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Excellent translational research in oncology: A journey towards novel and more effective anti-cancer therapies



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ABSTRACT

Comprehensive Cancer Centres (CCCs) serve as critical drivers for improving cancer survival. In Europe, we have developed an Excellence Designation System (EDS) consisting of criteria to assess “excellence” of CCCs in translational research (bench to bedside and back), with the expectation that many European CCCs will aspire to this status.

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There is a growing awareness of the importance of identifying conditions that can contribute to translational cancer research success (Pozen and Kline, 2011). A need to improve performance is also a priority, in order to reduce the time taken to translate successful innovations from the laboratory into the clinic (Contopoulos-Ioannidis et al., 2008), and to take observations made in clinical studies back to the lab for further investigation or for the discovery of new biology. The increasing cancer burden and the fact that the performance of European cancer research could be considerably improved were the underlying drives for the EU Sixth Frame Work Programme (FP6) to fund clinical research for the first time (Busquin, 2002).

The Eurocan+Plus project (Eurocan plus report, 2008), funded in October 2005 (FP6), carried out a comprehensive analysis of European cancer research to identify barriers that hampered collaboration between various stakeholders, nationally as well as between European countries. One of the main conclusions of this project was the need to strengthen the collaboration between cancer research centres in order to achieve critical mass and share the infrastructure necessary for innovative translational cancer research. The concept of a Comprehensive Cancer Centre (CCC) was considered of great importance, being the only organisational form in which cancer treatment and care are closely integrated with research and education and, therefore, optimal for translational research.

As a follow-up to the Eurocan+Plus project, in 2011, the European Commission (EC) funded the EurocanPlatform, which brings together 23 European cancer research centres and 5 cancer organizations to structure translational cancer research. The long-term goal of this platform is to create a sustainable translational cancer research platform with the critical mass of expertise, resources, infrastructures, and patient numbers that are needed to facilitate innovation and improve performance in all areas of cancer research, particularly translational research. Recently, six EurocanPlatform centres established Cancer Core Europe (CCE) (Eggermont et al., 2014) as a significant first step towards establishing such platform (Eggermont et al., 2014; Celis and Ringborg, 2014).

As requested by the EC (Ringborg, 2008; Brown, 2009), a work package was dedicated to developing a methodology to quality assure and designate “CCCs of Excellence” that could qualify for future European funding. Developing a methodology for identifying and assessing CCCs of Excellence in translational research was one of its primary goals. Towards this aim, we previously reported the steps that were taken to develop a draft Excellence Designation System (EDS) (Rajan et al., 2013). This included evidence from current literature and a European stakeholder consensus exercise, covering a 2-year (2011–2013) period and involving researchers, managers, clinicians and patient representatives from cancer institutions across Europe. Now, we describe a final EDS that has been developed in collaboration between the EurocanPlatform and the European Academy of Cancer Sciences (EACS) and that has been piloted with three European CCCs. Its relevance for CCCs and translational research is discussed.

Translational research has rapidly evolved in the past decade (Doroshov and Kummar, 2014) and numerous

definitions currently exist (Woolf, 2008; Rajan et al., 2012). However, only few cover the complete cancer research continuum from bench to bedside and vice versa (Rajan et al., 2012). One definition (National Institutes of Health, 2014) that does, was put forward by the staff of the National Cancer Institute (NCI) while working with Dr. Richard Klausner, its former Director:

“Translational research uses knowledge of human biology to develop and test the feasibility of cancer-relevant interventions in humans OR determines the biological basis for observations made in individuals with cancer or in populations at risk for cancer. The term “interventions” is used in its broadest sense to include molecular assays, imaging techniques, drugs, biological agents, and/or other methodologies applicable to the prevention, early detection, diagnosis, prognosis, and/or treatment of cancer”(National Institutes of Health, 2014).

We present this perspective in three parts: (i) an introduction to the EDS that we piloted with 3 European CCCs (see acknowledgement for composition of peer-review team), in September 2014 at Helsinki University Central Hospital Cancer Center, Cambridge Cancer Centre and The Netherlands Cancer Institute; (ii) a summary of the pilot results (see Table 1) as well as the experiences of CCCs and the peer-reviewers (Pozen and Kline, 2011) from taking part in the pilot; and (iii) a discussion of the relevance of the system for translational oncology and an overall conclusion.

1. Excellence Designation System (EDS) in translational research for CCCs

European CCCs already go through several assessments at the national level. In addition, they undergo European/international assessments such as the accreditation and designation system developed by the Organization of European Cancer Institutes (OECI). Hence, it was felt that the EDS should not reinvent the wheel nor add bureaucracy by creating a totally new assessment system. So, it takes the existing national/international assessments as a basis. The reason that the EDS criteria are made descriptive is primarily that it builds on the OECI accreditation & designation system and secondly that various scientometric and quantitative analyses are already part of both the OECI-system and other reviews. At present there is no quantitative rating system for EDS as it was felt that expert review is at present the best way to judge the excellent status of translational research. The EDS covers only criteria that are not included in the OECI standards for CCCs. The standards related to inventory and core facilities exist in the OECI programme and this information will be obtained from the OECI designation report. Moreover, excellence can be found in fields that do not necessarily overlap. European CCCs that have an OECI CCC designation are eligible to apply to this programme. However, balancing between maintaining a high standard of the excellence program and allowing CCCs that apply to have a fair chance at achieving the designation status is a challenge. In the EurocanPlatform project the system is meant to set criteria for entry in European Translational Research platforms, which is considered for instance for

Table 1 – Pilot designation status of the 3 Comprehensive Cancer Centres and key findings.

Dimensions	Helsinki University Central Hospital Cancer Center	The Netherlands Cancer Institute	Cambridge Cancer Centre
Pilot designation status	Actual potential for excellence	Excellent	Excellent
Strengths or existing excellence	<ul style="list-style-type: none"> -Small country with excellent global survival statistics -Attracting the best people in the country -Strong position in Nordic research -Outstanding population-based registry -Young centre with opportunity to embrace rapidly evolving technologies and huge potential in precision medicine -General direction – open to change, translational research and international collaborations -Strong individual leaders in research (angiogenesis, precision medicine, haematology) -Bench to bedside & back programs -Evidence of research reducing mortality -PhDs and postdoctoral students very satisfied with the work environment 	<ul style="list-style-type: none"> -Extraordinary examples of deep translational science based on mechanistic basic science in a continuum to clinical care and back again particularly regarding resistance mechanisms -26% of patients on clinical trials -Strong investigator-driven clinical trials with biomarkers -Three programs developing based on a decision by the Translational Research Board: immunotherapy, image-guided radiation therapy, precision medicine -The model of twinning (pairing basic and clinical scientists) is successful, based on the projects, the fact that there are 39 MD-PhD students and 200 PhD students – provides an exciting model and a third of publications are generated from this mechanism -Shared labs, monthly staff meetings, clinical rotations for PhDs -Open, strong and visionary new leadership for the institute and candid views regarding ways to improve the program -National collaborations within the context of Centre for Personalized Cancer Treatment are exciting and lead to further opportunities for novel clinical trials -Also allows for the development of biobanking and IT 	<ul style="list-style-type: none"> -Extraordinary conduit between basic, translational and clinical trials and back again to the laboratory -Superb leadership in bringing in basic science departments within the virtual cancer centre -Exciting primary basic research leading to clinical trials (BET, DNA repair) and clinically driven projects with important implications for outcome-Barrett's and endoscopy studies and Breast -Solid approach to innovation and creative collaborations with pump priming projects, research sessions for National Health Services staff and director's funds -Impressive backing of clinician-scientist careers and input to oncology research across training schemes-the trainees were committed to hypothesis-based clinical trials and have clinical support and protected time -External networking within European partners with up to 70,000 new patients per year for trials -First approach to network within major UK Cancer Centres with harmonization of trial and e-health infrastructure -Impressive 16–50% entry into trials across departments and all histology
Opportunities for further excellence	<ul style="list-style-type: none"> -Biobanking – annotation and real time acquisition of samples-priority for sites. -New money for high risk/high gain innovative collaborations in house: has infrastructure but not resources for novel collaborations; integrated neurology, immunobiology, obesity should be integrated in cancer -Improved relationship with university regarding discovery: protect intellectual property -Combination drugs testing -More academic trials (proof of concept studies, First in Human trials, testing drug resistance), phase I–II Clinical trials network/opportunity to become a national early phase center-need improved accrual – Biomarker driven trials -Selection of 3 cancer types; use of 3D cultures, patient derived xenografts, genomics-precision medicine 	<ul style="list-style-type: none"> -Increasing the time commitment to research for clinician-scientists beyond 50%. Recognize it is a priority; strong thrust in molecular pathology -Efforts to engage basic cancer researchers in translational cancer research where this is relevant and possible. This should take into account that basic research creates the foundation on which to build translational research. -Continue strong, new biological studies combining radiotherapy research (especially image guided radiation therapy) with basic and translational research fields such as targeted agents, DNA repair, immunotherapy and mechanistic studies regarding tissue side effects. -Transparent and branding approach (used by Foundation) to practice-changing publications (i.e. 	<ul style="list-style-type: none"> -Expectations from experts to excel in national and international leadership in cancer research driving to the clinic -Unique opportunities from strengths (e.g. marry genomics to imaging with respect to tumour heterogeneity) -Opportunities to marry strong immunobiology to immunotherapy -15% trials where the biology was discovered by the cancer center (30% of investigator initiated)-should be improved -Consider resources for increased control over robust biomarkers leading to increased patient stratification for trials (e.g. using patient derived xenografts models to test the DNA repair inhibiting studies) -Have an integrated structure to supervise all the clinical

(continued on next page)

Table 1 – (continued)

Dimensions	Helsinki University Central Hospital Cancer Center	The Netherlands Cancer Institute	Cambridge Cancer Centre
(Haematologic oncology, Colorectal, Breast) -Query lack of clinical scientist translational training -Regular scientific advisory board meetings (monitoring/closing/opening trials) -Strategic vision of a global architecture of an integrated information system -Strong vision statement taking into account the unique strengths/needs of the cancer centre -Explicit support from the clinical research/medical oncology -Establishment of a foundation to support translational work (transformative donor)	develop metrics of intramural and extramural interest -IT systems need to be operationalized to prospective collections and auditing and working out the bugs in next year	trials in terms of scientific interest, feasibility, costs and decide opening/follow-up and closing if low/no patient accrual and/or if question is not relevant -Ratio between academia and industry initiated trials is still not clear. Mostly focused on discovery done here (Being original is important) can be more! Figure should increase. -Opportunities for IT and e-hospital in which there in direct links to genomics and imaging and outcome databases across all histology (in addition to breast)	trials in terms of scientific interest, feasibility, costs and decide opening/follow-up and closing if low/no patient accrual and/or if question is not relevant -Ratio between academia and industry initiated trials is still not clear. Mostly focused on discovery done here (Being original is important) can be more! Figure should increase. -Opportunities for IT and e-hospital in which there in direct links to genomics and imaging and outcome databases across all histology (in addition to breast)

Cancer Core Europe (Eggermont et al., 2014; Celis and Ringborg, 2014).

Ultimately it is expected that through this and other platforms a league of excellent CCC's will emerge that can act as leaders in the field both for their peers as well as for, governments, the EU and various agencies.

To give each CCC flexibility to prove their excellence, experts agreed to begin the EDS process without a rating scale and only to consider adopting it after broader implementation and accumulation of sufficient and firm empirical data. Experts/peer-reviewers decided not to define certain terminology in the criteria (e.g. what are high risk/high-gain projects), as they wanted evidence of high-risk/high-reward projects to come using a bottom-up approach rather than pre-defining what the nature of those items should be.

The assessments were conducted with impartial evaluation involving independent experts using existing reports available in English and not older than 5 years. This allowed the reviewers to check the validity, feasibility and relevance of the excellence criteria, and to formulate questions (see [Supplementary file](#)) to be addressed at the on-site meetings.

1. Articulation of a vision of the Cancer Centre's philosophy, scientific directions, and goals for the next 5 and 10 years; and which projects and translational science studies are expected to change the paradigms of clinical oncology.
2. Demonstration (with organisational data and publications) of at least three multidisciplinary programmes that are being pursued in great depth from basic discovery through pre-clinical development to clinical studies. These may be disease or discipline-based but must address major unanswered questions in the field and unmet clinical needs.
3. Experience with and commitment to a team science approach with basic and more applied scientists working together to achieve translational goals.
4. Tangible evidence of a commitment to collaboration both within the Cancer Centre's own country and internationally, as a single Centre usually will be less effective in developing and testing new approaches that lead to changes in clinical practice.
5. Establishment of shared resource facilities (Cores) to support the research programmes.
6. National and international peer review systems (including evaluation by funding and government bodies) assess the Centre on a regular basis to help maintain and improve the overall quality of the programmes, leadership, shared facilities (e.g. biospecimen banks) and research/clinical studies.
7. Commitment to a program of training of new translational scientists and re-training of established basic, clinical, or population scientists who wish to redirect their careers into translational cancer research.
8. Establishment of an up-to-date fully and clinically annotated biospecimen bank (or banks) with an information technology system or network for tracking specimens and linkage to clinical outcome and follow-up data. To optimize the impact of the bank, specimens should be shared with other researchers or collaborators.

9. Ability and commitment to perform hypothesis-driven and hypothesis-generating clinical and population studies.
10. Demonstration of a sufficient patient population to support bench to bedside studies in all the programmatic areas cited. Smaller cancer units should collaborate in their clinical trials in an effort to reach large enough numbers of patients to render the outcomes of these studies valid and effective.
11. Commitment to funding high-risk/high-reward projects to seize new and exciting research opportunities.
12. A detailed demonstration of the ongoing ability and a clearly articulated intention to leverage funding and/or resources obtained as a result of an “excellent” designation.
13. Involvement of patient advocates in advisory committees.

Below we highlight relevant quotes from the pilot participants.

“For us, to be designated as an Excellent CCC should not be a mere honorific or demographic distinction, but should, above all, induce and result in new translational research missions, roles, and high value/high clinical impact discoveries for such institutes” Peer Reviewers.

“There is no need to be anxious about the detailed Excellence Designation System even at the smaller and younger institutes. Yes, it will likely identify weaknesses. True, your institute may not shine as brightly yet as some older institutes. But detection of the weaknesses may allow improvement, and identification of the strengths may allow networking with the best cancer centres in Europe.” Helsinki University Central Hospital Cancer Center.

“Preparing for the pilot of European CCCs in translational research helped us identify our strengths and weaknesses and where translational research can contribute to better treatment and care for cancer patients. The interaction with and the feedback from the site visit committee were essential and highly appreciated in this process. The pilot has stimulated internal discussion, which will lead to further strengthening of our translational cancer research

2. Pilot experience of the Excellence Designation System in 3 European CCCs

Participants in the piloted CCCs, as well as the peer-reviewers/experts, felt that the excellence criteria for CCCs in translational research were very helpful in identifying areas of existing excellence as well as areas for further improvement.

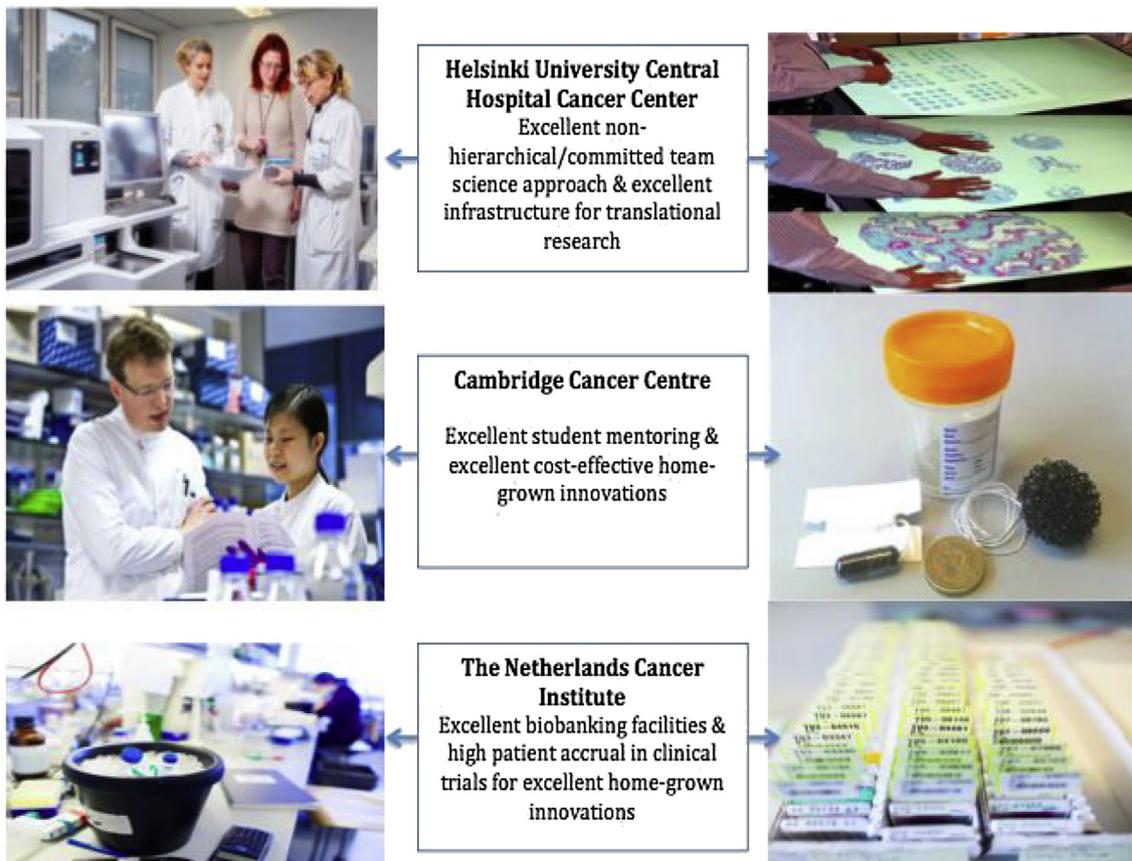


Figure 1 – Examples of excellence identified in the European CCCs.

programme. Other Centres can benefit from the best practices being identified in this process.” Cambridge Cancer Centre.

“A high level review such as this (but without a large burden of paperwork) is useful in catalysing discussion among colleagues as to the priorities and performance of the Centre, and identifying things that need attention. The discussions with the panel were lively and to the point; they reinforced some things we knew about but should attend to, and highlighted new ones. The pilot was well designed to elicit characteristics and metrics of the Centre that are truly relevant and a reflection of excellence, rather than the more usual measures of volume without examination of excellence. It will create a network of centres where ideas and scientists can be shared making it ideal for high quality collaborative science” The Netherlands Cancer Institute.

3. How can we ensure that these criteria are suitable for identifying and improving excellence in translational cancer research?

The EDS was developed based on multiple sources of evidence: existing literature; expert opinion from inside and outside Europe (from certain National Cancer Institute-designated Comprehensive Cancer Centres in the US and similar institutions in Canada and from the Cancer Research UK assessment process); stakeholder views (researchers, clinicians, managers and patient representatives across Europe) through a survey and a focus group discussion; as well as reports of existing national assessments for CCCs in Europe. To our knowledge, this is the first systematic attempt to exclusively focus on identifying and designating excellent performance of CCCs in translational cancer research. We used available evidence to develop and pilot these criteria. The site visitors, the expert team and the involved institutions were unanimous in their opinion that excellent performance can be identified in CCCs using the EDS.

We feel that a flexible approach is needed to identify and assess excellence that may also fall outside the scope of the excellence criteria used. All piloted CCCs shared a strong emphasis on the physician-scientists career. Similarly, increasing the quality and number of academic trials and making better use of different features of Information Technology were common opportunities in all CCCs (see [Table 1](#) and [Figure 1](#)). Distinctive examples of strengths and opportunities were also identified.

Outputs such as publication impact and citation are certainly important. In our systematic literature review ([Rajan et al., 2012](#)) we found process-related criteria to also be suitable for performance assessment. The EDS focuses on evaluating excellence based on key inputs (e.g. facilities and human/financial resources), outputs (e.g. publications) and outcomes (e.g. effect of innovations in addressing unmet clinical needs and the patient/population impact) but also on evaluating and improving the process of translational

research (e.g. creating a suitable environment for conducting translational research).

Aristotle said: “We are what we repeatedly do. Excellence, then, is not an act, but a habit”. Thus, excellent performance of CCCs in translational research should be a habit, built into the mind-sets of the CCCs rather than a one-time qualifying act for an assessment. Experts strongly believe that CCCs should have a sustainable organisational culture of excellence across the continuum of basic research, development, education and patient care and connect all individual parts in order to succeed. This starts with having a strong organisational vision for translational research.

4. Conclusion

The positive experience of the piloted European CCCs as well as the acceptance of these excellence criteria among the EACS membership and key international experts in oncology cause us to believe that the EDS is sufficiently validated to be implemented. We have applied available knowledge, existing evidence and past experience of experts to develop and pilot this system. Our experience has already shown that assessment of translational research excellence can deliver positive impacts and added value to future developments in oncology. We conclude that this system is ready to be implemented through European and international excellence initiatives in translational cancer research. However, it will need close monitoring to be further adapted to cover different approaches in developing and sustaining excellence during and beyond implementation.

Note

The peer-reviewers who piloted the EDS are: Prof. David Livingston MD, PhD (Dana-Farber/Harvard Cancer Center, USA), Toby T. Hecht PhD (Translational Research Program, National Cancer Institute, USA), Prof. Robert Bristow MD, PhD (Princess Margaret Cancer Center, Canada), and Prof. Thomas Tursz MD, PhD (Honorary Director Institut Gustave Roussy, France). The review team was selected by the EACS.

Appendix A. Supplementary file

Supplementary file related to this article can be found at <http://dx.doi.org/10.1016/j.moslnc.2015.12.007>.

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