, and as a partner in one ANR emergence and one INCa PL Bio grant. The ability to raise funds is a strong point in this team.

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

The team participates actively in different programs for high school students “apprentis chercheurs” “Kit campus” and “Fête de la science”.

The team obtained contacts with industrials and raised several private funds over the past five years.

Active participation in Canceropole Nord-Ouest. The junior scientist who recently joined the group, has recently filed a PCT patent on PTC activation. In addition, the team leader obtained two industrial contracts.

Assessment of the unit's involvement in training through research

The contribution to the teaching of students is satisfactory, with 3 PhD in the past 5 years. The team leader and one member of the team are involved in M1 and M2 courses. The MCU-Lille 1 is director of the master “Genomic and Proteomic” (Université Lille 1).

Assessment of the strategy and the five-year plan

The proposed project is a continuation of the previous one. It is mainly focused on understanding the molecular mechanisms leading to abberant Met receptor activation during tumorigenesis. New goals are based on translational projects.

The proposed project follows three main axes. The first is the study of Met fragments (caspase and Calpain fragments) in cell death mechanisms (apoptosis as well as necrosis). The role of mitochondria and the subcellular localisation of these fragments will be evaluated. A knock-in animal model has been generated (at the caspase cleavage site) and will be a useful tool in the future. An element of risk taking should be encouraged on this program.

This second part is directly associated with clinician collaborations, with several joining the team. They will try to establish whether the Met extracellular fragment dosage in the sera of patients with NSCL carcinoma could

represent a diagnostic tool to evaluate Met targeted therapy. The access to clinical samples and the molecular biology platforms (from Université Lille 2 and IBL) are clear added values.

The last part is distinct, and proposed by a junior scientist with the goal of identifying compounds able to activate PTC in models of rare diseases (Cystic fibrosis and Duchenne Dystrophy) as well as in cancer models, by rescuing expression of tumor suppressive genes. This final part is a continuation of its "avenir" program, but within the context of the team 5.

Conclusion

- **Strengths and opportunities:**

- good ability to attract young researchers and collaborators;

- pathologists and clinicians joining the team will aid the transferability of this project;

- links with industrial partners.

- **Weaknesses and threats:**

- low post-doc attractiveness. The lack of post-docs needs to be corrected, particularly in view of the high level of funding obtained and the high number of senior positions in the planned project;

- moderate number of publications and these publications are in journals of IF 5 or lower;

- the international collaboration of the team is rather limited;

- the project is solid and in direct line with the previous one, but its originality is moderate (at least for the first part). The expected level of risk for a project proposed by a team leader is also moderate.

- **Recommendations:**

- increase their interactions with team 4;

- the overall level of publications should be improved;

- the PTC project is original but highly risky and should receive more support if continued.

Team 6: Immunoregulation of Viro-induced Cancers

Name of team leader: Ms Nadira DELHEM

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	2
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5**	**4**

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

- ## Detailed assessments

Assessment of scientific quality and outputs

The team directed by Mr Yvan DE LAUNOIT has now split into two teams for the next term (teams 6 and 7). Ms Nadira DELHEM is head of team 6, Mr Yvan DE LAUNOIT (head of the unit) joined Ms Martine DUTERQUE-COQUILLAUD (head of the team 7). The scientific interests of the team are centered on the study of immunological events occurring in tumor pathologies associated to viral infections, such as hepatitis C virus (HCV) and Epstein - Barr virus (EBV) infections, involved in hepatocellular carcinoma and epithelial malignancies, respectively. In particular, they study effector and regulatory T lymphocyte (Treg) immune responses during tumor development and have developed immunotherapy approaches based on viral peptide vaccines and oncolytic viruses. The team has published 18 original articles of wich 13 are from the team, 3 reviews and 1book chapter since 2008. The highest cited paper is cited 100 times. They have made a PCT extension of patent n°11883814 and will file a new patent this year.

Over the last 5 years, the team has developed an immunotherapy approach based on a promiscuous class II peptide vaccine to activate CD4+ T-cell response against EBV latency II malignancies. They discovered that nasopharyngeal carcinoma-derived exosomes recruit via CCL-20, expand and up regulate biological activities of human Treg. Finally, they have determined the role of Treg in HCV fibrosis progression to hepatocellular carcinoma and in recurrence of HCV after liver transplantation.

Overall, although the field of investigation is difficult due to the team's dependence on access to primary human pathological tissues, the production of the team is good, taking into consideration its small size. However, the impact of the original findings of the team is limited and the level of publications rather low. This last point will be significantly improved when the manuscript on NPC exosome on Treg will be definitively accepted for publication.

Assessment of the unit's academic reputation and appeal

Relative to its small size, the team has a very good level of recognition. The team leader and another team scientist are members of several scientific and clinical international networks (HerPas, ISEV, GARNOR networks, Agence Biomédecine, INCa, ACHBT) and they are both invited speakers at national (10) and international (7) conferences. Another team member is the scientific director of Canceropole. All 3 coordinate national multicenter programs (2 ANRS, 1 OSEO,1 SIRIC ONCOLille). The team leader received the special Prize of ARC 2009 for Immunotherapy of EBV-associated cancers. They have organized several national meetings (10 since 2009).

In terms of international attractiveness, the team has hosted a foreign assistant professor from Algiers University (2-3 months/year since 2011) and 3 foreign students (3-6 months, Howard Hughes program and Erasmus-Mundus program).

They have been quite successful in obtaining grants: ANRS (95k€; 63k€; 85k€; 110k€), ARC (50k€), Ligue régionale (55k€), CNRS/PED (94k€), CNRS/Valorisation (40k€), OSEO/Region (50k€), PHRC Cancer (184K€), FRM (15,6k€), SIRIC ONCOLille (20k€).

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

Relative to its small size, this team has an excellent level of impact at the economic level. In particular they pursue 2 immunotherapy strategies lending themselves to drug development: promiscuous HLA class II EBV peptides in nasopharyngeal carcinoma, and Galectin 9 targeting to neutralize Treg. These 2 approaches are covered through patents, recognized by funding and drug development agencies (OSEO, CNRS Valo, Region, SIRIC ONCOLille) and pursued through industrial partnerships (Galpharma, Japan). One of the team members, scientific director of Cancéropôle Nord-Ouest, is involved in evaluating MATWIN projects.

Regarding cultural interactions, the team is strongly involved in scientific communication towards young people through participation in the "Fête de la science", conferences for a non-scientific audience (1-3 each year), and hosting 20 college and high school students for a week (2008 to 2013).

Assessment of the unit's involvement in training through research

The team (2 HDR) is actively involved in teaching, both through training PhD students (5 since 2008) and also through direct teaching contribution with 3 out of 4 permanent scientists of the team deeply involved in teaching duties (364 h/year). Furthermore, the team directly supervises all levels of students each year: BTS, L3, M1, M2R and M2 pro (22 in 4 years). Finally, the team leader is "Directeur des Études" of the new University Diploma « Tremplin - Réussite » of Lille 1 (Undergraduate Degree).

Assessment of the strategy and the five-year plan

The project is centered on tumor escape from immunosurveillance and on immunotherapeutic strategies for cancer associated with HCV and EBV infection.

Mechanism of tumor escape from the immune system: the team will pursue the investigation of Treg in HCC and in HCV infection to determine whether Treg aggravates viral pathology and/or HCV recurrence after liver transplantation. This project, relating to Treg as a target of HCV infection and a reservoir of HCV, appears quite fragile and risky. A second part is to analyze tolerogenic DC in establishment and persistence of cancer-induced immunosuppression in nasopharyngeal carcinoma (NPC) linked to EBV infection to determine whether this might represent a potent mechanism of escape from immunosurveillance.

Proposal for immunotherapeutic strategies in cancers: the team will evaluate their peptide immunotherapeutic antiviral strategy against EBV-associated NPC, alone or in combination with anti-Galectin-9 mab. In addition, they will develop neutralizing anti-Gal-9 therapeutic mAb for immunotherapy strategy in virus associated cancers. Preliminary observations of the team suggest that neutralizing anti-Gal-9 mAbs inhibit Treg suppressive activity.

The ambition of the project is in line with the size of the team, as well as with their strong links with the clinics, thus facilitating access to rare biological material. Their approaches based on these human samples should be pursued and are encouraged. Finally, the 2 immunotherapy approaches (Class II promiscuous EBV epitopes, anti-Gal9) appear promising and should be pursued and supported.

Conclusion

- **Strengths and opportunities:**

- the research at the interface of fundamental research and therapeutic applications;

- several discoveries and patents recognized and supported by business transfer structures;

- strong research questions;

- having a transplant surgeon in the team facilitates the access to valuable human material;

- good success in securing financial support;

- strong involvement in training and teaching;

- good national recognition;

- return of a former PhD of the team and currently post-doc in an US laboratory, NIH, Washington), for 2 years;

- acceptance into the maturation program of Matwin: "Development of a drug candidate: from research to early clinical trial."

- **Weaknesses and threats:**

- the scale of publication and citation, although this point has to be moderated considering the size of the team) which, however, remains good for the size of the team;

- the research is highly dependent on human pathological samples limiting the quantity of information extracted and may lead to over-interpretation;

- no full time researcher in the team (the only scientist without teaching duties is the scientific director of Cancéropole);

- no grants from international organisms;

- strong competitiveness in the primary hepatocellular carcinoma field.

- **Recommendations:**

- the project on Treg as a target of HCV infection and a reservoir of HCV appears fragile, caution should be exercised in perusing this avenue;

- the widespread use of new, efficient anti-HCV therapies is imminent, at least in developed countries. The team must seriously consider the future clinical relevance of the HCV project;

- recruitment of a full-time researcher would be important to strengthen the team.

Team 7: ETS proteins and associated diseases

Name of team leader: Ms Martine DUTERQUE-COQUILLAUD

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		1
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	2	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5**	**7**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	4

• Detailed assessments

Assessment of scientific quality and outputs

The team directed by Mr Yvan DE LAUNOIT has now split into two teams for the next term (teams 6 and 7). Mr Yvan DE LAUNOIT (head of the unit) and Ms Martine DUTERQUE-COQUILLAUD (Head of the team 7) both have a strong expertise in the ETS field, working for over a decade on PEA3 and ERG proteins, respectively. The project proposed by team 7 is based on original and interesting observations. Taking advantage of a transgenic mouse model, they first highlighted the role of the ERG protein on cell determination, ERG depletion in chondrocytes leading to the induction of an adipogenic program. They next focused their interest on the TMPRSS2-ERG gene fusion, recurrently observed in a large proportion of prostate cancers. In light of the role of the ERG protein on chondrocytic differentiation and the homing of prostate cancer cells to the bones, the team analysed the impact of ERG expression on metastasis development. Ectopic expression of the fusion protein into a prostate osteotropic cancer cell line promotes osteoblatic lesions over osteolytic lesions. Although the underlying mechanism remains to be established, this likely

reflects the ability of the TMPRSS2-ERG to affect the interactions between metastaticrostate cells and the bone environment. Gene expression profiles were performed to identify potential targets genes. Among them, the PLXNA2 gene which likely contributes to osteoblastogenesis, was confirmed to be co-expressed with the TMPRSS2-ERG fusion on human samples (by IHC) and shown to associate with a poor survival prognosis. Lastly, in a collaborative context, a specific chemical inhibitor of ERG has been identified and validated in a reporter assay.

Their work has led to the publication of 36 original manuscripts published in international journals (with an IF<10; *Exp Cell Res; Mol Cancer Res; Oncogene; Nucleic Acids Res…*) as well as oral presentations in an international (2011) and a national (2012) congress and has been supported by INCa and LNCC grants. A patent on chondrocyte culture was filed in 2010.

Assessment of the unit's academic reputation and appeal

Ms Martine DUTERQUE-COQUILLAUD and Mr Yvan DE LAUNOIT have both been involved in the jury for PhD fellowships at the "École Doctorale Biologie & Santé de Lille" as well as in committees of Foundations ("Inbev Baillet-Latour", "Eyes and brain deseases"). Mr Yvan DE LAUNOIT is additionnally a member of multiple committees (Cancéropole Nord-Ouest, SIRIC ONCOLille, advisory board of the Pasteur Institute, Eurasanté, AERS experts committees), is the director of the unit as well as of the GDS3366. Both contributed to the organization of a one day meeting at the IBL on ETS fusion proteins (2013).

Both of them have reviewed publications submitted to numerous international journals (*Nature*, *EMBO J.*, *NAR*, *MCB*, *MBC*, *Oncogene*), demonstrating a very good academic reputation.

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

Mr Yvan DE LAUNOIT was invited to several public manifestations (including a TV show) and was a guest of the ARC foundation for "Café de la recherche". The team leader contributes to a journal designed to appeal to the wide public "Parlons science" and annualy welcomes students to the IBL for an introduction to science.

Assessment of the unit's involvement in training through research

Two M2R students have been trained during the last quadrienal. The team also includes a post-doctoral fellow.

Demonstrating a strong involvement in teaching, the team leader and Mr Yvan DE LAUNOIT are in charge of teaching modules (Genetic and Microbiology, Fundamental Oncology and Clinic) in the Université Lille 1, Lille 2 and give lectures at the Université de Picardie/Faculté de Pharmacie Amiens. Mr Yvan DE LAUNOIT gives lectures at the Faculty of Applied Sciences in Belgium. Another team member (MCU) is also director of the Master (M1-M2) "Génomique et Protéomique" Université lille 1.

Assessment of the strategy and the five-year plan

The project proposed by the team is a continuation of their previous work. The first objective consists of identifying a gene signature associated with the expression of the TMPRSS2-ERG fusion protein in an attempt to ascertain novel targetable proteins. Direct target genes will be identified by CHIP-seq. Similar experiments will be performed with the TMPRSS2-ETV1 fusion to compare the two signatures. Functions of the fusion proteins will also be addressed by deciphering their impact on the transcriptional regulation activities and by identifying the involved ETS-partners as it was previously shown in the team for the AP1 complex and the nuclear receptor.

Secondly, the impact of the TMPRSS2-ERG fusion protein on bone microenvironment will be further evaluated by performing co-culture experiments with a focus on secretome analysis. Finally, the impact of the TMPRSS2-ERG fusion protein on bone tropism will be assessed through intracardiac injections of cells.

Overall, the project suffers from a relative lack of ambition. To avoid competition, the team focuses on mechanical aspects rather than addressing the pertinent questions (e.g. role of the fusion protein in cell reprogramming and malignant progression), thereby limiting their international visibility in the future. The model proposed is not optimal. They transfected the *TMPRSS2-ETV1* gene into a cell line which is already osteotropic without expressing the fusion gene constitutively. Introducing the *TMPRSS2-ETV1 fusion* gene into this cell line is not the best strategy to unveil the molecular roles played by the *TMPRSS2-ETS fusion* gene.

Conclusion

- **Strengths and opportunities:**

- high expertise in the ETS field;

- accessiblity to a cohort of human prostate cancer samples (tissue banks of the CNO and CHRU of Lille);

- the project is based on interesting and original observations and concerns an important unresolved public health problem: the metastatic dissemination of prostate cancer.

- **Weaknesses and threats:**

- the size of the team is a limiting factor with one post-doctoral fellow;

- the proposed research project lacks ambition and is not connected to other projects developed in the research unit;

- too few international collaborations;

- no participation in European research projects;

- no high impact factor publications.

- **Recommendations:**

- the team should be strengthened by the arrival of new post-doctoral fellows;

- international collaborations should be further developed;

- the research program should be more ambitious to gain in visibility.

5 • Conduct of the visit

Visit dates:

Start: Thursday January 09 th 2014, at 09.00 am

End: Friday January 10th 2014, at 07.00 pm

Visit site: Institute of Biology in Lille

Institution: UMR 8161 CNRS

Address: 59000 Lille

Conduct or programme of visit:

Thursday 09th

09.30 am Director of the unit (presentation + discussion): presentation of the past activities and project

10.30 am Coffee break

11.00 am Team 1 – Initiation of Epithelial cancer (Ms Corinne ABBADIE)

11.45 am Team 2 – Functional studies of the tumor suppressor gene HIC1 (Mr Dominique LEPRINCE)

12.30 pm Lunch

02.00 pm Parallel meetings with personnel:

- discussions with engineers, technicians, administrative
- discussions with staff scientists
- discussions with students and post-docs

03.30 pm Team 3 – Egfl7 functions during physiological and tumoral vascular development (Mr Fabrice SONCIN)

04.15 pm Coffee break

04.45 pm Team 4 – Cancer Biology and Chemistry (Mr Oleg MELNYK)

05.30 pm Debriefing on the team presentations

Friday 10th

09.00 am Team 5 – Signalling, Apoptosis and Cancer (Mr David TULASNE)

09.45 am Team 6 – Immunoregulation of viro-induced cancers (Ms Nadira DELHEM)

10.30 am Coffee break

11.00 am Team 7 – Ets protein and associated diseases (Ms Martine DUTERQUE-COQUILLAUD)

11.45 am Discussion with the representatives of the managing bodies (CNRS, Université Lille 1, Institut Pasteur de Lille, École Doctorale)

12.30 pm Lunch

01.30 pm Private discussions with each of the team leaders

02.30 pm Discussion with the head of the unit

03.00 pm Private meeting of the experts committee (in presence of the AERES scientific advisor)

06.00 pm End of the visit

Specific points to be mentioned:

Mr Gilbert BAILLAT (INT, Marseille, representative of ITA CNRS) was present during the visit.

6 • Supervising bodies general comments

Université Lille1
Sciences et Technologies

DIRVED
Direction de la Recherche,
de la Valorisation et
des Etudes Doctorales

Le Président de Lille1,

Sciences et Technologies

A

M. le Président de l'AERES

Objet : réponse au rapport sur le laboratoire IBL
Vos références : E2015-EV-0593559Y-S2PUR150007531-005131RT
Nos Réf : DIRVED -2014-343

M. Le Président,

Je tiens à remercier le comité de visite de l'AERES pour le temps consacré à l'évaluation, la qualité des échanges et les recommandations pertinentes proposées. Le laboratoire IBL, Institut de Biologie de Lille, s'engage à mettre en œuvre, dans les meilleurs délais, ces recommandations.

Vous trouverez ci-joint la réponse de la part du laboratoire ; elle comprend :

- Des demandes de corrections factuelles,
- des observations générales portant sur le rapport d'évaluation.

Je vous prie d'agréer, cher collègue, l'expression de toute ma considération.

Villeneuve d'Ascq, le 7 Avril 2014

Le Président de Lille1,
Sciences et Technologies

P. Rollet

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Institut de biologie de Lille

Institut Pasteur de Lille

Lille 2 Université du Droit et de la Santé

UMR 8161

Institut de Biologie de Lille

Université Lille1

M. Le Président,

Veuillez trouver ci-dessous la réponse au rapport d'évaluation de l'AERES concernant l'UMR 8161, Institut de Biologie de Lille.

Au nom des responsables d'équipe et de l'ensemble des membres du laboratoire, je souhaite adresser des remerciements tout particuliers aux membres du comité de visite qui s'est tenu les 9 et 10 janvier 2014. En effet, leurs remarques constructives émises lors de l'évaluation ou indiquées dans le rapport nous ont permis d'infléchir certaines orientations prises par l'une ou l'autre équipe. Nous avons tenté de prendre en considération et de répondre de la façon la plus satisfaisante aux recommandations proposées par le comité.

1. Observations sur le rapport d'évaluation :

Comme indiqué ci-dessous, nous avons considéré et suivi, dans la mesure du possible, les recommandations principales du comité de la façon suivante :

Assessment of the unit.

- The members of the committee pointed out on **page 5**, as a weakness, an insufficient ambition of some scientific programs probably due to the "lack of in vivo approaches" developed by the different teams. The term "lack" seems to be inadequate since all of the 7 teams have in vivo mouse research programs, which of course need to be reinforced. It is thus proposed to replace the sentence "lack of in vivo approaches" by "**too few in vivo approaches**".

- The committee recommends (**page 5 last sentence**) to strengthen interactions with clinical departments. Although this has been initiated in 2011 on the hepatocarcinoma program, this has been reinforced by the recent recruitment of four clinicians, mainly on lung and breast cancer programs. Other clinicians from the CHRU of Lille and the CLCC (Centre Oscar Lambret) are now highly interested to join the lab in order to directly participate to other translational research programs, such as prostate metastasis.

- It is also strongly recommended to increase the interactions between the different teams. Although during the 5 last years, all of the unit members met twice a year (2 day-meeting in spring and fall), it is recommended to have more frequent scientific meetings. The Board of Directors of the unit decided to organize two times per month (Tuesday morning) a scientific meeting. However, let us mention here that some inter-team collaborations already exist, as materialized by publications signed by at least two different teams of the unit (for example between teams 1 and 2 and between teams 4 and 5).

- Finally, the committee strongly recommended initiating a strategy to increase attractiveness, scientific ambition of the teams and international networks and grants. The team leaders are aware of this and will take this recommendation as a priority. They for example propose to reinforce the link with bio-structuralists which could open new avenues in the different research programs of the lab.

Detailed assessments.

- **Page 8 : 1st paragraph** of Assessment of the Unit's organization and life : As suggested, a written report following each team leader meeting will be transmitted to the whole unit.

- **Page 8 : 3rd paragraph** of Assessment of the Unit's organization and life : In order to increase the interactions between the Chemistry team and the other the teams of the unit, the regular scientific meetings will be crucial.

- **Page 8 : last paragraph** of Assessment of the Unit's organization and life : The General Secretary of the unit, in close collaboration with the team leaders and the board of the laboratory members, will write an Internal Procedures document (Réglement Intérieur).

- **Page 9 : first paragraph** of Assessment of the strategy and the five-year plan : The "ambition", which seems to be weak as felt by the members of the Committee will be strengthened in the next few months by for example creating inter-disciplinary programs.

Team 2.

Page 14, first paragraph : *No high risk avenues are taken and innovative character is missing at times (i.e. lack of attempts to integrate state of the art technology).* This sentence is not right. In fact, team 2 previously published more of 50% of the known HIC target genes, mainly through microarray approaches. The team also used proteomics (mass spectrometry) 1) to characterize and validate HIC post-translational modifications and 2) to characterize its partners. In parallel, they identified HIC1 partners through two-hybrid screen. ChIP and ChIP-Seq experiments are currently developed.

Team 3.

Page 17, in the "Weaknesses and threats" section, the committee suggested that team 3 should elaborate a strategy to choose the most interesting genes which will arise from the HTS. Indeed, such strategy has been detailed as a 3-step validation process in the INCa PL Bio 2013-2017 grant demand which now supports this project.

Team 6.

Page 27, Recommendations section:

- *"the project on Treg as a target of HCV infection and a reservoir of HCV appears fragile, caution should be exercised in perusing this avenue":* This subject developed by a PhD student in team 6 cannot be considered as fragile but rather risky. Indeed, this project pushes a number of dogmas concerning "exclusive" hepatotropism of HCV and her work is regularly awarded (6 oral presentations in Congress since 2011 and 3 special prizes).
- *the widespread use of new, efficient anti-HCV therapies is imminent, at least in developed countries. The team must seriously consider the future clinical relevance of the HCV project.* As mentioned in the AERES report, the main research program of this team will be refocused firstly on the establishment of anti-tumor immunotherapy strategies and secondly to study the role of Treg in tumor tolerance with two models of cancer : malignant diseases associated with EBV and CHC regardless of HCV infection. The sofosbuvir is still in clinical testing and should be available in 2015 only in some industrialized countries due to the exorbitant price of the treatment (56 k€ for 12 weeks). Basic research remains thus crucial and it is believed that many teams will continue to work on HCV as previously observed for HBV for which a preventative vaccine exists since 1982.

Team 7.

Page 29, last paragraph:

The AERES report focused on "*lack of ambition*" of the project and the team strategy "*to avoid competition*". Actually, since the metastatic evolution of prostate cancer is considered as the main incurable issue, particularly bone metastasis, and due to the "*interesting and original observations*" (Strengths section), team 7 decided to focus on deciphering the molecular mechanisms of TMPRSS2-ETS fusions in prostate bone metastasis formation instead of addressing other possible "*pertinent questions (e.g. role of the fusion protein in cell reprogramming and malignant progression)*".

Concerning the two last sentences, team 7 is well aware that the chosen cell line model cannot alone unveil all the molecular roles of both tropism and local development of bone metastases. Therefore, we propose to temper these sentences: "The model is not optimal to study bone tropism. The transfection of the *TMPRSS2-ETS* genes into a cell line which is already osteotropic without expressing the fusion gene constitutively will only study the metastastic formation in a bone microenvironment. Introducing the *TMPRSS2-ETS* fusion genes into this cell line is not the best strategy to unveil the molecular roles played by the *TMPRSS2-ETS* fusion gene in bone tropism."

Veuillez agréer, cher Collègue, l'expression de mes sentiments les plus respectueux.

Yvan de Launoit
Directeur – UMR 8161