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Evaluation of LIH-DONC

Report by the external peer review committee

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Professor Pierre Hainaut (Chairman)
Professor Colin Watts
Dr Rolf Apweiler
Geert van der Veen, Anke Nooijen (rapporteurs)

Executive summary

This report presents the results of the peer review of the Department of Oncology (DONC) of the Luxemburg Institute of Health (LIH). The review covers the period 2014-2017 and considers scientific performance, relevance for society including client and partner interaction and the governance and organisation as requirement to sustain the ability and suitability for promoting both scientific performance and interaction with clients).

The audit was performed by an independent external assessment committee, consisting of three internationally renowned researchers in the field of the research of the Department, prof Pierre Hainaut, prof Colin Watts and Dr Rolf Apweiler. Geert van der Veen and Anke Nooijen (Technopolis Group, The Netherlands) acted as support for the peer review committee.

The committee concludes that, during the past 5 years, DONC has successfully gone through a developmental phase to establish itself as viable and recognized scientific structure. Given its current level of operation and scientific quality, DONC has a clear opportunity to move from *excellent* to *outstanding* level in the next 5 years. This will require a clear plan for providing DONC with better infrastructure and integrating its activities in a well-defined strategic plan at national level, within LIH and with the medical sector. The main threats currently faced by DONC are (1) strengthening its governance and management structure; (2) strengthening its relevance towards the development of cancer control and therapeutic innovation in Luxemburg; (3) strengthening its international position by accessing EU grants such as ERC and H2020.

The Committee has 5 key recommendations, formulated in order to support DONC development with respect to its core missions and to its progress from *excellent* to *outstanding* level.

1. Provide **comprehensive strategic planning** at the national level within a general framework for building and developing a national health campus and for promoting translational and clinical cancer research in hospitals throughout the country.
2. The comprehensive strategic framework should include an investment plan for providing DONC with adequate **infrastructure**, competitive at international level, and supporting its development over the next 20-30 years.
3. **Governance, work culture and resources**: Attention should be brought to the mechanism for recruiting and appointing the next director. The governing structure of DONC should be revised to provide more clarity, strategic planning and transparency in decision-making for budget prioritisation and allocation. Efforts should be made to promote a broader work culture more supportive for innovation and collaborations with start-ups, spin-offs and private sector.
4. **International outreach:** DONC should strive to obtain a larger share of its resources from international competitive grants such as ERC and H2020, as well as from research contracts with the private sector. As part of this greater visibility, DONC should strive to have key PI supported by ERC grants.
5. **Clinical research and training of MDs:** the Committee strongly supports the strategy of DONC to be a leader in the development and coordination of a National Centre of Excellence in Research in Oncology.

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1 Introduction

1.1 Background

This report presents the results of the peer review of the Department of Oncology (DONC) of the Luxemburg Institute of Health (LIH). LIH has the mission to deliver scientific, economic and societal value for Luxembourg by performing research, studies and developments in the fields of clinically-oriented biomedical research and public health. LIH's activities lead to the generation of new knowledge in disease mechanisms, epidemiology, diagnostics and treatments of human diseases, and they improve the understanding of health determinants and of the financial structures of health care. Since its formal establishment and restructuring in 2014, the Department of Oncology (DONC) has positioned itself as a central actor within oncology research and training in Luxembourg, with focused research areas in neuro-oncology and immuno-oncology where international competitiveness has emerged.

The peer review is part of an evaluation of the three research institutes under the responsibility of the Luxemburg Ministry of Education, Science and Research (MESR). The evaluations cover the period 2014-2017 and take into account scientific performance, relevance for society including client and partner interaction and the governance and organisation as requirement to sustain the ability and suitability for promoting both scientific performance and interaction with clients. The evaluation has been assigned to Technopolis Group (www.technopolis-group.com).

The results of this peer review feed into the evaluation of LIH as an institute and into the evaluation of the three institutes at national level. For this reason, the chairman of the DONC peer review also participates in the peer review of LIH at institutional level. The results are intended for MESR to (re)define their relation to the institute; for the institutes to help them to improve their performance further and for other (mainly public) stakeholders to use as they find suitable.

The peer review set-up has been designed by Technopolis Group, based on the Terms of reference from MESR. It aligns with good practices used in many evaluations.

1.2 Composition of the Committee, independence, data provided and procedures followed

1.2.1 Composition of the Committee

The audit was performed by an independent external assessment committee, consisting of three internationally renowned researchers in the field of the research of the Department:

- Chairman: Pierre Hainaut, PhD, Professor of Cancer Biology, Université Grenoble-Alpes; Director of Institute for Advanced Biosciences, Grenoble France
- Colin Watts Professor of Neurosurgery & Chair Birmingham Brain Cancer Programme University of Birmingham
- Dr Rolf Apweiler, Director EMBL-EBI, Cambridge, UK

Short CV's from all assessment committee members are attached in Appendix A.

Geert van der Veen and Anke Nooijen (Technopolis Group, The Netherlands) acted as support for the peer review committee.

1.2.2 Independence

Any existing personal or professional relationships between committee members and programmes under review were reported and discussed in the committee meeting to safeguard an independent assessment of the quality of DONC and its research programmes in an unbiased and independent way. The Committee concluded that there were no close relations or dependencies and that there was no risk in terms of bias or undue influence.

1.2.3 Data provided to the Committee

In preparation of the review the peers received the following information:

- A self-assessment report of LIH at institute level
- A self-assessment report of DONC at department level
- A background report for the peer review of LIH prepared by Technopolis Group, including a.o. an analysis of the participation of LIH in FNR and EC research projects and a bibliometric analysis of the publications of LIH (by ECOOM).

The assessment in combination with the discussions of the peer review committee with the research leaders, researchers and stakeholders allowed an objective evaluation of DONC.

1.2.4 Procedures followed by the Committee

The final assessments are based on the documentation provided by the Institute, the key publications and the site visit to DONC in Luxembourg on 10-11 September 2018 (programme in Appendix B).

At the beginning of the site visit, the Committee was briefed by Robert Kerger of MESR and Geert van der Veen and Anke Nooijen of Technopolis Group about the objectives of the evaluation in general and of the evaluation by the committee in particular. During this meeting, several questions were clarified. The Committee also agreed upon procedural matters and aspects of the assessment.

At the end of the site visit and interviews the Committee discussed the conclusions and recommendations. Preliminary draft conclusions were presented to the participants in the discussions including the management of DONC and LIH and representatives of the Ministries of Research and Health.

A first version of this report was drafted by the peers in the week after the site visit to Luxemburg. The report was finalised through email exchanges. The consolidated version was presented to the Institute beginning of October 2018. The reaction of DONC was discussed by email by the Committee and led to adjustments of some factual points. The final report was then submitted to MESR.

For the assessment of the quality of the research, DONC was compared at the international level with their peers. Publication and citation records were examined; major achievements were considered and the capacity to be competitive in application to international funding and in attracting highly qualified students and collaborators was discussed. For obtaining a view of the relevance for science, elements such as recognition as a knowledge centre, participation in expert groups, leadership in EU projects, membership on editorial boards and professional societies were used.

The relevance of DONC in relation to health research was judged at the international and national level. Services and expertise rendered to private and public clients and partners and the impact on the general public served to assess the relevance for society.

The aspects of governance and organisation of DONC were mainly focused on the discussion about the strategy with DONC staff members. The findings are presented in this report. The findings related to the departmental organisation show adequate robustness, since they have been discussed with the most relevant stakeholders. The findings related to the positioning of the department within LIH and the positioning of LIH in the health (research and education) landscape in Luxembourg and in international perspective give the reflection of the peers on the vision of DONC but require further input from other stakeholders inside and outside LIH. Therefore, these findings are preliminary and will feed into the evaluation of LIH at institute level.

It has to be noted that the budget- and financial management of DONC and its coherence with its missions and scientific program have not been evaluated in detail. This is due to lack of sufficiently precise and specific information made available to the Committee neither in the self-assessment report, nor in the background report prepared by Technopolis Group, nor during the site-review.

2 The positioning of DONC research: rationale and strategy

2.1 DONC strategy and targets

The overall missions and goals of DONC as outlined in its SAR (Self-Assessment Report) are the following:

- To be instrumental in the development and execution of world-class cancer research within prioritized areas in line with the national research focus defined through the National Cancer Plan (Plan Cancer).
- To provide a training ground for the next generation of cancer researchers in Luxembourg and abroad, and should be a reference point for cancer research at the national level.
- To strengthen ties with the University of Luxembourg through collaborative projects, joint PhD student training and the establishment of joint professorships.
- To act as knowledge hub for cancer research within Luxembourg and to set up and coordinate a National Centre of Excellence in Research in Oncology.
- To be proactive in establishing new investigator-driven clinical trials in Luxembourg, in close collaboration with local hospitals and the Clinical Investigation Center (CIEC) of LIH.

Overall, the Committee considers that these missions are appropriate and commensurate with the current state of development and integration of basic, translational and clinical research in Luxemburg. The Committee notes that these missions are adequately focused on the development of these activities and on the need for Luxemburg to get organized in order to improve access and deliver the full range of cancer control modalities commonly encapsulated in the terms “personalized” of “precision medicine”. This implies building strong and focused competitive research; training and providing competitive career paths for outstanding individuals who will be tomorrow’s leaders; structuring collaborative networks across the entire range of national stakeholders including academia, health services/hospitals, public health, industry and patient’s organizations, and translating these actions through medical innovation and clinical trials.

The Committee notes that DONC summarizes its strategy under the headlines “excellence is cancer research geared towards translational output”. This is an appropriate summary of the missions. The current research activities of DONC are consistent and coherent with these missions. The Committee also notes that research is adequately focused on defined areas of excellence and that very significant progress has been achieved over a few years, under the leadership of the current Department Director, to bring initially disparate research projects into a logical research agenda. The Committee notes that DONC has a strong basis of excellence in fundamental and mechanistic cancer research and that currently aims at expanding its translational outreach. Milestones in this respect are the recruitments in 2017 of two translational research groups, one headed by Dr Michel Mittelbronn, a neuro-pathologist who is also in charge of national cancer pathology services, and Dr Antonio Marchini, who is developing a program on oncolytic viral cancer therapies (collaborative program with DKFZ, Heidelberg). DONC states as concrete goal for its strategy to set up a National Center of Excellence in Research in Oncology (NCER-ONCO), aimed at developing translational research in dedicated areas and at developing strong interactions with hospitals. Another strategic action of DONC is its involvement in the CLINNOVA project, a H2020 Teaming application aimed at establishing a center for innovative medicine on e-health and big data. During the review, the Director presented as flagship program for the future the creation of a new research unit/platform (TRONC; Translational Oncology) to set up a project aimed at profiling patient’s biopsies through a FDA drug panel. The aim of this platform is to identify the individual tumour responses to drugs in order to inform therapeutic decision. This project is proposed in the context of a collaboration with Ksilink, a French company developing an integrated process for multiplexing and functionally testing patient’s cancer biopsies for a panel of 50-300 drugs.

The Committee however expresses concerns at the fact that many of the missions assigned to DONC are critically dependent upon external factors, which are not under the control of DONC management structure. The two most significant issues in this respect are:

- The lack of developments in structuring medical training, medical services and clinical trials, making it difficult for DONC to establish a sufficiently strong and stable basis for developing translational and clinical cancer research;
- The lack of an adequate infrastructure to fulfil the integrative vision outlined by the missions, in particular the lack of appropriate housing within an environment that physically supports the networking and integrative activities DONC is expected to carry out (e.g. Luxemburg Health/Cancer Campus).

These external factors make it difficult for DONC to develop fully operational and clear forward looking strategic and implementation plans for putting the vision and missions into practice. The Committee feels that the main obstacle is the lack of a sufficiently coherent strategy from the level of ministries of health and education/research downwards. The Committee notes the lack of a clear agenda jointly endorsed by these two major governing bodies and stakeholders, providing a framework on how to develop a strategy fulfilling all aspects of the mission. To date, DONC has reached an undisputed overall level of excellence in performing research (see section 3.1 of this report) and it is in a position to align broad scientific strengths across the teams Norlux, LECR and computational quantitative biology. These activities have reached a degree of scientific maturity that makes it possible to generate a stronger impact on therapeutic innovation in cancer and on the development of cancer control in Luxemburg. Importantly, the Committee notes an excellent sense of vision and direction at the level of individual groups, which all have a relatively clear program, agenda and strategic plan, compatible with their specific missions. Much more could be realized, however, if these groups were more able to interact, share their skills, and develop joint programs aimed at translating the best of their scientific and technological capacities towards the clinics.

Importantly there is an urgent need to develop an overarching strategy and sense of scientific identity/mission. This will allow realization of flagship projects to emerge, drawing on the broad skill sets available, that can be aligned to a broader LIH strategy orientated toward the healthcare and research needs of Luxembourg.

2.2 DONC clients and stakeholders

The key communities served by DONC are: national stakeholders who are responsible for defining the agenda for health services; academia; medical doctors/oncology; cancer patients; R&D/innovation sector; and the community as a whole.

Besides the fact that the Luxembourg Ministry of Health has an observer role in the Board of Directors of LIH, the Committee notes that none of these communities appear to be formally involved in the operations of DONC. The Committee has not identified a consulting board of stakeholders, or similar structure, which would be in a position to provide advice and information at regular interval to DONC leaders on the scope and general direction of their activities, as well as on opportunities, expectations and external threats. The Committee has the impression that most of these contacts exist at an informal level. On the other hand, the Committee acknowledges that the problem may primarily be due to a lack of organization at the level of these stakeholders.

The Committee notes that DONC has established an external Scientific Advisory Board (SAB), which formally met in 2016. This SAB was composed of suitably qualified international experts. In its report, the SAB formulated a number of useful recommendations, in particular on how to better integrate the activities of the different research units. The Committee did not see the response of the Director to these recommendations. On the other hand, this SAB meeting appears to have taken place only once, with no formal follow-up. It is not clear whether the SAB has been consulted on the strategic plans presented for this review.

3 Assessment of DONC

3.1 Research quality

The current research portfolio of DONC encompasses three research units:

- *Norlux Neuro-Oncology Laboratory* (Head: Simone Niclou), comprising 5 research groups: Luxemburg Center of Neuropathology (LCNP; Dr Michael Mittelbronn), Luxemburg Oncolytic Viral Immunotherapies (LOVIT; Dr Antonio Marchini), Norlux-DNA repair and chemoresistance (Dr E Van Dijck), Norlux-Glioma Biology (Dr Simone Niclou) and Norlux-Cancer metabolism (Dr. Johannes Meiser).
- *Laboratory of Experimental Cancer Biology* (LECR; Heads: Dr Guy Berchem and Dr Bassam Janji), comprising 3 research groups: LECR-CCP- cytoskeleton and cancer progression (Dr Clément Thomas); LECR-TM tumor microenvironment (Dr Bassam Janji) and LECR-TSI tumor stroma interactions (Dr Emmanuel Moussay). The team also includes a platform of confocal imaging (Dr Céline Hoffmann).
- *Genome and Proteome Research Unit* (GENPRO; Head: Dr Gunnar Dittmar), including 2 research groups: Bioinformatics and Modelling (BIOMOD, Dr Francesco Azuaje) and Discovery proteomics (DISPROT, Dr Gunnar Dittmar). This research unit also hosts the newly created Genomic Center (GenLux, Dr Gunnar Dittmar).

In addition to the 3 research units, DONC also runs the LIH animal facilities and in vivo imaging platform (under the overall responsibility of Dr Simone Niclou).

During the review, each of the research unit was audited separately (1h30), in the presence of the leaders of each research group. The review focused on the quality of research, on future plans and on strategy/coherence at the level of the research units (not individual teams within the units). Platforms and technological activities were not formally audited.

Overall, the peer review committee considers that the research carried out at DONC is of *good* to *excellent* quality. Its standing is such that this research is internationally visible and active to an international degree, with the clear potential to become an even stronger player on the international stage. The quality of publications is generally good to excellent with papers being cited more than average for the relevant journal[1]. This scientific excellence is well identified in the bibliometric analysis made available to the review committee, which rates the scientific production as being in the upper segment of the international production in each relevant field. The research units consistently publish

[1] As indication, the terms of evaluation used in the present assessment are defined as follows:

- *Outstanding*: top 10% of competitive research at EU level. Typical markers at this level are: ERC funding, coordination of H2020 programs, flagship publications as first/senior author in top generalist journals at IF>20 (Nature, Science, Cell, Lancet, NEJM, etc.), patents with subsequent industrial/commercialization impact, invitations to major international meetings, attractiveness for industrial grants.
- *Excellent*: top 11-25% of competitive research at EU level, top 10% at national level. Typical markers are: partner in H2020 programs, flagship publications in reference journals in the field at IF 10-20, co-authorship on papers at IF>20, patents with commercialisation plans, frequent oral presentations in top meetings in the field
- *Good*: above EU research average, top 25% at national level. Typical markers are: competitiveness in attracting national funding, flagship publications in specialist international journals at IF 5-10, IP/patents in development, visibility at international meetings
- *Average*: EU research average, 26-50% at national level. Typical markers are: sustained national funding, flagship publications at IF 3-5, national recognition.
- *Non-competitive*: below EU research average, <50% at national level. Typical markers are: piecemeal funding mainly from non-competitive sources (e.g. local foundations), scattered publications mostly below IF 3, limited visibility.

A general comment is that the assessment of the Committee is not exclusively, and even not mainly, based on the bibliometric analysis provided in the report. It takes into account the views of the Committee on the design, quality and impact of flagship productions, independently of their numeric bibliographic impact. As disclaimer, the assessment is not intended at ranking, comparing, or otherwise scoring the activities or abilities of individual PIs.

their production in leading journals of their field, at an impact factor of 5-15. Broadly, the Committee rates this research as competitive at a level equivalent to the best research centers in the broad area around Luxemburg (universities/research centers in Belgium, Southern Netherlands, Western Germany, North-Eastern France). The Committee however notes the absence of truly outstanding publications in the world's top journals such as Nature, Science, Cell, The Lancet or New England Journal of Medicine. This indicates that the level of scientific production is one/two notches under the very best/top competitive research groups in Europe. A fair assessment is that it ranges in the top 11-25% at competitive EU level. This overall excellent level of scientific performance is to the credit of the Director, research unit and team leaders.

As a result, the international standing of the key scientific leaders is also good to excellent. They are well-known and recognized in their communities. The group leaders would be competitive for similar positions in academia/research in neighbouring countries. Norlux, an established program that relies on a strong and structured collaboration/integration with the University of Bergen, Norway, has established itself as a flagship European program on glioma biology and genetics, although its international credit is not entirely attributed to Luxemburg since its stronger clinical basis is in Norway. LECR has assembled a coherent agenda of research programs driven by young team leaders who have made an impressive mark in the past 2-3 years by publishing excellent papers in top-ranking journals. Both units are present and contributing at international meetings and conferences in their areas. GENPRO is in transition, following the departure of Dr Bruno Domon and his replacement by Dr Gunnar Dittmar. Overall, proteomics activities in Luxemburg have achieved international recognition for their contribution to technology and methodology in this field. Their international standing on cancer biomarker discovery is less strongly established.

One of the indicators of excellence that does not fulfil the expected standards is the participation to international projects competitive (H2020) and also ERC grants at the various levels. The Committee sees this as an anomaly, since several team/unit leaders appear to have appropriate achievements and credentials to successful apply to such programs, and since the positioning of the research is competitive and appealing at international level. The Committee feels that this situation is in part due to the specific research environment, which enables unit/team leaders to readily access less-competitive national funding, while it lacks a proactive "grant access" program to help researchers in developing and preparing complex and more demanding international grant applications.

Thus, to some extent, in the opinion of the peer reviewers, the scientific success of DONC have been achieved despite rather than because of the infrastructure and research environment.

3.2 Value for Luxemburg

As can be derived from the above, the value for Luxemburg of DONC research activities as a whole is evident and undisputable. The Department is at the forefront of science in the country and contributes to its international recognition. However, beyond reputation, the benefits of this research activities remain underexploited and do not sufficiently translate in added value for Luxemburg. In other words, there is currently an imbalance between the quality of science, which is high, and the value delivered at country level, which is lower and more in the medium range.

More specifically, in terms of value for Luxemburg, the main assets delivered by DONC are:

- Reputation
- Scientific leadership and capacity to training young scientists and MDs in cancer research
- Attraction of international post-docs and scientists
- Technical platforms amenable for biomarker cancer discovery and also clinical testing
- Collaborative network with excellent centers in Europe (e.g. DKFZ, University of Bergen)
- Good positioning of research in order to attract investments from private sector
- Capacity to operate as accelerator for the implementation of personalized cancer medicine

The areas where value/impact in terms should be greater are:

- Impacting on national health and biomedical innovation systems
- Cooperating and sharing resources with other departments of LIH
- Delivering value through patents, start-ups, or services for private sector
- Having an accelerating effect on the development of personalized medicine and cancer prevention at national level
- Training MDs/oncologists to translational and clinical cancer research

As noted in section 2.1, the limited overall value (compared to the scientific potential and achievements) is at least partially due to factors that are external to DONC.

3.3 Assessment of specific units

In the following paragraphs, some remarks are provided about the activities and performance of each of the three research units of DONC. This section contains a general assessment of the quality of the research by each unit, based on the presentations, publications, report and bibliometric information made available to the Committee, and on the discussions with PIs during the review. The general assessment is formulated according to the same scale as for DONC as a whole (see footnote 1).

3.3.1 Norlux Neuro-Oncology Laboratory Head: (Simone Niclou)

The Norlux Neuro-Oncology Laboratory is organised in five subgroups focusing on glioma biology, drug resistance and systems approaches. They collaborate closely with the neurosurgery department of the Centre Hospitalier Luxembourg (CHL), and have established a platform for patient derived xenograft (PDX) models and for small animal *in vivo* imaging (MRI, PET) dedicated to brain tumour imaging. The group is led by Prof Simone P. Niclou, PhD. Her field of expertise includes biology of malignant brain tumours with a focus on angiogenesis, invasion, tumour metabolism and tumour heterogeneity. She also has strong expertise in patient derived animal models for gliomas.

Prof Niclou is an adjunct professor at the KG Jebsen Brain Tumour Research Center, University of Bergen, Norway. Prof Rolf Bjerkvig is chairman of this centre and also chair of DONC. Prof Niclou was originally recruited as a senior scientist in his group in Luxembourg. Prof Niclou has an international profile for her research and is a regular invited speaker & guest lecturer at numerous international scientific conferences, national and international universities. She served as a representative of Luxembourg, as Council Member of *the European Association for Cancer Research* (EACR) and has been appointed President of the Board of Directors of the Laboratoire National de Santé in 2015.

The research quality of this group is *excellent* evidenced by the importance, impact and citation of their work, numerous national and international collaboration and participation to international meetings. The Unit has flagship recent publications in EMBO Mol Medicine (IF 10.33) and in Nature Cell Biology (co-author position, IF 19.06). The visibility and impact of these scientific achievements substantially contributes to the high markers of bibliometric excellence at department level. The unit also has a number of activities engaging stakeholders in health and in the private sector. Of note, however, the Unit does not have a record of success in international grants (e.g. H2020) that matches its scientific excellence.

Major strengths are the development and use of patient-derived cell lines and orthotopic PDX model of glioblastoma, and diversification of the unit's knowledge base by the attraction of a translational research group on oncolytic viral therapy (Dr Antonio Marchini, recruited in 2017 through a collaborative research agreement with the German Cancer Research Center - DKFZ - in Heidelberg)), and the establishment of a research group on DNA repair/genome stability (Dr Eric Van Dijck). The recruitment of Dr Michel Mittelbronn through a PEARL national program of excellence, a pathologist engaged in both research and in national pathology service, is a clear asset that builds a strong direct link with clinical activities. If fully developed, this will provide the unit with a bridge operating bidirectionally to increase translational output for researchers and to get clinicians more involved into

research. The peers were also introduced to Dr Johannes Meiser, a bright young researcher just recruited through an ATTRACT national program of excellence as junior PI to develop a program in metabolomics. Whereas the presentation to the Committee was delivered by Dr Niclou, the peers perceived that each group leader enjoys a certain degree of autonomy and independence in defining the positioning of their research. With this broad and diverse human capacities, the unit appears well equipped to remain highly competitive at international level.

The main threats identified by the peers regarding future programs are:

- The relatively narrow clinic/biological focus of the unit (glioma), a rare cancer for which recruitment and clinical leadership is limited in Luxemburg. Since the expertise of the group is applicable to other pathologies and contexts, it would be important to consider carefully expanding this base to develop a more inclusive translational agenda. Among possible areas for expansion, the peers have discussed the interest of addressing brain metastasis as a main cause of therapy failure and cancer mortality.
- The fact that the clinical base of Norlux mainly resides in Norway. Although the link between DONC and KG Jebsen Brain Tumour Research Center appears extremely strong, this situation places Norlux in a situation of being dependent of strategic priorities decided by others. The main challenge will be to re-define a management structure for this collaboration after the retirement of Prof Rolf Bjerkvig.
- The lack of cooperation between Norlux and IBBL. In principle, IBBL should be in a position to give strong support to Norlux by providing access to a world-class biobank and data repository. However, this does not appear to be the case. Researchers in Norlux (and in other units) complain about the difficulties they have in integrating IBBL in their pre-analytic processes. They identify IBBL as too much oriented towards service to private sector, and not enough towards the development of translational research in Luxemburg.

Overall, in order to progress from *excellent* to *outstanding* status, the group will need to have access to much better research infrastructure including cross-cutting support e.g. enhanced imaging facilities and dedicated bioinformatics support within the team. Currently, the laboratories are housed in a modular structure that is insufficient, overcrowded and not organized in a way that facilitates collaboration and sharing (e.g. very limited space for meetings and seminars). Importantly, there is limited cross-fertilisation between the Norlux team and other units within DONC (and broader LIH). It would also be beneficial for the Norlux group to have better input from other teams within DONC in defining their research agenda and strategy. In particular, the knowledge developed in LECR (on cell-extrinsic mechanisms, such as microenvironment and immunity) is extremely complementary to the core expertise of Norlux (mostly on cell-instrinsic mechanisms). Overall, the strategy should tend providing a unifying theme for the groups within Norlux.

3.3.2 Laboratory of Experimental Cancer (Guy Berchem)

LECR comprises 3 independent research groups, under the general direction of Dr Guy Berchem, who is both a practicing oncologist and a researcher. The Committee notes that Dr Berchem has been a pioneer in developing this double activity in Luxemburg over the past 20 years, in a context which, prior to the establishment of DONC, has provided little support or recognition. His experience is therefore of great value to improve the integration between research and clinical activities. The presentation during the peer review consisted of 3 distinct short talks by the leaders of each of the research groups: Dr Bassam Janji (who is also co-director of the unit: micro-environment and immune response, MIR); Dr Etienne Moussay (Tumor-Stroma Interactions, TSI) and Dr Clément Thomas (Cystoskeleton and Cancer Progression, CCP). These presentations showcased the specific activities of each of the group, but left the peers with less time to discuss and focus on the overall aims and strategies of the unit.

Overall, the scientific performance of the unit is *excellent*. The impact of research is highlighted by excellent recent publications with strong impact, and the perception that most activities are enjoying a strong dynamic of progress and development. Flagship recent publications are in Proc Natl Acad Sci USA (IF 9.50) and in Blood (IF 15.13). Each team has a coherent thematic positioning, with clearly

identified strengths in terms of topics and leadership. While the thematic complementarity between the groups is evident, the Committee perceived that each group is operating quite independently. Shared problems encountered by LECR and NORLUX are the difficulty in attracting young MD into research, the lack of collaboration with IBBL, the need for appropriate research infrastructure, and a lower-than-expect rate of success in H2020 grants, given the level of science.

Whereas commenting on each specific group is beyond the scope of this review, the level of scientific information given during the presentations was sufficient to formulate a general opinion on each program:

- MRI (Dr Janji) appears to be an extremely strong research activity, with an interesting positioning in basic research and a well-defined translational vision. The group has made breakthrough findings on inhibition of autophagy as a mechanism for increasing sensitivity to immune checkpoint blocking therapies. Using well-designed mouse models, the group is in a position to deliver preclinical proof of principle and has developed a collaboration towards this with Sprint Biosciences, a start-up Pharma based in Sweden. This line of research appears to have reached maturity and is in a position to significantly contribute to the development of a translational program at department/institute level.
- TSI (Dr Moussay) is focusing on understanding the biology of tumour cell-stroma interactions in B Cell Lymphoma/CLL. The research strategy focuses on exosomes as biomarkers, as signalling "units" and as vectors for biomarker-based therapies. Whereas this strategy is coherent and well formulated, it addresses an extremely competitive field. It will be important to identify specific targets within this broad topic, on which the group can claim a position of originality and leadership at international level. It may be interesting to consider carrying a forward-looking analysis of areas for patenting and to focus the group's activities on research that has the best chance of delivering the expected translational and innovation impact.
- CCP (Dr Thomas) is actually the re-deployment in the cancer field of a research group that was previously focusing on cytoskeleton in plant biology. This re-deployment appears to be a success, to the credit of both the researchers and managers involved. The group has an interesting and original angle on actin-remodelling processes and actin signalling, which represents a strategic niche of great potential impact. The main threat for this team will be to continue building up its expertise in the field of cancer in order to maximize the translational opportunities generated by their original positioning.

The main threats identified by the peers regarding future programs are:

- Risk of dispersion. Each of the research themes addressed by the 3 teams may lead to a diversification of potentially interesting projects. While this is clearly a strength, it carries the risk of having a too broad and diverse research agenda, with a lack of impact. Careful focus will be needed to prioritize projects that have the best chances of making a difference in terms of impact for Luxemburg. In particular, the themes addressed by LECR are very complementary to those of Norlux: it would be wise to prioritize projects that have transversal impact, e.g. addressing complementary translational aspects across the two units.
- Lack of cooperation with IBBL. The same limitations with respect to the role of IBBL as those noted for Norlux also apply to LECR (see comments by the peers).

3.3.3 Proteome and Genome Research Unit (Gunnar Dittmar)

The Proteome and Genome Research Unit (GENPRO) is led by Dr Gunnar Dittmar. He was appointed on 1st October 2016, as the successor of Professor Bruno Domon, who set up and headed the Proteomics Research Group for the last 5 years. While Professor Domon was very successfully focusing on Mass Spectrometry technology development, Dr Dittmar moved the research unit into a technological platform for genomics and proteomics-based research much more interacting with DONC, LIH as a whole and also with LNS. The research within GENPRO is focused on tumour target identification and biomarker discovery. This unit also represents a knowledge hub for proteomics and genomics within

Luxembourg and beyond. Based on the strong need to obtain and analyse complex biological information from tumours and host tissue, a priority has also been to further strengthen the bioinformatics research within DONC.

The genomics part requires further development which will soon be implemented through the establishment of LUXGEN. This will trigger a restructuring at LIH level, moving the GENPRO out of DONC to establish a LIH-wide effort of technological activities. The overall leadership of the restructured GENPRO will be provided by Dr Dittmar and the new activities will be roughly divided into three sections. (i) The LUXGEN collaboration of LIH and LNS will handle NGS and Microarrays, (ii) the Bioinformatics platform and the Modelling of complex systems research will be under the leadership of Dr Francisco Azuaje, and (iii) the Proteomics platform, the RPPA platform and the Laboratory for Proteomics of cellular signalling will be directly led by Dr Dittmar. Both Dr Dittmar and Dr Azuaje were successful in both the research and service aspects of their work.

The research quality of their groups is well evidenced by the strengths of scientific and technological outputs and the impact and citation of their work. A flagship publication by the Luxemburg proteomics group is in Trends in Analytical Chem (IF 7,03). Dr Dittmar has focused the proteomics and genomics services activities in a way very beneficial not only to DONC and LIH but for the whole of Luxembourg. While the hardware and personnel situation on the genomics side looks adequate it became apparent that major investments into the proteomics hardware are overdue.

When GENPRO will become a transversal activity for the whole of LIH it is necessary that GENPRO and Dr Dittmar have an appropriate seat at the table where research and infrastructure are discussed and strategies and investments will be decided. From the research point of view, the Committee notes that there is a strong potential for innovative research on biomarkers. Creating a separate entity for technology/platform activities, distinct from other departments of LIH, carries the risk that research becomes second priority compared to transversal service activities as a platform. Indeed, the scientific basis for such biomarker discovery (targets, models, cohorts, etc.) resides in departments such as DONC. When created as a separate entity, it is essential that the head of GENPRO has a clear input on overall strategies at institute level and in particular on the prioritization of innovative transversal research programs. Likewise, the continued excellence of GENPRO is critically dependent upon long-term investment and staffing plan for research, methodological developments and service related activities. These needs cannot be covered solely within a platform business model where costs are supported by service activities.

Bioinformatics and modelling service activities in DONC were centralised around a year ago and LIH needs to discuss the right level of staffing, the balance between centralisation of service activities and embedding of bioinformaticians in research groups, and the coordination of all service-oriented bioinformaticians (in research groups and in the platform) as well as strengthening the interplay between research bioinformaticians and service-oriented bioinformaticians.

The main threats identified by the peers regarding future programs are:

- There is a risk of loss of impact and expertise if activities become too much oriented towards service to other department/units of LIH at the expense of original research. Research is essential for making sure that proteomics activities in Luxemburg remain at the forefront of their field.
- Sequencing activities in LUXGEN need to be well connected with large programs in genomics in other EU countries and at EU levels. Exploiting data in genomics requires large datasets. In the field of cancer, data generated from patients in Luxemburg will remain limited in size and numbers. Their proper exploitation in translational research and in the clinics, will require comparing them with similar data from patients in other countries.
- Inappropriate distribution of skills and expertise in bioinformatics. There is a need to find a good balance between bioinformatics resources available centrally and within units (which will be in greater demand in the coming years). Within-unit bioinformatics need to be interconnected and integrated with central resources in order to avoid dispersion of expertise in small clusters that do not sufficiently communicate. On the other hand, placing all bioinformatics resources in a central

unit will prevent units to develop the type of "bench bioinformatics" they need in their daily activities, and will delay the dissemination of a bioinformatics culture among students in the various teams.

3.4 Innovation quality and impacts

Life science research, and especially the more molecular-oriented disciplines, is increasingly relevant to clinical research and, in some cases, practicing medicine. This is because the costs of automated data-gathering technologies – most notably DNA sequencing but also proteomics and metabolomics – have dropped precipitously over the past decade and continue to fall. Coupled with cost–effective imaging techniques, large quantities of data can be gathered and integrated to help inform both clinical research and practicing medicine. To realise the potential of research in impacting society through improved healthcare needs a joint-up thinking between the healthcare sector, research and innovation. Luxembourg needs to think how it can diminish hurdles and barriers between these sectors in order to improve outputs into clinical research and care delivery, as well as into innovation. This implies creating a general context and framework which empowers healthcare providers such like hospitals in feeding back into the research agenda and process. It also requires having a strong portfolio of innovative business activities tightly connected with research, providing opportunities for great ideas generated in the lab to get implemented in the form of new products and services.

3.4.1 Impact on healthcare

DONC (and LIH as a whole) have an important role to play here, and much has been achieved already in form of research results that will eventually lead to better informed medical actions and decision-making. However, so far the impact of DONC in this area has been so far rather limited. DONC activities have not led to the development of original clinical trials in Luxemburg and their impact on training MDs through research has also been limited. An area in which DONC may provide critical expertise is cancer genomics in the clinics and access to therapeutic innovation using treatments based on molecular biomarkers. The peers note that DONC is aware of this and has a clear view of its mission in this respect, as shown by its positioning as leader in developing a National Center of Excellence in Research in Oncology (NCER-ONCO). Developing this National Center will enable DONC to get involved at its proper place in the chain of actions from basic to translational and clinical research and, ultimately, impact on healthcare.

3.4.2 Industry access, innovation and value creation

During the peer review, three international companies (selected by DONC, in UK, Germany and Sweden) presented their cooperation projects in the field of joint-innovation of new equipment or new molecules. When questioned about the nature of their working relationship with DONC, all of them commended the professionalism and straightforwardness of DONC in organizing these collaborations (MTAs, IP negotiations, contracts, etc.). In two instances, the companies identified as main reason for collaboration the specific scientific strengths of the units (i.e. access to unique cell/animal models; testing of specific innovative targets). In one instance, the company indicated that a major advantage was the central position of Luxemburg as showcase for innovation by the company. Overall, DONC appears to be an internationally competitive place with regard to the quality of innovation and capacity to collaborate with business. However, the peers noted that there have only been a few of these collaborations and that these collaborations provide only limited outlets for the innovative potential that exists throughout the department. In particular, there does not appear to be an active local cancer business community and there is a lack of clear of plans for how to develop start-ups and spin-offs for translating research into value creation. Critical components in this respect are:

- Proof-of-concept programs aimed at moving lab discoveries up the Technology Readiness Level (TRL), to a point where they can be patented or otherwise valorised;
- Involvement into European innovation networks in the area of cancer molecular medicine;
- Network of small business/start-ups and services with interests in cancer prevention, screening, detection, therapy and management.

It should be considered that having a clear innovation strategy backed-up by such components is an incentive for bright students and young researchers to develop local careers into innovation and business, thus providing attractive opportunities in addition to academic research.

DONC lists only 4 patent processes in its annex report (1 granted, 1 closed, 2 pending). No information is given as to the commercialisation avenues for these patents. The development of the patent on OVT seems to be at early pre-clinical stages. DONC acknowledges in its report that "innovation has not been [its] primary focus" and underlines the need to create "an innovation culture supporting and encouraging employees to take more risk in their daily activities (e.g. by rewarding creativity)". The Committee welcomes this statement and agrees that such a culture should be developed, but notes that no precise plans towards this seems to exist. In its report, DONC also identifies that one the threats it faces is "[…] too much focus on value creation at the expense of high-quality academic output". The Committee does not agree with this concern. Quite the opposite, the Committee considers that an innovation culture should operate as leverage to enhance academic output by showcasing its relevance and impact. Thus, the peers consider that DONC could be more ambitious and less risk-averse given the relative security of the long-term funding commitment of Luxembourg through the block fund.

3.4.3 Policy influence

Currently, DONC does not have specific programs or activities aimed at policy making and does not identify this as a core mission. In this respect, DONC operates more like an academic/research institute than as branch of a national institute of health. However, DONC has a good understanding of its potential impact on research and healthcare policies at national level and appears to be willing to play a role. The main obstacle is it lacks people and structures with whom to talk in this respect. If properly integrated into a national agenda, DONC has the potential to strongly participate into the development of a broad cancer agenda for Luxemburg, in cooperation with other departments of LIH and with the healthcare sector. Such an activity could be developed in the framework of the National Center of Excellence in Research in Oncology (NCER-ONCO). Indeed, this center should be supported by a clear political agenda (e.g. national cancer plan).

3.4.4 Budget usage and increasing revenues from external sources

The Committee was not given sufficiently detailed information on how budget is actually broken down among the different teams and activities, and how decisions in this regard were made. Overall, the Committee understand that DONC broadly fulfils its contractual requirement of having 40% of its resources from external sources (however this is not completely clear). As for external sources, the Committee notes that over 75% are national public income (competitive national research grants) and that the 20-25% reminder is from unspecified sources such as national or international NGO and foundations. DONC does not have substantial income from paid service or contract research. The Committee considers that the share of income from EU Framework Programmes does not reflect the true international competitiveness of DONC and that there is much room for improvement in this respect. One of the obstacles identified by the Committee is that, since DONC units are quite successful in accessing national grants (for which success rate is about 25%), they have little incentive to access more complex European grants (for which success rate is generally less than 5%). To improve in this respect, DONC develop a proactive "hunting" approach to identify suitable calls well in advance and to mobilize administrative and managerial support for developing grant applications.

The Committee also expresses the more general concern on whether the "60-40" contractual basis is adequate for supporting the growth and competitiveness of the department. Given that most of external funding comes from national grants, for which competition is relatively small and success rate relatively high, the current budget structure does not seem to represent a sufficient incentive for researchers to target competitive international grant applications.

3.5 Management and governance

As DONC is an integral part of LIH, the management and governance of DONC are mainly determined by the overall governance and management of LIH. These will primarily be discussed during the institute

level peer review of LIH. However, during this departmental peer review, a number of issues was noted that feed into this institute level peer review.

3.5.1 Leadership

In terms of leadership, the success of DONC in establishing its research standing in a short time is a credit to the current director and his team of unit/group leaders. The Committee does not perceive that there are conflicts or major difficulties and that the different leaders and activities within DONC seem to co-exists in a good general working atmosphere. The current leaders all appear duly qualified, with good to excellent scientific credentials and appropriate management skills. The recruitment, both at PI and collaborator/Postdoc/PhD level, seems quite international. Overall, the department seems to be able to attract the right people. A number of good senior staff has already been with the institute for a while, while recently, with help of FNR (ATTRACT, PEARL programmes) one senior and one junior PI have been attracted. Also, the PIs and the junior researchers that participated in the peer review seemed capable, and often had international experience in prominent research organisations. The gender distribution is not very well balanced, although the deputy director is a woman (Pr Simone Niclou).

3.5.2 Management structure

In terms of management structure, the Committee has been informed that DONC promotes a participatory approach, with monthly meetings between the director, the unit heads and the PI during which questions related to strategic objectives, organizational aspects, financial governance and human resources are addressed in a consensual manner. Each unit and PI within the unit enjoys substantial independence with regard to research direction and use of the budget assigned to each group. The budget is prepared annually by the director and unit heads based on a proposal by the LIH finance department, and approved by the executive committee of LIH.

In terms of supervision, the peers have met with a diverse group of students and postdocs from various units/groups, who appear to be extremely satisfied with their working environment and conditions, the quality of supervision and the opportunities they have to develop their research. They however pointed out that communication between groups and units was limited. One of the postdocs pointed out that the general working atmosphere lacked the competitive edge often found in top international research centers. Another had conflicting views on this, explaining that the general working atmosphere was more reassuring and less negatively competitive than in a previous postdoc experience abroad. Students and postdocs unanimously commended the supportive attitude of the person in charge of their status at LIH administration.

Whereas this management structure is simple and straightforward, the Committee has identified the following problems/difficulties:

- The director is physically present in Luxemburg only 1 week/month, with many of the daily director duties executed by the deputy. Whereas this arrangement seems to have operated successfully over the past year, the future development and performance of DONC will require a more substantial presence of the director (if possible permanent).
- The hierarchy of decision levels between DONC management itself (monthly meetings of PIs) and the executive committee is not clearly defined. In practice, it seems that most strategic and budget decisions are taken at executive committee level, and that DONC has limited autonomy.
- A further governance difficulty faced by DONC, which should be addressed at the level of LIH review, is the lack of strategic coordination with IBBL, which operates under a separate CEO/executive committee than the other LIH departments. This does not seem to adequately consider the fact that biobanking and access to tissues are strategic needs for DONC. Overall, the impact of IBBL across the DONC department is very low and individuals look outside Luxembourg to access tumour and tissue samples. IBBL has in the opinion of DONC researchers a commercial agenda that is separate from DONC research agenda, while it is being managed under a separate branch of LIH. DONC researchers say that they store their tissue “anywhere but the IBBL”.

- The budget of DONC (and LIH as a whole) seems to be constructed by assembling separate "boxes" corresponding to the budget of each group and unit. This approach does not promote common themes and common strategic goals. Furthermore, the budget seems to be almost entirely committed to each specific group/unit. According to Annex 3 of the report/expenditure per unit, only less than 0.5% of the total budget seem to be available for coordination and strategic investment at the level of the department (the rest seems to be entirely committed to units, or to personnel and maintenance costs). This leaves almost no strategic reserve for risk-taking and forward-looking initiatives.
- Overall, there seems to be a general lack of in-depth communication, at least between units and in the department, as a whole. People seem to get on together quite well but appear relatively unaware of what other groups/units are doing. Throughout the evaluation, the committee has heard polite remarks and complaints about this by scientists of all ranks, including PIs from each unit, postdocs and students. In relation to this problem, the Committee notes that the DONC building has only a small meeting room (accommodating maximum 20-30 people), sufficient for group/unit meetings but insufficient for joint meetings of different groups.

3.5.3 Workplace and infrastructure

The Committee briefly visited DONC laboratories, which are located in a temporary building on the hospital campus, within walking distance of LIH main building (the latter hosting the GENPRO unit). This temporary building, which is over 10 years old, is well kept and maintained but not particularly attractive and is not internationally competitive. The distributed infrastructure and aging equipment and buildings mean that DONC & LIH struggle to support the scientists working there. For example, the Committee was informed that the flow cytometry facility was only partially functional due to disrepair of a key piece of equipment. The development, management and mentorship of aspiring scientists is weakened by the current arrangements. The research infrastructure does not support research to be as effective as it might be and core facilities need to be strengthened and made more widely available. A good example of this latter issue is the need to develop bioinformatics and quantitative biology as a core resource while allowing the evolution of a distinct new department within LIH to realize the potential for research in this field and support opportunities for technological innovation.

The lack of good quality buildings is a disadvantage for DONC researchers compared to their competitors and partners at EU level. It constitutes an obstacle for progression from the current level of excellence to Outstanding level. To date, a "bottom up" approach has led to a research architecture spread across multiple buildings and multiple small groups with limited cross-cutting support structures. The organisational and physical environment (LIH spread across 6 buildings) is not conducive to collaborative research and impacts negatively on teaching and training. This approach is counterproductive especially since it is one of the rare situations where the small size of Luxemburg is a definite competitive advantage at the international level: it would be in principle possible to organize a thriving, dynamic and multidisciplinary health campus at "human" size where people could share resources and interact with each other across themes and disciplines. From a practical viewpoint, the modular building in which the Norlux and LECR groups are housed is overcrowded and with limited facilities to hold joint meetings that hampers inter-group interaction. As a consequence of the spatial dispersion, several students complained that it was difficult to get to seminars and lectures in other institutes (a problem compounded by heavy traffic). The time is now ripe for some "top-down" strategic oversight to bring coherence. The need to create a single building and more strategically a biomedical campus (with a hospital on-site to facilitate translational research) is critical if DONC, the LIH and other departments/stakeholders are to realize their full potential to become internationally competitive.

3.3.4 Management and administrative functions

Although the evaluation meetings were held in the LIH administrative department, the Committee did not meet with members of LIH administration in charge of DONC. The peer's feedback on administrative functions is therefore essentially based on information given by the researchers. Overall the researchers perceived that the management and administrative functions to support DONC and the LIH more widely appear fractured, inefficient and lacking in transparency. Especially the lack of

transparency in budget/finance organization and decision making seems an issue of serious importance that requires immediate attention and repair. It is important to understand how the block grant is spent in order to improve how the money is used. Even more concerning, when specifically asked about this, the director and team leaders provide only very vague and general answers, explaining that the mechanisms of budget management of LIH are not transparent to them either.

Scientists at DONC have indicated that grant management and administration support required to apply for Horizon 2020 funding is not available. The need for this support has been recognized by LIH's management in 2018, but it is not known how this will be addressed. The committee would like to emphasize the importance of this support for researchers who want to apply for Horizon 2020 or FP9 funding. In addition to basic clerical functions, expertise in grantsmanship and an ability to understand the requirements of both researchers, grant administrators and funders is essential.

4 Conclusions

- DONC is performing relevant cancer research, compatible with its missions. It fulfils its stated main mission of "[being] instrumental in the development and execution of world-class cancer research within prioritized areas". Over a short period of time, DONC has established a clear and strong research agenda, focused on well-prioritized areas, with good complementary across units and between teams within units, and with highly capable scientific leaders at all levels.
- Given its limited size and critical mass, DONC has a strategic requirement to focus on well-defined research areas, with the ambition of being internationally visible while delivering added value for cancer control in Luxemburg. This requires striking a delicate balance in making strategic choices, between focusing on rare cancers (providing a niche at international level) or addressing common ones (corresponding to medical needs in Luxemburg but overly competitive with respect to large cancer centers in EU). On the past 5 years, DONC has found an adequate balance by focusing on glioma through the Norlux unit, which develops an integrated program from basic to translational research, whereas several other teams develop mechanistic studies on breast, lung cancers or chronic lymphocytic leukemias.
- The current focus on glioma relies on structured long –term collaboration with the KG Jebsen Brain Tumour Research Center, University of Bergen, Norway. While this collaboration has served DONC very well, it places it in a satellite position with respect to clinical activities developed in Norway. In future research plans, DONC will have to build-up a stronger clinical basis in Luxemburg itself, making it less dependent upon strategic decisions made elsewhere.
- The overall quality and impact of research at Department level is *good* to *excellent*, mostly corresponding to a level equivalent to "best 25%" at EU level. Scientific production itself qualifies as excellent. Markers that justify this assessment are (1) the overall publication record, with recent flagship publications consistently at IF 10-20 and a tendency to attract more citations than other papers in the same journals; (2) international networking, with strategic collaborations with centers such as DKFZ, Germany and University of Bergen, Norway. However, other markers of quality are less than expected and do not match the same level of excellence as demonstrated by the publication record. These markers include (a) success in competitive international grants (ERC, H2020), which is low; (b) IP, patenting and subsequent commercialisation plans, which are very limited.
- DONC has been able to attract excellent team leaders, several of them recruited at international level. Overall, DONC appears to have strong human resources with adequate scientific and management skills at all levels. However, there is a lack of participation of MD in DONC research programs, and DONC appears to have only limited impact on training MD through research.
- In terms of training young researchers, DONC is successful in attracting excellent students at doctoral/postdoctoral level, with a good proportion of international students. Mentorship appears to be adequately organized and the students met by the Committee appear to be satisfied with the supervision, training they receive. They however seem to lack a clear vision of their future career prospects.
- The general working conditions and infrastructure are not particularly attractive and are not internationally competitive. The dispersed infrastructure and aging equipment and buildings mean that DONC (and LIH) struggle to support the scientists working there. The current "temporary" building does not have a spatial organization that favours synergy between teams (only one meeting/seminar room of limited size).
- There appear to be only limited scientific interactions between units. The Committee perceived that there is a general lack of awareness of what other units are doing and that overall research plans may benefit from better communication and sharing, since there is evident complementarity between the research agendas of different units.
- The management and administrative functions to support DONC (and LIH more widely) appear fractured and lacking in transparency. Especially the lack of transparency in budget/finance organization and decision-making seems an issue of serious importance that requires immediate

attention and repair. The Committee could not obtain clear information on how the budget is being assembled and how priorities were assigned. The general impression is that the budget is assembled from patching together the needs of different teams/units, with very few resources left to develop and implement a strategy at Department level.

- There is currently no support for researchers in applying for Horizon 2020 funding. The committee emphasizes the importance of this support for researchers that want to apply for Horizon 2020 or FP9 funding.
- Interactions of DONC with other departments of LIH are limited. The Committee welcomes the plan of developing the current Proteomics unit into a larger structure, GENPRO, that serves the needs of LIH as a whole. Care will be needed (1) to provide an adequate framework for GENPRO to develop research and not only service, (2) to find a good balance between bioinformatics resources developed centrally (within GENPRO) and locally (within each DONC unit).
- A specific problem identified across all DONC units is the low impact of IBBL as a platform to facilitate tissue and data collection and sharing. Most members of DONC perceive IBBL as a structure that pursues independent goals in global (and commercial) biobanking, and not as a support activity for the development of cancer research in Luxemburg.

In conclusion, during the past 5 years, DONC has successfully gone through a developmental phase to establish itself as viable and recognized scientific structure. Given its current level of operation and scientific quality, DONC has a clear opportunity to move from *excellent* to *outstanding* level in the next 5 years. This will require a clear plan for providing DONC with better infrastructure and integrating its activities in a well-defined strategic plan at national level, within LIH and with the medical sector. The main threats currently faced by DONC are (1) strengthening its governance and management structure; (2) strengthening its relevance towards the development of cancer control and therapeutic innovation in Luxemburg; (3) strengthening its international position by accessing EU grants such as ERC and H2020.

5 Recommendations

This section highlights 5 key recommendations by the Committee, formulated in order to support DONC development with respect to its core missions and to its progress from *excellent* to *outstanding* level.

1. Comprehensive strategic planning

DONC needs a strong and comprehensive strategic plan in order to move from the current development phase to the next phase of fully operational branch of a national institute of health. This requires first a very clear strategic plan at national level to better align DONC within the health research and community in Luxemburg. At LIH, university and ministry levels, the future of DONC should be organized within a general framework for building and developing a national health campus and for promoting translational and clinical cancer research in hospitals throughout the country.

Developing this strategic planning has broad implications beyond DONC: both a top down and bottom up approach in developing a strategy for Luxembourg will be necessary and DONC (and LIH) must create their strategic concepts to bring them into the Luxembourg-wide framework of discussion on how cancer research and healthcare can maximally profit from each other in Luxembourg. Key components, external to DONC, to take into consideration are:

- Permeability between research and clinics and training of young clinicians into research
- Clinical research/trial infrastructures and resources to organize them according to international standards
- Implementation of molecular and data medicine in clinical practice through platforms for delivering molecular analysis for healthcare (e.g. Genomics)
- Organisation of a regulatory framework for facilitating patient's recruitment and consent for participation into research, sample and data sharing and biobanking.

Overall, these components should be incorporated into a broad plan for developing and increasing cancer patients access to medical and therapeutic innovation. In developing such a plan, medico-economic evaluation should be carefully considered.

2. Infrastructure

The comprehensive strategic framework should include an investment plan for providing DONC with adequate infrastructure, competitive at international level, and supporting its development over the next 20-30 years. The location of this infrastructure should be carefully evaluated to location to take advantage of the short distances within Luxemburg and locate DONC within a significant critical mass of research, medicine and innovation. The investment plan should take into account the need for modern laboratory building, with adequate spatial layout to facilitate multidisciplinary programs and platform/equipment acquisition and renewal programs.

3. Governance, work culture and resources

Attention should be brought to the mechanism for recruiting and appointing the next director. It is essential that he/she be very well connected with medical sector and strategic health decision-making at national level. It is also important that his/her appointment be endorsed by a high-level international advisory board, giving him/her a clear authority to develop leadership on ambitious programs that make the best of the scientific and medical strengths existing across the department.

The governing structure of DONC should be revised to provide more clarity, strategic planning and transparency in decision-making for budget prioritisation and allocation. Scientific animation and sharing across teams and units should be strengthened by appropriate programs of seminars and meetings involving personnel of all ranks. It may be wise to allocate resources as incentives for joint actions or small, risk-taking projects by different teams across the department, using a bottom-up approach. DONC should use its relatively healthy core budget to provision sufficient central resources for supporting joint programs, shared resources and strategic planning at department level. Whereas the Committee does not recommend that core resources should be diminished, it recommends that

attention be given to how these resources are spent, focusing on capacity building, investment into innovation and risk-taking, infrastructure and support towards competitiveness rather than on direct funding of research programs that could be run on external contracts.

DONC is currently very much oriented towards academic research. Whereas this focus is part of DONC "DNA" and should be maintained, efforts should be made to promote a broader work culture more supportive for innovation and collaborations with start-ups, spin-offs and private sector. DONC should build an IP portfolio based on a realistic assessment of patentable outcomes of its research, and develop plans for pushing this portfolio up the TRL scale. The Committee recommends identifying a R&D "champion", or of start-ups in the area of innovation for cancer, who could help in organizing an agenda for starts-up and private sector.

4. International outreach

DONC should strive to obtain a larger share of its resources from international competitive grants such as ERC and H2020, as well as from research contracts with the private sector. Given its current level of excellence, DONC has no difficulty in competing for national funds. This, coupled to the healthy core budget, does not provide an incentive to access more competitive and uncertain international grants. Incentives, benchmarks and grant development support should be developed in order to stimulate PIs to apply for international grants, thus increasing the financial resource available for DONC programs while boosting international visibility and competitiveness. As part of this greater visibility, DONC should strive to have key PI supported by ERC grants.

5. Clinical research and training of MDs

In order to fulfil its broader missions of "providing a training ground for the next generation of cancer researchers in Luxembourg", "be a reference point for cancer research at the national level", "strengthen ties with the University of Luxembourg" and "act as knowledge hub for cancer research within Luxembourg", the Committee strongly support the strategy of DONC to be a leader in the development and coordination of a National Centre of Excellence in Research in Oncology. As part of this program, DONC should develop a cursus for training young MD/oncologists through research and for providing support four investigator-driven clinical trials, in the form of expertise, access to resources and infrastructure and clinical trials. An interface should be built to involve clinicians, oncologists and patient's organizations in the strategic orientations of DONC.

Appendix A Members of the Assessment Committee

Professor Pierre Hainaut (born 1958, Belgium) is PhD in Biology, University of Liège, Belgium, 1987. After postdocs in France and in the UK (Nice, Cambridge, York; 1988-1994), he joined the International Agency for Research on Cancer (IARC, World Health Organization) in 1994, where he held the post of head of Molecular Carcinogenesis from 1999 to 2011. In 2012, he joined the International Prevention Research Institute as Research Director. Since 2014, he is Professor of Cancer Biology and Chair of Excellence in Translational Research at Université Grenoble Alpes (UGA), France. Since October 2014, he is Director of the Institute of Advanced Biosciences (https://iab.univ-grenoble-alpes.fr/institute?language=en), a multi-thematic research centre supported by Inserm, CNRS and UGA, dedicated to Epigenetics, Chronic Diseases and Cancer (19 research teams, 300 staff). He is also responsible for Cancer Molecular Diagnosis at the University Hospital Grenoble Alpes (CHUGA). His research focuses on TP53 mutations and on biomarkers of transition from chronic diseases to cancer. From 1994 to 2011, he has led the development of the international IARC database of TP53 mutations, a source of information on the causes and consequences of mutations affecting the p53 suppressor protein in cancer. His current research focuses on the roles of p53 in cell bioenergetic metabolism and epigenetics, with applications to prevention and early cancer (Li-Fraumeni Syndrome).

Pierre Hainaut is author of over 435 publications and 50 book chapters (32,000 citations; h-index 93, Google Scholar; 81, research gate). He has co-edited two books on p53 ("25 Years of p53 Research" 2005, 2007, Springer, "p53 in the Clinics", 2011, Springer), a textbook of Molecular Epidemiology ("Molecular Epidemiology: Principles and Practice", IARC Press, 2011), and a textbook on human biobanking ("Human biobanking: Principles and Practice", Springer, 2017). He is co-editing (with Paolo Boffetta) the 3rd Edition of the Encyclopedia of Cancer (Elsevier, 2018). He is editor of the section "Cancer Biology" for Current Opinion in Oncology (since 2011).

Dr Rolf Apweiler is Director of EMBL-EBI, together with Ewan Birney. Prior to this position he was Joint Associate Director, after many years of leading protein resources such as UniProt. Rolf has made a major contribution to methods for the automatic annotation of proteins, making it possible to add relevant information to proteome sets for entire organisms. He has spearheaded the development of standards for proteomics data, and his teams have maintained major collections of protein identifications from proteomics experiments (PRIDE) and molecular interactions (IntAct). He also led EMBL-EBI's contribution to the Gene Ontology and is the current Director of Open Targets. Rolf received his PhD from the University of Heidelberg in 1994, and has been at EMBL since 1987. His major contribution to the field of proteomics was recognised by the Human Proteomics Organisation's "Distinguished Achievement Award in Proteomics" in 2004 and his election to President of the Human Proteomics Organisation, which he held in 2007 and 2008. In 2012, he was elected as a member of EMBO and in 2015 he was elected to an ISCB (International Society for Computational Biology) fellow.

Professor Colin Watts leads the newly established Brain Cancer Program at the University of Birmingham. His research aims to improve the treatment and survival of patients with glioma by understanding the molecular genetic heterogeneity of individual tumours and using that data to develop novel molecular and functional stratification suitable for application in clinical trials. His clinical practice specializes in neurosurgical oncology with a particular interest in intrinsic gliomas and cerebral metastases. Prof Watts qualified from the University of Newcastle upon Tyne and trained in neurosurgery in Cambridge and London where he completed his specialist training in 2004. He was awarded his doctorate from the University of Cambridge in 1999 and appointed as an MRC Clinician Scientist in 2004. He became a HEFCE Clinical Senior Lecture in 2010 and was appointed Associate Professor in Neurosurgical Oncology University of Cambridge in 2016. He has published over 160 papers, articles, book chapters and reviews and serves on the editorial boards of Neuro-oncology and the European Journal of Surgical Oncology.

Appendix B Site visit programme

Day 0 (no presence of LIH) – September 09

Time	Programme	By
late afternoon, early evening	Arrival of peers in Luxembourg	
19:00 – 22:00	Get together of the panel (over dinner), inform peers about peer review goals and approach, presentation of preliminary analysis	peers, client (MESR)

Day 1 – September 10

Time	Programme	By
09:00 – 11:15	General introduction to the Institute and to the Department of Oncology (and critical self-assessment of the department) Discussion	Department management: **Prof. Dr. Rolf Bjerkvig**, Director; **Prof. Dr. Simone Niclou** , Deputy Director**; Ulf Nehrbass,** CEO LIH
11:15 – 12:30 12:00	Tour around the department Client phone call with Fabrice Chaumard, MR Solutions (UK)	
12:30 – 13:30	(Simple) Lunch	in presence of department management (**Rolf Bjerkvig**, **Simone Niclou)**
13:30 – 15:15	Presentation and discussion on research theme 1 'Neuro-Oncology' 13:30-14:00 Presentation and strategy of the NORLUX Neuro-Oncology Laboratory **Simone Niclou** (Head of lab)	**Prof. Dr. Simone Niclou** – Head of the laboratory & PI; **Prof. Dr. Michel Mittelbronn** – PEARL fellow & PI; **Dr. Johannes Meiser** – ATTRACT fellow & junior PI; **Dr. Eric van Dyck** – PI; **Dr. Antonio Marchini** – PI; **Dr. Anna Golebiewska** – Researcher; **Dr. Alessandro Michelucci** – Researcher
15:15 – 15:30	Tea/coffee	
15:30 – 17:15	Presentation and discussion on research theme 2: 'Tumor microenvironment' 15:30 – 15:35 Overview of the Laboratory of Experimental Cancer Research (LECR) and strategic priorities, **Guy Berchem** 15:35 – 15:43 Improving cancer immunotherapies by targeting tumor microenvironment factors, **Bassam Janji** (PI - Tumor Microenvironment group) 15:43 – 15:51 Interactions between leukemia cells and their microenvironment **Etienne Moussay** (PI - Tumor Stroma Interactions group) 15:51 – 15:59 Actin cytoskeleton as a therapeutic target to inhibit tumor metastasis and immune escape **Clement Thomas** (PI - Cytoskeleton and Cancer Progression group)	**Dr. Guy Berchem** - Head of laboratory; **Dr. Bassam Janji** - Assistant head of laboratory & PI; **Dr. Etienne Moussay** – PI; **Dr. Clement Thomas** – PI; **Dr. Jerome Paggetti** - co-PI; **Dr. Zaeem Noman -** postdoc
17:15 – 17:30	Tea/coffee	
17:30 – 18:30	Informal group meeting (with young researchers: PhD students and Postdocs)	PhD students: **Yue Zhang** (GENPRO – Bioinformatics team); **Yolanda Pires Afonso** (NORLUX – Glioma Biology team); **Matthieu Gobin** (NORLUX – DNA repair team); **Hannah Wurzer** (LECR - Cytoskeleton team); **Marina Wierz** (LECR - Tumor Stroma team) Postdocs: **Abhishek Sharma** (NORLUX – DNA repair team); **Virginie Neirinckx** (NORLUX – Glioma Biology team); **Anne**

Time	Programme	By
		Largeot (LECR – Tumor Stroma team); **Joshua Brown-Clay** (LECR - Cytoskeleton team)
18:30 – 19:00	Draft conclusion of the first day	Peers only
19:00 – 20:00	Transfer to hotel, free time	
20:00	Dinner	In presence of department management & lab heads at Le Fin Gourmand

Day 2 – September 11

Time	Programme	By
08:45 – 10:30	Presentation and discussion on research theme 3: 'Proteomics & Bioinformatics' 8:45 – 8:55 General strategy of the Proteome Genome Research Laboratory **Gunnar Dittmar** (head of the laboratory) 8:55 – 9:05 Proteomics **Gunnar Dittmar** (PI - Discovery proteomics) 9:05 – 9:15 Bioinformatics **Francisco Azuaje** (PI - Bioinformatics)	**Dr. Gunnar Dittmar** – Head of laboratory & PI; **Dr. Francisco Azuaje** – PI
10:30 – 10:45	Tea/Coffee	
10:45 – 11:45	Phone calls with two clients/partners of the department (Jessica Martinsson, chief operating officer of Sprint Bioscience (Sweden); Dr. Andreas Bruchmann, managing director of the Axel-Semrau GmbH)	
11:45 – 12:15	Time reserved for clarification of questions from the peers	**Rolf Bjerkvig ; Simone Niclou; Guy Berchem**
12:15 – 13:15	(simple) Lunch	Peers
13:15 – 15:00	Time to draft preliminary conclusions	Peers
15:00 – 16:00	Presentation of preliminary conclusions and discussion on possible recommendations	to the department and institute management, client (MESR) and others where relevant
16:00	End of programme, transfer to train station/airport	

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