

REPORT
CCA/V-ICI Site visit

April 9, 2009

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Foreword

This report presents the assessment of the research by the VU University medical centre's Cancer Centre Amsterdam/VUmc Institute for Cancer & Immunology (CCA/V-ICI) conducted April 9, 2009. It is based on advance documentation presented to the review committee, and on meetings with the various representative bodies and persons of CCA/V-ICI. The committee wishes to express their appreciation for the open and informative discussions with all persons with whom they have met.

Remarks by the committee are printed in this type font

Amsterdam, April 9th, 2009

Prof. dr CJM Melief, chairman

Dr M van Leeuwen, secretary

1 The Review

The Review Committee consisted of:

Prof. Dr CJM Melief, Chairman	<i>Immunohaematology and Blood transfusion, Leiden University Medical Centre</i>
Prof. Dr H zur Hausen	<i>Deutsches Krebsforschungszentrum (DKFZ)</i>
Prof. Dr LFMH de Leij	<i>Medical Biology, University Medical Centre, Groningen</i>
Prof. Dr B Löwenberg	<i>Haematology, Erasmus Medical Center, Rotterdam</i>
Prof. Dr P Quirke	<i>Gastrointestinal Cancer Research Group, Pathology and Tumour Biology, Leeds Institute of Molecular Medicine, UK</i>
Prof. Dr WA Weber	<i>Nuclear Medicine, University of Freiburg, Germany</i>
Dr M van Leeuwen	<i>Former Executive Director, Health Council of the Netherlands, secretary</i>

The present assessment was commissioned by the Board of CCA/V-ICI. It is based on the documentation provided to the Review Committee (*further referred to as the committee*), on interviews with the programme leaders and CCA/V-ICI's Management and the Dean of the VU University medical centre (VUmc), on poster presentations and discussions with members of the scientific staff, postdocs and graduate students. In their assessment the committee focused, *inter alia*, on the results of the 2006 merger of CCA and V-ICI. The committee also took note of the recommendations in the report of the previous external assessment, which took place in December 2004.

The committee had received the *CCA/V-ICI Self Evaluation 2004-2008*, the *V-ICI Site Visit Report of 21 December 2004*, as well the background document *Standard Evaluation Protocol 2003-2009 for Public Research Organisation*, published by VSNU, NWO and the Koninklijke Nederlandse Akademie van Wetenschappen.

The site visit was conducted April 9th, 2009.

After an initial meeting with the Board, the committee met with the programme leaders of CCA/V-ICI, the Scientific Research committee (CWO), the Education committee and the Dean of the VUmc. The committee then discussed their impressions and findings. In a final meeting with the Board of CCA/V-ICI the committee reported their main findings and recommendations.

2 Background information

CCA was founded in 2004. It facilitated the V-ICI programmes, in order to strengthen the translation of basis research into clinical care. In 2006 CCA and V-ICI merged, in order to strengthen the integrated research efforts of the patient related, fundamental cancer and immunology programmes.

CCA/V-ICI states that it is the institute's mission to coordinate and stimulate:

- Top level fundamental, translational and patient related research in immunology and cancer;
- Top level multidisciplinary patient care;
- Creation of excellent facilities for research and patient care;
- Training of young investigators to ensure excellent fundamental and clinical researchers;
- Optimal training of health care workers.

2.1 Organisational structure

CCA/V-ICI is one of five research institutes of the VUmc. It reports directly to the Board of Directors of the VUmc, by submitting a long-term research programme and a scientific annual report. The CCA/V-ICI board and the Board of Directors of the VUmc meet twice yearly.

2.2 Research by CCA V-ICI

The research efforts of CCA V-ICI are concentrated in four programmes:

1. Oncogenesis

This programme covers basic and translational research. It comprises three subthemes:

- Viral oncogenesis
- Cancer genomics
- Genetic predisposition

2. Immunopathogenesis

This programme deals with fundamental and preclinical research of immunological processes underlying homeostasis control of inflammatory, cancer-related diseases. There are three subthemes:

- Homeostasis control and inflammation
- Host-pathogen interaction
- Tumour immunology and preclinical immune therapy

3. Disease profiling

The focus of this programme is on fundamental and translational research aimed at identifying new determinants for diagnosis, prognosis and tailored treatment for immunological diseases and cancer. The programme comprises three disease oriented research lines:

- Solid tumours

- Haematological malignancies
- Chronic inflammatory disease

4. Therapy

This programme deals with translational research within the field of oncology and immune-mediated, non-oncological diseases. It comprises five research lines:

- Chemotherapy
- Immunotherapy
- Radiotherapy and surgery
- Gene therapy
- Quality of life

2.3 Training and education

CCA/V-ICI offers various educational and training programmes, at the bachelor, master, graduate (PhD) and postgraduate levels.

3 Some general observations

The committee had constructive and informative discussions with the leaders of the four research programmes. These are briefly summarized in chapter 5. Some general observations from these discussions:

- The participants generally considered the merger between CCA and V-ICI a logical one. CCA focuses on patient care, whereas V-ICI is a research institute. CCA is largely financed by private contributions. The participants saw the merger as beneficial to the quality of the research and to the promotion of interactions between research groups and individuals. The members of the Advisory Board (i.e. heads of departments) expressed their wish for further integration of research and clinical activities.
- Primary funds for V-ICI come from university sources and are meant for staff appointments. Annually there is approximately 7500 k€ available, of which 1500 k€ are institutional funds, mainly used to appoint PhD-students; the other 6000 k€ is provided by CCA, for equipment (2000 k€) and large projects, such as new building infrastructure (4000 k€).
- The two sources of money cannot simply be combined, because part of the donations to CCA are targeted at patient care or even earmarked for specific cancer type(s), which creates a considerable hurdle for spending of these resources on basic research projects. This situation has led to a perception by several groups and individuals that the distribution of funds is not very transparent. To some extent it also interferes with a desirable level of collegial and cooperative cohesion within the institute. Also, at the present time the question to what extent fundamental research can be funded through the institute is insufficiently clear. The perception by many was that the rules of the game need to be clearer, and that the operational application of earmarking rules in

practice should be made more flexible.

4 General conclusions and recommendations

This chapter presents the conclusions and recommendations that transcend the individual research programmes. An assessment of the latter is found in chapter 6, with a grading according to the Standard Evaluation Protocol presented in table I.

From the 2004 Site Visit report: “The committee recommends that the programme leaders make more detailed choices and conduct an additional analysis of the immunology/cancer synergy ...”

And

“In both the oncology and the immunology programmes there are research groups with excellent track records and wide-spread international recognition. (...) The committee suggests the development of a strong oncology and a strong immunology programme. This may be accomplished by combining the strengths, know-how and expertise of these two programmes.”

Conclusion and recommendations

- *CCA/V-ICI is an internationally competitive cancer centre, with very strong translational research and many internationally competitive research groups. The basic immunology stands out as internationally excellent.*
- *The committee finds that the two founding institutes CCA and V-ICI still largely operate independently. We appreciate that--because of the recent merger of CCA and V-ICI--interaction between the two is not yet optimal. We propose an active strategy to promote closer integration*
- *Management decisions regarding funding, at all levels of decision-making, should treat translational research and basic immunology equally. Earmarking of funding by the donors must be discouraged as much as possible. Of note: there is experience in other organisations (e.g. the Dutch Cancer Society) that circumvent strict earmarking rules imposed by funding donors by creative mechanisms so that the budget can be assigned according to quality and institutional priorities.*
- *All levels of decision-making should foster close integration between clinical and fundamental immunology programmes. We suggest to appoint a team composed of members from each programme to foster integration and cohesion and to develop novel innovative research based on joint expertise. Preference could be given to clearly cooperative programmes.*

Scientific Advice

The Institute seems to obtain scientific advice from two Scientific Advisory bodies. The committee believes that to be somewhat overdone.

From the 2004 Site Visit report: "The committee suggests the installment of an independent Advisory Council of non-V-ICI members that reports directly to the dean of the VUmc."

Recommendation

- *The committee wishes to paraphrase the recommendation from the site visit 2004: There should be a single strong, scientific advisory board, composed of (external) top scientists.*

Tenure track

It was not clear to the committee how the tenure track procedure works in actual practice, and what its relation is to the honours programme.

Recommendation

- *A well-defined and transparent tenure track system is deemed crucial for the future of the institute.*

Distribution of funds for research

The committee perceived some friction regarding the way the 2 financial sources (CCA and institutional) are distributed.

- *The committee would like to see the funds for PhD-positions increased, coincident with redistribution of resources based on merit. The institute should have more influence on the final decisions.*

From the 2004 Site Visit report: "The committee recommends a seat at the table where the money of CCA will be divided, and where future/strategy is made."

The format and the nature of the site visit

The site visit was very well prepared and the committee was provided with a large volume of documentation. However:

- *One day for this site visit was too short. The committee would have liked to have more time to meet with PhD-students and postdocs and to prepare its report. A minimum of 1½ day would be needed.*
- *It would have been appreciated if the chairman of the committee had known that the committee was to have a secretary.*
- *The self evaluation, which in various respects was insufficiently informative and lacked relevant documentation:*
 - *Needs to provide more substance and detail in its descriptions of past*

- performance and future plans*
- *Should more clearly indicate what has been achieved both scientifically, medically and educationally*
- *Elaborate and defend the general strategy and milestones for the next period including collaborative programs*
- *Provide only references to papers published in top journals during the past 5 years.*

5 The individual research programmes

5.1 Programme 1 – *Oncogenesis*

Subtheme Viral oncogenesis

This program mainly consists of translational research. The main goal is to ultimately apply the research findings to patient benefit. An example is the search for biomarkers as early indicators of disease.

Immunology could have been part of programme 1, but has been brought under programme 2 (Immunopathogenesis) because this enabled bringing people together using the same methodology. There is, however, a good interaction with programme 2 (Immunopathogenesis)

A test has been developed to detect non-melanoma skin cancer, based on the skin HPV-types detected. Further fundamental work on HPV is presently ongoing at a low level. For example the role of micro RNA's in HPV oncogenesis is being studied. The moment to fully step in was said to also depend on the competition as evident from the scientific literature.

In the area of HPV, the focus is now on HPV-screening for cervical carcinoma. In the area of EBV research, the main goals are improved non-invasive diagnosis of Nasopharyngeal Carcinoma and EBV vaccine development.

Subtheme Cancer genomics

A number of independent core facilities exist, such as models allowing high-throughput screening, in cooperation with the NKI (Netherlands Cancer Institute, NCI), and microarrays. The group has a proteomics platform with state-of-the-art equipment.

Biobanking

A large biobank effort has been started. As yet there are no central storage facilities, but this is being discussed. Tissues are controlled by the hospital, but the material is available for all researchers. The biobanking infrastructure is being improved by the national Parelsoer initiative. ICT is lagging behind the biobanking efforts.

5.1.1 *Conclusions and recommendations*

- *The committee noted that nearly all research within this subtheme is translational; the committee noted only limited fundamental research activity. In the long run this can lead to a lack of source research for translation.*

- *The committee suggests that, if the goal was to develop in vitro models of genetic predisposition for even a limited number of cancers, the enterprise could become too much to handle, because of the large number of different tumour types studied. The committee advises to make choices for in-depth analysis of a few defined cancer types.*
- *Safeguarding continuity*
The committee expressed some concern that the group might be vulnerable in terms of continuity and suggested to focus on its strengths, such as its internationally outstanding HPV pathology, Fanconi anaemia and colorectal cancer research lines. Being more selective will make the research efforts more effective.

5.2 Programme 2 – Immunopathogenesis

This programme consists of basic immunology research that is largely not related to cancer and of cancer immunology research with many highly translational aspects. It was noted that so far basic immunology has not integrated with cancer research within CCA-V-IC. This appears to be due to the relatively recent fusion of CCA and V-ICI. With respect to the basic immunology research we cite from the self-evaluation:

“The program may stand on its own in splendid isolation (...) without any connections with other V-ICI programmes”.^a

The committee had a thorough discussion with the members of the group about the reasons for this and the possible mutual benefits of harbouring the group within the Institute. The group stated that they do the “hard core” immunology research, with so far only few links with other groups within CCA/V-ICI. Yet, nationally and internationally much collaboration is going on. For translational purposes a better relationship can be forged with other ongoing research in the institute, starting from the inflammatory nature of tumorigenesis, including its pre-malignant phases.

One perceived problem is the earmarking by fund donors of resources to specific cancer-related goals. The group mentioned that the Board is now attempting to explain to funders that they should consider contributing the money generically, *i.e.* for *good research*, rather than for specific cancer projects. Both the cancer-oriented researchers and the basic immunology researchers noted that further integration of their activities and development of joint projects is highly desirable and possible and that they are committed to actively striving for achievement of these goals in the future. On the other hand appreciation of basic immunology projects and funding of projects in this area was also felt to be necessary as a driving force of good quality translational research.

^a CCA/V-ICI Self evaluation 2004-2008

External collaboration

There are incidental projects together with the AMC and the Netherlands Cancer Institute (NKI).

Future goals

Besides the points already discussed, the group would like to see:

- Representation of all 4 programme platforms in the Board
- More links between the 4 research groups.

5.2.1 Conclusions and recommendations

- *The committee recommends and discerns many possibilities for improved interactions in immunology and oncogenesis in CCA-V-ICI between the existing tumour immunology oriented researchers and the fundamentally oriented researchers to promote the goals of the Institute.*
- *The committee also recommends enhancing the critical mass of the overall immunology effort by greater involvement and better immunology training of young clinicians.*
- *The committee is of the opinion that a better understanding of the cellular micro-environment and inflammatory and other immunological processes in cancer and in persistent infections could have significant potential for innovating cancer therapy and therapy of persistent infections. The program could be very vocal in developing interrelated research plans in this area that utilize the joint expertise of both the fundamental and cancer immunology groups. The perceived gap between the lab and the clinic can be further bridged by, training clinicians in the lab and by organizing a retreat of the CCA V-ICI during which these issues are being discussed. Part of the budget could be reserved for interactive grants.*
- *The committee recommends the promotion of more initiatives in the area of clinical immunotherapy of cancer in combination with other treatment modalities. The availability of immunologically trained physicians will support such initiatives.*
- *The committee discerns various possibilities for linkage between oncogenesis and immunopathology. The knowledge and expertise of the basic oncogenesis and basic immunology groups offer interesting opportunities for interactive and innovating research.*
- *Creating tenure track positions for the most-talented post docs together with the medical faculty could enhance the visibility of the institute.*

5.3 Programme 3 – Disease profiling

This program contains both imaging and molecular diagnosis activities. The programme leader explained that a few molecular imaging and molecular diagnosis lines are integrated. Subthemes 1 (solid tumours) and 2 (haematological malignancies) are not really integrated, except in a few cases in which individuals have taken the initiative to combine forces.

All major imaging efforts will be united in a new building: radiology, PET, laser, data analysis, tracer development, etc. This new facility will be operational in 2014. It will comply with stringent GMP standards.

Bioinformatics

The researchers have good access to the Computer Science Department, which has a staff of 15 FTE, but only 1 FTE for proteomics and 2 FTE for genomics analyses. The institute acknowledges that there is presently insufficient infrastructure in place to store and analyse the vast amount of data generated by the programme. It was noted that internal funding is more important for proteomics, because this activity was initiated only relatively recently.

Research time

The members of the group find it quite challenging for clinical researchers to obtain sufficient time for doing research. The situation, however, has improved over the years.

Goals for the future

- *Rheumatology*: in the next 5 years to perfect the probes for macrophages
- *PET scanning*: develop new imaging methods; new targets and ligands.
- A drug development department to be started; develop new ligands; the plan is to validate 5 targets to be introduced into the clinic.
- The ambition is to develop image-guided therapy.

5.3.1 *Conclusions and recommendations*

- *The committee finds this an interesting programme, with a good input/output balance. Its three subthemes have two approaches in common: imaging and profiling. The programme might in selected areas further benefit from more integration of imaging and profiling.*
- *The committee expressed reservations regarding the diversity of the programme and the lack of a focused future-related vision. For maximal effectiveness assigning priorities for the future is important with the limited funds available. The committee suggests that profiling even one solid tumour type would yield vast amounts of data. The path to finding validated targets and therapy is also quite long. It recommends that there be more focus on one or two selected cancer types.*
- *The committee finds that the bioinformatics unit has insufficient manpower*

available to handle the vast amount of proteomics and genomics data generated. (Only 1 FTE for proteomics and 2 FTE for genomics analyses).

5.4 Programme 4 – Therapy

Of all the programmes this programme was lacking most in substance and detail concerning past performance and future plans. The programme invests in 3 innovative research lines: immunotherapy, gene therapy and oncolytic viral therapy and to maintain a good balance between clinical care for cancer patients and research.

Animal models for new therapies

The Animal research facility is being rebuilt. For the next few years developing animal models for new therapies will be a focal point. Some models have already been developed. Radiotherapy in animal model systems will become available for combination therapies.

5.4.1 Conclusions and recommendations

- *Lack of Focus*

This program is organized according to 5 medical specialties, apparently following the hospital structure rather than a scientific research plan. Modern science, however, has become a multidisciplinary endeavour, and one would expect to see this reflected in the group's research plan. There is a mix of activities for particular tumour types that cover the full spectrum from prevention, via biological research through diagnosis and treatment development to palliative care, while other tumour types have a limited representation. A multitude of cancer types are represented in this programme. There are no clearly defined research themes that characterize this programme in a way similar to the other (sub)programmes of CCA/V-ICI. Thus the Therapy programme lacks clearly identifiable objectives and goals and in its current presentation makes a broad and diffuse impression. Innovative aspects in this subprogramme are not clearly distinguishable. The committee suggests that innovation will require choices to be made.

The committee assumes that within this programme there may indeed be strong projects and research activities with focus and scientific productivity, but the committee was unable to discern these among the material provided.

- *Because of the paucity of documentation provided and the very broad ambition of the programme, the committee advises to not evaluate this program now, but to evaluate it a year from now, when choices can have been made and the programme can be the subject of a more detailed and strategic document.*

Table I: Formal evaluation and rating of the research programmes

The 5-point scale recommended by the Standard Evaluation Protocol 2003-2009 for Public Research Organisation has been applied, as follows:
1: unsatisfactory; 2: satisfactory; 3: good; 4: very good; 5: excellent

Programme	Subtheme	Rating	Comment
Oncogenesis	<i>Cancer genomics</i>	3	<i>Covers too many cancer types; needs more focus</i>
	<i>Viral oncology</i>	4	<i>Should maintain a sufficient volume of basic research</i>
	<i>Genetic predisposition</i>	5	<i>Needs to maintain its excellence by appointing young staff members</i>
Immunopathogenesis	<i>Homeostasis control and inflammation</i>	5	<i>Further integration is desirable within the programme and the institute</i>
	<i>Host-pathogen interaction</i>	5	<i>Needs to better interact with translational scientists and clinicians</i>
	<i>Tumour immunology and preclinical immune therapy</i>	3/4	<i>Needs better implementation of clinical immunotherapy programs</i>
Disease profiling	<i>Imaging</i>	4	<i>This is a strong nuclear programme. It was not clear to the committee if it was being developed as a core service for others to use, or for research. It was difficult to evaluate the programme from the paper work provided, both with respect to achievements and future plans.</i>
	<i>Profiling</i>	4	<i>Too few FTEs for bioinformatics analysis of proteomics and genomics data</i>
Therapy		n/a	<i>This programme lacks focus and a sufficiently detailed description of past performance and plans for the future. This paucity of information made it difficult to judge the programme. The committee therefore has great hesitations rating it.</i> Recommendation: <i>Because of the importance of the programme for VUmc and the institute we recommend a separate evaluation of this programme in about a year's time, supported by detailed data of past performance and future plans.</i>
Institute overall		4	<i>The Institute is built on a fusion between a cancer research and an immunology institute. The combined expertise in these areas is of an internationally high level. If the opportunities of the newly-built institute are used and if the research is focused on selected cancer types, the future looks very bright.</i>

6 Summary

- *The site visit has revealed the considerable potential of the merger of CCA and V-ICI that has led to the formation of CCA/V-ICI, incorporating many internationally known groups in the area of oncology and immunology. Nevertheless it appears that the merger has not yet led to a sufficient level of collaboration and translation, or to the necessary choices for sufficient focus and depth to reach critical mass in a limited number of well-defined cancer types. The committee recommends that the policy that only high quality is the criterion for research funding is maintained but that apart from that a special stimulatory program is installed in which collaborative projects between basic researchers and cancer-oriented researchers are funded with priority as an instrument to foster collaboration. Also, the institute should promote training of more clinicians in the basic doctrines that constitute the critical knowledge base of the institute, such as immunology, virology and genetics.*
- *The Oncogenesis programme, subdivided into the subthemes cancer genomics, viral oncogenesis and genetic predisposition contains excellent research groups. The cancer genomics subtheme however, is advised to make a choice for only a very limited number of cancer types to be studied in depth. The subtheme viral oncology should maintain a sufficient level of basic research to feed its translational excellence also in the future. The subtheme genetic predisposition is appropriately focused on just a few cancer types. The current senior staff should eventually be succeeded by younger staff of equal eminence.*
- *The programme Immunopathogenesis consists of the subthemes homeostasis control and inflammation, host-pathogen interaction and tumour immunology and pre-clinical immunotherapy. This programme hosts several internationally excellent researchers, but collaboration between the two fundamentally oriented subthemes and the translational immunologists as well as clinicians has not materialized. The committee discerns many opportunities to achieve this. The committee is of the opinion that a better understanding of the cellular micro-environment and inflammatory and other immunological processes in cancer and in persistent infections will be of great importance for innovating cancer therapy and therapy of persistent infections. The institute could be very vocal in developing interrelated research plans in this area that utilize the joint expertise of both the fundamental and cancer immunology groups.*
- *The programme Disease profiling consists of the subthemes imaging and profiling. Both subthemes harbour internationally recognized research groups. The imaging is supported by a very strong nuclear medicine group but it is not very clear which activities are service to others and which ones are autonomous research activities. With respect to profiling, the committee advises to expand the number of FTEs assigned to bioinformatics analysis of genomic and proteomic*

data.

- *The Therapy program harbours many clinicians and researchers of international reputation, but due to the paucity of information on past performance and future plans and a general lack of focus, a multitude of cancer types and plans are represented in this programme. There are no clearly defined research themes that characterize this programme in a way similar to the other (sub) programmes of CCA/V-ICI. Thus the Therapy programme lacks clearly identifiable objectives and goal in its current presentation. Because of the paucity of documentation provided and the very broad ambition of the programme, the committee advises to not evaluate this program now, but to evaluate it a year from now, when choices can have been made and the programme can be the subject of a more detailed and strategic document.*

