External Research Review
Cancer Genomics Centre (CGC)
2006

Quality Assurance Netherlands Universities (QANU)
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Chapter 1: The review committee and the review procedures

Scope of the assessment and structure of this report
The Review Committee was asked to perform a research assessment of the Cancer Genomics Centre, which is one of the centres of excellence of the Netherlands Genomics Initiative (NGI). This assessment covers the activities and the research at Cancer Genomics Centre for the period 1 October 2002 – 31 December 2005.

The Committee's tasks were to assess the quality of the Centre and the research programmes of the Centre on the basis of the information provided by the Centre and through interviews with Cancer Genomics Centre management and research leaders, and to advise how this quality might be improved.

- Chapter 1 describes the composition of the Committee, its activities and the procedures followed by the Committee.

- Chapter 2 contains the assessment of the Centre.

- Chapter 3 contains the assessment per theme, in scores and in text.

Composition of the Committee
The composition of the Committee was as follows:
- Dr. Iain Mattaj, Director General of the European Molecular Biology Laboratory in Heidelberg;
- Prof. Peter Rigby, Chief Executive of The Institute for Cancer Research, London;
- Prof. dr. Philip Avner, Director of the Department of Developmental Biology, Institut Pasteur;
- Prof. dr. Pier Giuseppe Pelicci, Director of the Department of Experimental Oncology at the European Institute of Oncology
- Dr. Richard Treisman, Director of the Cancer Research UK London Research Institute.

The Bureau of QANU (Quality Assurance Netherlands Universities) appointed dr. Alexander van den Bosch as secretary to the Committee.

A short curriculum vitae of the Committee members is included in Appendix 1.

Independence
All members of the Committee signed a statement of independence to safeguard that they would assess the quality of the Institute and research programmes in an unbiased and independent way. Any existing professional relationships between committee members and programmes under review were reported and discussed in the committee meeting. The Committee concluded that no such relations existed and that there was no risk in terms of bias or undue influence.

Data provided to the Committee
The Committee has received detailed documentation consisting of the following parts:
1. self evaluation of the Cancer Genomics Centre;
2. a selection of key publications;
3. the bibliometric study on genomics research in the Netherlands 1996-2004;

4. background information about the NGI.

The documentation included all the information required by the Standard Evaluation Protocol (SEP).

Remark about the Standard Evaluation Protocol
The Standard Evaluation Protocol (SEP) provides guidelines to evaluate *traditional* university research institutes and their research programmes. For the purpose of comparability SEP was also used in this NGI-review. However, the Cancer Genomics Centre is not a traditional university research institute, but represents a distributed organization. The Cancer Genomics Centre self-evaluation describes these activities and the committee is aware of the fact that the Standard Evaluation Protocol must be interpreted differently for this type of organisation.

Procedures followed by the Committee
The Committee proceeded according to the SEP. Prior to the Committee meeting, each theme was assigned to a first and a second reviewer, who formulated a preliminary assessment. The final assessments are based on the documentation provided by the Centre, the key publications and the interviews with the Cancer Genomics Centre management and with representatives of the themes. The interviews took place on November 8 and 9 (see the schedule in Appendix 3).

Preceding the interviews, the Committee was briefed by QANU about research assessment according to SEP and by the director of NGI about the NGI-consortia and the purpose of this review. On the same day, November 8, the Committee discussed the preliminary assessments. For each theme a number of comments and questions were decided upon. The Committee also agreed upon procedural matters and aspects of the assessment.

After the interviews the Committee discussed the scores and comments for the Cancer Genomics Centre as a whole and for each theme and made draft texts. A draft version of the report was sent to the management of the Netherlands Genomics Initiative and the management of the Cancer Genomics Centre in November 2006 for factual corrections and comments.

Chapter 2: Assessment on the level of the Institute

Introduction
In this chapter several aspects of the Cancer Genomics Centre (CGC) as a whole are assessed. These include its leadership, strategy and policy, the centre's adequacy of resources, funding policies and facilities, the academic reputation, societal relevance and strengths and weaknesses. This chapter concludes with an overall evaluation.

But first, what is the Cancer Genomics Centre? In the self-assessment report it is stated that the CGC is a collaboration of cancer research groups from four research institutions. It was established to further strengthen cancer genomics research in the Netherlands, to improve understanding and knowledge of the disease process and to translate this knowledge into economic and societal value. The four institutions are the:

- Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI) in Amsterdam
- Erasmus Medical Centre (Erasmus MC) in Rotterdam
- Hubrecht Laboratory / Netherlands Institute for Developmental Biology (NIOB) in Utrecht
- University Medical Centre Utrecht (UMCU)

A consortium of prominent cancer researchers from these four different institutes constitutes the CGC. These researchers were selected based on the scientific excellence, complementarity, and clinical relevance of their work. The following groups were asked to join the CGC:

- Frank Grosveld: Regulation of gene expression
- Jan Hoeijmakers: Genome (in)stability
- Jan Klijn: Molecular profiling of breast tumors
- Anton Berns: Gain of function screens using insertional mutagenesis
- René Bernards: Functional screens in cultured mammalian cells
- Laura van 't Veer & Sjoerd Rodenhuis: Molecular profiling for disease staging and therapy response
- Hans Clevers: TCF factors, mediators of Wnt signaling
- Ronald Plasterk: Protection against genomic instability
- Hans Bos: Signal transduction by small GTPases.

The stated mission of the CGC is to combine top scientists and knowledge, technology and infrastructure within the Netherlands striving for better insight in clinical treatment of cancer and to form a basis for development of (1) diagnostic and prognostic tools and (2) new therapeutic targets. Subsequent product development will preferably take place in a commercial environment formally separated from the research program (start up companies, joint ventures) and should add substantial economic value to society. The CGC program therefore focuses on:

- identification and characterization of new targets for prevention, diagnosis, early detection and therapeutic intervention;
- development of new diagnostic and prognostic tools for cancer;

- utilization of this knowledge to develop new prevention and intervention strategies through close collaboration with existing and new start-up companies and through joint ventures.

The research program of the CGC is divided in a 'Diagnostic' part and the 'Target identification and validation' part. The latter is subdivided in the research themes 'DNA repair and imprinting', 'Functional screens', and 'Proteomics'.

Together these parts comprise the four research themes of the CGC, which are reviewed individually in the next chapter. In the following paragraphs the review panel comments on several aspects of the institute as a whole

Leadership, strategy and policy
The panel was very impressed by all of these aspects of the CGC. The leadership has attracted the top Dutch researchers in the cancer field and organised a set of programmes that enable them to work productively and synergistically together. Cancer is clearly a major health problem nationally and internationally and the CGC programme makes excellent use of existing strengths in Holland.

The Molecular Profiling programme for example is made possible by the unusually well organised and maintained banks of patient tissue available, particularly in the area of breast cancer. This, in combination with patient records and access, none of which is available on other continents, represents an example of why European researchers can play a leading international role in health genomics.

The decision to utilise genomics technologies both in the Profiling work and in the other cancer models programmes provides cohesiveness and opportunities for collaboration that have been used to great advantage in the CGC. At a time when "genomics" is often used to artificially relabel existing scientific projects the CGC deserves high praise for actively developing and implementing genomic technologies to tackle a topic of the importance of cancer.

In other words, the CGC has helped a group of highly respected and successful scientists to adopt a set of new and important technologies to tackle a problem that is important for society. In addition, the CGC has enabled an unusually high level of collaboration between basic and clinical scientists and between these scientists and industry partners. Neither class of collaboration is easy to bring about and the CGC deserves high praise for its success in these areas.

Adequacy of the resources, funding policies and facilities
Genomics technologies are expensive. The CGC funding has been intelligently deployed to allow the setting up of new technologies, to train young people in their use and to pay the high cost of consumable supplies. The funding has been distributed unequally and we support the internal prioritisation undertaken by the CGC participants that this uneven distribution reflects.

The CGC groups are generally well-equipped and they have used the CGC funding to improve their facilities, for example in the initial purchase of the shRNA libraries, in setting up mass spectrometry and advanced light microscopy and in a series of investments in

people and equipment for the bioinformatics analysis that is such a critical component of the analysis of all genomics data.

The panel indeed feels that the amount of funding available in Holland through "topping-up" funding mechanisms such as the CGC is insufficient to support internationally competitive genomics research in the medium and long term. There is a serious possibility that the Netherlands will lose its current international standing in this field unless it can establish a funding system that supports individual and network projects in genomics (and in fact in other areas of modern biology) in a way that reflects their real cost.

Academic reputation
This group of researchers, both individually and collectively, are at the international forefront. The academic reputation of members of all the programmes simply could not be better. Holland is lucky to have such a distinguished group of senior cancer and genomics researchers who are able and willing to work together toward common goals. For example, the genomic analysis of breast cancer carried out by members of the institute is one of the best and best known examples of the application of genomic technology to a health problem reported in the scientific literature to date.

Societal relevance
Cancer is a very important health problem. Understanding the molecular basis for cancer is a prerequisite for the generation of reliable tools for cancer detection, disease prognosis and, in the future, potentially devising additional therapies. The interests of the CGC span all of these aspects and the network is thus of great societal relevance.

Two other aspects of the CGC activity that are outside the remit of the panel but which we will mention here are the "Science and Society" activities and technology transfer (valorisation). The CGC has supported and is engaged in a selected group of outreach activities. The review panel was very enthusiastic about the choice of projects made by the CGC and by the successful pursuit of these activities. We recommend that the documentation of these activities should be shared with cancer organisations in other countries that may wish to benefit from the good ideas and initiatives of the CGC.

In terms of technology transfer the CGC scientists are engaged to an unusually high extent with companies and are clearly carrying out their remit to help society exploit their discoveries in a very active manner.

Strengths and weaknesses
In terms of weaknesses we feel there is a need to find a better mechanism to promote the integration of younger independent scientists into this group, potentially by the provision by the NGI of a dedicated additional funding stream. While young researchers in the participating organisations do benefit from the infrastructures put in place by the CGC groups, more active participation through funding is something that in our opinion should be encouraged. This is very important for the future of cancer research in Holland. Encouraging very good young independent scientists to work together with this internationally recognised group of senior researchers is the best way to ensure the optimal preparation of the next generation of leaders.

Although of minor importance to our final evaluation we also felt that the documentation produced by the CGC did not do justice to its performance. Several misconceptions among

the panel members arose because of incomplete descriptions of the activities in the written materials that were only corrected by the site visit. Repetition of this should be avoided. For example, we felt it would have been better to organise the report either according to individual researchers or by combining the four "basic research" sections into one section about genomic screens and a second about the follow-up studies to these screens. Also, it would have been very useful to provide a copy of the original application together with the report so that we could more easily assess progress.

Overall evaluation of the Institute: 5 (excellent)

Without repeating too much that we have already said, the CGC is tackling a major societal problem, cancer, in a way that combines basic research, clinical research, development of diagnostic and prognostic tools for cancer as well as identifying potential pharmacological targets for cancer therapy. All of these activities are being carried out at a level that is internationally leading. The participants are also active individually and collectively in outreach and technology transfer activities. In summary, the CGC is an excellent institute and deserves the highest mark (5) as well as continued and indeed significantly increased funding in the future. Genomic technologies are expensive and a mechanism needs to be found to fund those groups doing excellent genomic projects in a way that reflects the real costs of such projects.

Chapter 3: Assessment of the themes

In this chapter the Committee presents its assessment per theme, both in scores and verbal comments.

The committee assessed the following themes:

1 Molecular profiling of cancer for individualised diagnosis

2 DNA-repair, genome stability and epigenetic mechanisms

3 Functional screens

4 Cancer proteomics

Theme 1, Molecular profiling of cancer for individualised diagnosis

Programme director	Laura van't Veer	
Research staff 2005	17,7 fte	
Assessment	Quality	5
	Productivity	5
	Relevance	5
	Viability	5

A short description of the research programme

The programme is centred solidly around the use of expression profiling as a means of identifying biomarkers of value for establishing tumour classification criteria and treatment prognosis for breast cancer. This work is being undertaken by the groups of Laura van't Veer (NKI) and Jan Klijn (Erasmus). Based on their transcriptional profiling programmes, prognostic expression profiling criteria for premenopausal and postmenopausal breast cancer patients, for lymph node negative breast cancer patients, for resistance to tamoxifen therapy and as a predictor of eventual bone metastases have been established. Of particular interest has been the finding that the transcriptional profiles of primary tumour and metastases show 97% similarity in expression profiles. Projects more restricted in size concern lung tumour and expression profiling (Frank Grosveld) where interesting progress has been achieved and oligodendrogliomas (Jan Hoeijmakers). The projected aim of establishing the genetic /epigenetic basis of the expression profiling differences so identified in the breast cancer cohorts has not so far been initiated to any marked degree.

All the groups participating have well-established international reputations. The two groups participating in the breast cancer screening have major international reputations based on their highly innovative input in the cancer diagnostic/prognostic field, and more especially in the field of breast cancer. Both the Van't Veer and Klijn groups participating in this sub-programme have been extremely productive and have been pioneers in this area of research. Whilst the reputations for scientific excellence of Frank Grosveld and Jan Hoeijmakers are not specifically associated with this field, the work on lung cancer is progressing in a highly encouraging manner.

A justification for the quantified assessment

Quality

The two major participating groups have published extensively in clinical and non-clinical journals of excellence. Both have established international and national reputations for the excellence and pertinence of their research. Funding from the CGC has been used for staff recruitment and consumables and has been critical to the rapid progress made on this research programme.

Productivity

Given both the start dates of the CGC project and of the assessment exercise and the considerable lag times inherent in this type of research, it is difficult to assess concretely the productivity due to CGC funding. The participating groups have however all published extensively over the 2002-2006 period. The productivity of the groups is clearly commensurate with their international reputation.

Relevance
Of all the sub-programmes within the CGC remit this is the one that is most immediately relevant to clinical cancer care. It holds the promise of providing both better-tailored clinical care and more cost effective treatment linked to this better tailored treatment.

Viability and feasibility
The programme has benefited from the excellence of the scientific leadership and the remarkable resource accumulated over many years represented by the tumour banks and patient material being exploited for the transcriptional profiling. The transcriptional profiling approaches used two different platforms and the committee, whilst recognising some possible advantages in this situation, was concerned that it complicated collaborations within the CGC.

The perspectives for this research appear outstanding though they are in large part conditioned by the feasibility of the endgame to develop limited panels of biomarkers of clinically predictive value. This will depend in major part on the robustness and universality of the markers discovered, which remains to be established by further research.

Overall remarks & Scope for further improvement
Assessing the scope for further improvement is hampered by the lack of detail provided about future plans. It is clear that the next steps, to move from research on prognostic markers to research aimed at establishing the genetic/epigenetic basis of these markers and their evaluation as drugable targets, will be a very difficult ones to make and may require additional expertise beyond that currently available in the participating groups.

Having said that, the groups participating in this sub-programme have some outstanding achievements to their name and everything suggests that this excellent level of performance will continue in the future.

Theme 2, DNA-repair, genome stability and epigenetic mechanisms

Programme director	Jan Hoeijmakers	
Research staff 2005	19,1 fte	
Assessment	Quality	5
	Productivity	5
	Relevance	5
	Viability	5

A short description of the research programme

The aim of this programme is to characterise the mechanisms and physiological significance of DNA repair processes, identify new genes involved in regulation of genome stability, and methods for characterising epigenetic and physical rearrangements of the genome.

A justification for the quantified assessment

Quality

Each of the groups within the program is headed by an internationally prominent investigator. All of the groups have well-established reputations for originality and productivity, recognised by professional awards and prizes, both within the Netherlands and internationally.

The Hoeijmakers group's main focus is on the analysis of DNA repair and its physiological consequences in the mouse, focussing on analysis of different repair phenotypes in the mouse, characterisation of DNA repair complexes, and analysis of the cell biology of the DNA damage response.

The Plasterk group develops and uses clever and elegant genetic approaches to the analysis of different types of DNA damage and repair processes, focussing on C elegans. They also develop methods for high throughput mutagenesis in higher organisms.

Grosveld's contribution to the programme forms part of a group of projects predominantly aimed at generating novel tools for genomics, including development of transposon mutagenesis technologies and genome mapping techniques; and novel reagents for genomic investigation, such as in vivo biotinylation tagging strategies and heavy-chain antibody technology.

The programme makes use of NGI funds to support research staff in each group, with bioinformatics support being especially important. The funding also brings in research infrastructure within the host departments, which benefits researchers associated with the CGC groups.

Productivity

All the groups in the programme are outstandingly productive in publication terms. Each of the groups has made substantial advances, and published extensively in high impact journals. Each of the members also contributes high-profile review material.

The Hoeijmakers group has used clever transgenic approaches to analyse the role of different UV induced DNA damages in the physiology of the response to UV; confirmed that a new TFIIH subunit first identified in yeast underlies group A TTD; shown that

ubiquitinylated H2A accumulates around DNA damage sites; demonstrated a dramatic match between the response to aging and DNA repair deficiency, leading to a new area of investigation of the relation between cancer susceptibility, aging and genome instability.

The Plasterk group continues to develop excellent and very innovative screens in C. elegans to detect novel genes implicated in genome stability. High throughput screens against other types of instability (G-tract instability) and other types of mutagen have been or are being developed. They also assess the significance of the genes isolated for tumourigenesis. Although this area is without concrete success as yet it is very logical to continue its pursuit. There have been publications on all these aspects.

The Grosveld group has further developed the 3C method into 4C, an array based protocol for analysis of proximity between different genomic regions, providing a new approach to mapping chromosome topography. This study is submitted for publication. They have also published extensively on their transposon mutagenesis and biotin-tagging work.

Relevance
The relevance of the current and proposed future work to the mission of CGC is substantial. Hoeijmakers' studies on the link between aging, DNA damage and cancer will be of increasing relevance to the likely impact of the western obesity epidemic upon cancer incidence. Plasterk's screening studies on aspects of the DNA damage response already have revealed new potential cancer targets, while the work on techniques to characterise the results of mutagenesis in higher organisms will provide new resources for genetics relevant to cancer and many other disciplines. Similarly, Grosveld's portfolio of genomics tools underpins the efforts of other CGC members as well as making important contributions to this programme.

Viability and feasibility
The future of this programme is innovative and exciting, and leads on from the studies already underway in these groups. Where appropriate the investigators will interact with each other or with other CGC members.

- Hoeijmakers will develop the studies on DNA damage / aging / cancer to establish the nature of the connections between these processes, which may lead to development of assays for agents designed to interfere with them.
- Studies on the cell biology of the DNA damage response promise to generate insights into how the DNA damage machinery functions in the context of intact tissue, rather than the cultured cell systems presently in use.
- Plasterk will continue the DNA damage screens in both C. elegans and mouse (no detail was given on the latter), carry out synthetic lethal screens for genes interacting with DNA damage pathways and analyse the mechanism of (heritable) RNAi.
- New approaches to the cataloging of null mutations on a genome-wide scale in higher organisms will be developed.
- The potential of the Grosveld 4C method will be evaluated using leukemias with a view to developing its use as a diagnostic tool. Transposon mutagenesis will be developed with Berns. Development and validation of the other tools with continue.

Overall remarks & Scope for further improvement
These research groups use genomic approaches to identify or analyse aspects of the cancer problem, and / or are developing new genomic tools critical for the CGC mission.

Theme 3, Functional screens

Programme director	René Bernards	
Research staff 2005	30,4 fte	
Assessment	Quality	5
	Productivity	5
	Relevance	5
	Viability	5

A short description of the research programme

This programme seeks to identify genes, and thus pathways, involved in the progression from a normal cell to a tumour cell. The primary approaches used are retroviral insertional mutagenesis in the mouse and RNAi screens in cultured cells. There is also work to develop new screening approaches, notably transposons, that can be conditionally activated in particular cell types.

A number of years ago the Berns laboratory demonstrated the value of small-scale insertional mutagenesis screens. They have now greatly increased the scale of their activity taking advantage of the massive sequencing capacity available at the Sanger Institute to identify insertion sites. Most of their screens are conducted on sensitised backgrounds, which greatly increases the efficiency of the process. They have identified some 600 insertion sites, many of which have been validated by large scale sequencing of human tumour DNA. A particular value of this approach is that it immediately provides information on the patterns of co-operation between dominantly acting oncogenes and tumour suppressor genes.

The Bernards laboratory has been a leader in the development and application of large scale RNAi screens in cultured cell systems, many of which are sensitisied. They have identified novel and interesting pathways, the most notable being the role of deubiquitinating enzymes in cellular regulation. They have also shown that this approach can be of particular value in identifying the mechanisms by which tumour cells become resistant to chemotherapeutic agents, a problem of great clinical relevance.

A justification for the quantified assessment

Quality

The research groups involved in this theme are uniformly of the highest quality and are regarded as world leaders in their fields. Their approaches are original and at the cutting edge and they make major contributions to the field, which are well exemplified by their numerous publications in the most prominent scientific journals.

Productivity

Given the resources available to them, which are quite modest on an international scale, these groups are highly productive in terms of publications and of very well trained young researchers. They are also extremely aware of the possibilities for translating their work for both economic and patient benefit.

Relevance
The work in this theme is totally relevant to both the present understanding and the future treatment of cancer. It clearly advances our knowledge and is efficiently disseminated through both scientific publications and interactions with commercial organisations.

Viability and feasibility
The past scientific performance is at the highest international standard and the future plans give confidence that this level of performance will be sustained.

Overall remarks & Scope for further improvement
No specific comment beyond the comments made about the whole institute in the last chapter.

Theme 4, Cancer proteomics

Programme director	Hans Bos	
Research staff 2005	10,3 fte	
Assessment	Quality	4
	Productivity	4
	Relevance	5
	Viability	5

A short description of the research programme

This research program focuses on three areas. The first area is the role of the Rap1 signalling pathway in the regulation of cell-cell junction formation and cell adhesion; its role in the metastasis process (H. Bos). The research plan involves a combination of: 2-hybrid screens using individual components of the Rap1 complex; synthetic lethality screens in C. elegans to identify genetic interactors of various components of the Rap1 complex; functional validation of newly identified proteins in mice (cell assays and mouse models). The PI also plans the execution of RNAi-based screens (of selected gene families) in mammalian cells to identify genes involved in the regulation of cell adhesion.

The second area this programme focuses on is the role of the Wnt/Notch pathway in the regulation of gut development and colon cancer (H. Clevers). This project is based on previous work of the PI that has provided robust in vivo and ex-vivo assays to investigate gut development and biology, with particular reference to the kinetics of crypt stem cells. The plan is to investigate the function (using knock-out mice) of about 50 bona fide targets of TCF4, a downstream effector of Wnt, that are specifically expressed in gut stem cells or progenitors (previously identified by the PI). The research plans are focused on the biological characterization of these novel genes. The PI also planned the execution of genome-wide ChIP-on-Chip experiments to characterize the binding profile of TCF4 in normal and transformed colon cells.

Finally the programme also focuses on the role of USP7 in the regulation of FOXO transcription factors (BM Burgering). This project is aimed at exploring the mechanism of FOXO regulation by oxidative stress (in particular monoubiquitination) and its role in the cellular response to oxidative damage.

The three groups have access to a number of centralized facilities for the execution of the planned screenings (proteomics, C. elegans lethality screens). Other high/throughput experiments are outsourced (two-hybrid screens).

- The Bos group's studies of EPAC and cAMP give important and novel insights into cAMP regulatory mechanisms. Two further interesting studies, on Ezrin-EPAC interaction, and a (Ras-Ral)-Jip3/Ask/Mek4-7/Jnk complex, are as yet unpublished.
- The studies on FOXO proteins by Burgering are allowing him to establish an international reputation in signalling by this protein family. The demonstration of a role for Ubiquitin in oxidative stress-induced regulation of FOXO relocalisation, and its functional interaction with beta-catenin, are novel and interesting.
- The Clevers group's studies of the Lkb1/Strad complex give important and novel insights into the mechanisms of cell polarization. They have now generated knockout mice for STRADalpha and beta, whose characterization is now in progress. A pygopus-

interacting E3 has been validated as new component of the Wnt pathway, although this has yet to be published. These results are novel from the point of view of signalling, cell biology and cancer.

- The UMCU group has established a core MS facility, run by Burgering, that has succesfully set up routine protocols for the identification of specific post-translational modifications.

A justification for the quantified assessment

Quality
The quality of the publications from the three groups involved in this programme is very high. In the last 3-4 years they have published relevant papers on top journals, including Cell, Nature and Science.

Productivity
The productivity of this research programme is very good. The three groups published 125 papers in peer-reviewed journals in the 4,5 year period of this grant (2002- 1 July 2006).

Relevance
This program is certainly relevant from an academic perspective. In particular, two of the questions that are tackled in this research program (cell-cell adhesion and regulation of asymmetric division in stem cells) are fundamental to biology and might provide critical insights for the understanding of the process of cancer metastasis and the hierarchical organization of tumours (cancer stem cells), respectively.

Signalling processes are central to cancer. Among them, the Ras and Wnt signalling pathways are certainly critical in the control of cell fate, proliferation and survival, and are frequently altered in tumours. Systematic characterization of the various components of these pathways is likely to provide important insights in cancer.

Viability and feasibility
For all three research programmes, the planned experimental approaches are solid and already functioning in the laboratories. Rationales are largely based on previous results generated by the same groups or by their own preliminary results. There is little doubt that the research programme is feasible and that the PI's will be able to adjust the experimental plan based on the results obtained.

Appendix 1: Curricula Vitae of committee members

Dr. Iain Mattaj (Chairman)
Dr. Mattaj was born in Scotland in 1952 and was trained in the UK and Switzerland. He came to EMBL in 1985, where he has led a very successful Unit since 1990, becoming Scientific Director for the whole of EMBL in 1999 and Director General in 2005. His early work focused on assemblies of RNA and protein [RNPs] in the cell, including those involved in messenger RNA production. Subsequently, Dr. Mattaj characterized mechanisms of macromolecular transport between the two major cellular compartments, the nucleus and the cytoplasm, and of the spatial regulation of structures and processes underlying cell division. He is a member of the European Molecular Biology Organisation [EMBO] and as Executive Editor helped make the EMBO Journal a highly successful international scientific journal.

Prof. Peter Rigby
Prof. Rigby became Chief Executive of The Institute of Cancer Research in London in February 1999. He is a molecular biologist with expertise in gene regulation and for thirteen years was Head of the Division of Eukaryotic Molecular Genetics at the Medical Research Council's National Institute for Medical Research. His pioneering work at the National Institute for Medical Research was concerned with developmental biology including understanding how muscles are made and how the structures of an organism come to be located in their proper position.

Prof. dr. Philip Avner
Philip Avner is currently Head of the Mouse Molecular Genetics Unit (CNRS URA 2578) and the Department of Developmental Biology at the Institut Pasteur. He was until recently also Scientific Director of the Mouse Genome project, Centre National de Sequencage (Genoscope) in Evry. He received his PhD in yeast genetics and biochemistry and an MSc in Molecular Enzymology at the University of Warwick. The current focus of his research is on mouse genetics and epigenetics. His main research interest in epigenetics is in X-chromosome inactivation and more specifically the role of the X-inactivation centre (Xic). Ongoing studies on mouse genetics in his laboratory include the analysis of mouse models for traits under multifactorial and polygenic control including type I diabetes. He has expertise in epigenetics, developmental genetics and mouse genetics. He is a research director with the CNRS and Professor at the Institute Pasteur. He is a member of the European Molecular Biology Organisation and Deputy Coordinator of the EU Noe Epigenome Project.

Prof. dr. Pier Giuseppe Pelicci
Prof. Pelicci is Director of the Department of Experimental Oncology at the European Institute of Oncology. After graduating in Medicine summa cum laude at the University of Perugia (Italy), he spent four years at the Department of Pathology of the New York University Medical Center as post-doctoral fellow, working on the structure of immunoglobulin and T-cell receptor genes in normal and neoplastic lymphoid cells (in particular the Ig-myc translocations of B-cell lymphomas). In 1986 Prof. Pelicci moved to the University of Perugia (Italy) where he became Chief of the Laboratory of Molecular Biology. There he cloned the translocation breakpoints of the Acute Promyelocytic Leukemia 15;17 translocation and the SH2-containing Shc, Sli and Rai proteins. In 1994 Dr. Pelicci became Professor of Oncology at the University of Parma and he is now full

Professor of Pathology at the University of Milan - Italy. In 1995 he joined the European Institute of Oncology in Milan as Chairman of the Department of Experimental Oncology. Prof. Pelicci's laboratory is working on mechanisms of growth control and leukemogenesis and on mechanisms which regulates life-span in mammals.

Dr. Richard Treisman
Together the Lincoln's Inn Fields Laboratories and its sister campus, the Clare Hall Laboratories, form the Cancer Research UK London Research Institute. Dr. Treisman is the Scientific Director of the Institute. He is also researcher at the Transcription Laboratory of the Institute. He received his PhD in 1981 at the Imperial Cancer Research Fund (ICRF)/ University College London. His research goal is to understand how the multiple signalling pathways activated by a particular extracellular signal allow gene transcription events to be coordinated with cell behaviour

Appendix 2: Overview of Scores of the Cancer Genomics Centre

5 = Excellent; 4 = Very good; 3 = Good; 2 = Satisfactory; 1 = Unsatisfactory

	Quality	Productivity	Relevance	Viability
Molecular profiling of cancer for individualised diagnosis	5	5	5	5
DNA-repair, genome stability and epigenetic mechanisms	5	5	5	5
Functional screens	5	5	5	5
Cancer proteomics	4	4	5	5

Appendix 3: Schedule Research Assessment CGC

Wednesday November 8

15.00 – 17.00	Meeting of the evaluation committee
20.00 – 21.00	Interview with **CGC management** • Anton Berns (director until March 2004) • Hans Bos (scientific director since March 2004) • Annelies Speksnijder (managing director since July 2004)
21.15 – 22.00	Interview theme 3 **Functional screens** • René Bernards (Theme director) • Anton Berns (Theme participant) • Hans Clevers (Theme participant) • Hans Bos & Annelies Speksnijder
22.15 – 23.00	Interview theme 1 **Molecular profiling** • Laura van't Veer (Theme director) • Jan Klijn (Theme participant) • Hans Bos & Annelies Speksnijder

Thursday November 9

09.00 – 10.30	Meeting of the evaluation committee
10.30 – 11.15	Interview theme 4 **Cancer proteomics** • Hans Bos (Theme director) • Hans Clevers (Theme participant) • Annelies Speksnijder
11.30 – 12.15	Interview theme 2 **DNA repair** • Jan Hoeijmakers (Theme director) • Ronald Plasterk (Theme participant) • Frank Grosveld (Theme participant) • Hans Bos & Annelies Speksnijder
12.30 – 13.30	Lunch
13.30 – 14.30	Interview with **CGC management** • Hans Bos (scientific director) • Annelies Speksnijder (managing director) • Frank Grosveld (representative Erasmus MC in CGC MT) • Ronald Plasterk (representative NIOB in CGC MT)
14.30 – 16:00	Meeting of the evaluation committee