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Dear Reader,

In the spring of 2014, OICR's Board of Directors initiated an independent strategic review of the Institute to look at the achievements to date and to provide advice with respect to the future directions of the Institute. The independent panel was co-chaired by Sir John Bell, FRS, HonFREng, PMedSci, Regius Professor of Medicine at Oxford University and Simon Sutcliffe MD, FRCP, FRCPC, FRCR, former CEO, BC Cancer Agency, who was appointed by the Ministry of Research and Innovation. The panel members included:

- Dr. Morag Park, Director, Rosalind and Morris Goodman Cancer Centre McGill University
- Dr. Irving Weissman, Director, Institute for Stem Cell Biology and Regenerative Medicine Director, Stanford Ludwig Center for Cancer Stem Cell Research and Medicine Professor of Pathology and Developmental Biology
- Dr. Jennifer Grandis, Department of Otolaryngology Eye & Ear Institute Pittsburgh
- Dr. Peter J van der Spek, Dept. of Bioinformatics, Erasmus University Medical Center, Rotterdam
- Dr. Ian Ellis, Professor of Cancer Pathology, Division of Cancer and Stem Cells, School of Medicine, University of Nottingham

The panel met in Toronto November 19 and 20, 2014. The Board has received the Strategic Review Report and is moving forward to incorporate the advice of the Review panel into the next Strategic Plan for OICR. The report concludes that "the creation of OICR—was a bold and innovative initiative. Much has been achieved and more can be achieved. Ontario scientists clearly welcome the opportunity to take translational research to greater levels of productivity, performance and impact." To do so the panel recommends the support of science in new areas of inquiry that show promise and with respect to the intramural programs that these can deliver a greater transformative change if they become "more outward facing" and facilitate "a broad set of collaborative programs in areas that need enhancement in the province". The report provides comments with respect to all of the programs and specific advice with respect to how each of the intramural programs can and should evolve within the context of the statement above. Many of the Institute Programs were deemed to be of exceptionally high calibre, including Cancer Stem Cells, International Cancer Genome Consortium, Innovations in Target Validation, Imaging, Immuno- and Bio-therapeutics and Health Services Research. The Panel also identified programs in need of further assessment in terms of their alignment with the key objectives of OICR going forward. There is particular emphasis on the importance of enhancing collaborative relationships with the clinical research centres, and specifically University Health Network, as these are central to the pursuit of a robust translational strategy.

The Report provides advice with respect to the current commercialization strategy and recommends consideration of approaches being undertaken in other jurisdictions. This includes determining the appropriate balance between supporting translational research in the academic setting and options for attracting private investment. The Report also identifies specific governance related matters for the Board's direct attention going forward.



Given the importance to the future success of the Institute of the next Strategic Plan, the Board has established an Ad Hoc Committee including both directors and outside advisors to oversee development of the Plan taking into account the recommendations of the Independent Strategic Review.

In the short term, action has already been taken to reflect the advice of the Review in finalizing the research budgets for the current year. Discussions have been initiated with respect to engaging Ontario researchers and clinicians (both internal and external) with respect to increasing synergies within the province and across Canada in areas that include cohorts, informatics, clinical genomics, pathology and drug discovery. Where opportunities are identified, these will be acted upon. Over the summer, there will be workshops to explore how best to implement the recommended directions as part of the Institute's multi-year strategy. The objective is to complete the development of the Strategic Plan in the fall.

As a Board we welcome the Review's acknowledgement of what has been achieved and are committed to taking the steps necessary to take translational research to greater levels as the panel has recommended.

A handwritten signature in black ink, appearing to read 'C. Stiller', is written over a horizontal line.

Chair of the Board of Directors
Ontario Institute for Cancer Research

Ontario Institute for Cancer Research Strategic Review

Report Summary

1. Ontario Cancer Research and the OICR

The establishment of a major cancer research institute by the province of Ontario to accelerate the translation of scientific discovery into individual, societal and economic benefit was visionary, innovative and prescient. Seven years into this initiative, the province has much to be proud of. Capitalising upon this initiative into the foreseeable future however, requires not only that excellent science be pursued, but also that excellent science enables the capabilities within the broad cancer research community in Ontario and is enabled by collaborative and constructive relationships between investigators, institutions and society.

2. The Translational Research Mission

Translational research enables scientific discovery to impact health and socio-economic outcomes and, as such, is a “team sport”. OICR has not been created in the context of a clinical environment. Thus, to have impact, OICR must achieve its intended translational mission through interactions with external partners. To this end, all partners must see value and continuously strive to sustain value through engagement in advancing their mission, the OICR mission and the goals envisaged by government with the funding commitment to a vibrant provincial cancer research environment.

3. OICR Programmes

To excel, OICR programmes must underpin excellent, innovative science, they must be relevant to clinical practice and improved health outcomes, they must achieve sufficient critical mass to excel, capable of expanding scientific and technological advances through collaborative relationships and, ultimately, they must be capable of influencing health practice through credibility and active integration into the clinical care environment. The panel found that the programmes advanced by OICR included:

- a) Programmes highly aligned to these characteristics: Cancer Stem Cells; Imaging; Health Services Research; Target Validation; ICGC; Immuno and Bio-therapeutics.
- b) Programmes that would benefit through further development of their alignment to these characteristics: Drug Discovery; Gene Technology; Bio- informatics and Biocomputing.
- c) Programmes whose potential has not yet been fully realised due to limited alignment: Transformative Pathology; Pancreatic Cancer.

- d) Programmes whose “fit” within the OICR portfolio might be reconsidered: Ontario Health Study; C3TN.

4. OICR: Evolving the Model

The original mandate for the OICR emphasised certain objectives—the creation of a strong institute with its own intramural and extramural programmes that would deliver benefits to the Ontario health system and to the economy of Ontario through the commercialisation of Ontario science.

With the experience of the last seven years, consideration should be given to further evolving the objectives of OICR within the culture of Ontario science:

- to foster and support established excellence across all programmes that can be translated into improved health and economic gain
- to work with partners to fill current gaps and provide the science capabilities that will be required to excel in translational research
- to catalyse more effective collaboration to maximise the potential for innovative, translational medicine.

5. Governance

Board governance necessitates that there is in place a plan to achieve the vision, mission and goals of the organisation, that there is effective oversight of the conduct of the organisation's business, and that there is in place a senior executive who can effect of the business of the organisation. The OICR Board has successfully accomplished this for the past seven years since inception of the OICR.

Going forward the Board may also wish to consider:

- How the Board assures itself that the strategic direction and quality of science funded by OICR (public funds) is both appropriate to mandate, to the standard accepted by the wider cancer research community, and independent of the interests and opinions of vested parties. This Board assurance is to be distinguished from the assurance provided to the Director through advisory committees reporting to the Director.
- Compensation equivalence across the medical and scientific community in Ontario.
- The level of investigator review and oversight commensurate with the need for accountability for public funds, but without excessive bureaucratisation that interferes with, and disincentivises, the conduct of research.

Conclusion

The creation of OICR through government funding was a bold and innovative initiative. Much has been achieved and more can be achieved. Ontario scientists clearly welcome the opportunity to take translational research to greater levels of productivity, performance and impact. The panel recommends that the intramural program of OICR be reconfigured to be more inclusive and interactive with the Ontario community. To do so will require a collaborative culture and more extensive engagement and alignment with the community to prioritise the use of resources. The evolution of OICR should

also allow the support of science in new areas of enquiry that show promise. Clearly, there remains a major role for OICR in the biomedical research community in Ontario, but it does need to adapt to ensure it achieves the maximum level of leverage and support from the wider community.

Strategic Review Report of OICR from the Advisory Committee

Professor Sir John Bell (Co-Chair)

Dr Simon Sutcliff (Co-Chair)

Dr Ian Ellis

Dr Jennifer Grandis

Dr Morag Park

Dr Peter van der Spek

Dr Irving Weissman

When the Province of Ontario Government created the mandate for the Ontario Institute for Cancer Research, they were making a bold decision to support an area of science which has the potential to change the lives of millions of patients who suffer from cancer globally and also to support and resource an innovation programme that could help to grow a different type of technology based economy in the Province. Since the establishment of the original mandate and the funding of the Institute, an enormous amount of work has ensured the creation of a powerful research engine in the Province. The programme has supported outstanding research around the Province, some of which is clearly internationally leading and, in addition, it has developed a set of core programmes within the Institute itself that have helped to underpin the programme. The Review Committee received a very thorough and extensive set of documentation that outlines the substantial achievements of the OICR over the past seven years and, on 19th and 20th November 2014, the Committee heard from many of the leading investigators who presented their programmes face-to-face. As one would expect, some of these programmes were truly outstanding while others, for various reasons, had achieved less. Our major conclusion from this review was that the Province had acted wisely in creating the OICR and continuing to fund it at a high level, despite a wide range of economic challenges. It is also our conclusion that there is much more that could be done and that continued support for the OICR will lead to even further achievements in terms of delivering new cancer diagnostics and therapeutics and the creation of economic growth. Like all institutions of this age we also believe that it would be timely for the Board to reconsider aspects of the strategy, which is now approaching ten years of age. The science has clearly moved on, but so has the understanding of this unique opportunity to drive and catalyse collaboration throughout the Province. We are confident that the OICR can continue to be a key research flagship for the Province and for Canada, but to sustain this position, evaluation of the strategic priorities and focus of the institution will be important.

Given the focus on translation in this programme, the Committee thought it challenging that the Institute was not based in the context of a clinical environment, had no patients directly associated with it and, indeed, had very limited clinical staffing. The problems associated with designating any single institution as the Province's Translation

Research Centre, however, made it sensible to create a free standing entity, the OICR. However, the corollary means that OICR can only achieve its intended translational mission through interactions with the external partners. This situation puts challenging pressures on the internal programmes to achieve translational outcomes over which they have little direct control. The term ‘translation’ has many meanings to many different people but our assumption was based on the written and verbal evidence provided to us that translation, in this context, was to focus on moving scientific discovery into commercialisation where, if successful, it could be applied to patient populations. In addition, it was clear that the Province intended this programme to help facilitate the healthcare system in Ontario to be more efficient and to implement effectively a range of cancer programmes targeted at cancer patients.

Although we can understand the focus of the original mandate for the OICR, we believe that this oversimplifies the nature of both basic and translational research. There is a crucial interaction between basic discovery and translational research activity that requires both activities to be successful and vibrant for the overall system to succeed. Much translation can also be achieved without directly focusing on commercialisation itself. For example, academic units in Ontario and elsewhere are perfectly positioned to undertake the thoughtful and challenging first-in-human experiments that provide crucial insights into the key biological effects of new therapeutic interventions. If this is to be done at scale, it needs to rely on pipelines in addition to those purely of the Institute or, indeed, of the academic community, and relies on a wider set of molecules available through the commercial sector. We enthusiastically endorse the view taken by the Province that this programme should have a balance between discovery and translational research, but feel that the definition of translational research should be wider than that originally conceived. We also believe that, although there has been a very innovative approach to create a structure which will improve commercialisation opportunities, the approach to commercialisation is still rather classical at a time when new approaches to dealing with the established problems of early stage companies are being tested, and we believe that there is significant scope for developing the existing model. This review will first provide a commentary of the programmes presented to us and then will deal with issues such as balance between intramural and extramural programmes, focus of the programme, governance and administrative structure, and commercialisation.

OICR Programmes

1. Cancer Stem Cells

This is an example of an external programme that is both high risk but also clearly world class. Toronto has a proud tradition in the stem cell field, and John Dick is undoubtedly a global leader in the field of cancer stem cells. OICR has systematically supported Dr Dick and his programme and this has helped to create very considerable leverage nationally and internationally for the programme. In particular, the group has identified a novel gene signature in acute myeloid leukaemia which it is now attempting to validate. The group has also identified a pre-leukaemic cell population which might be a new target amenable to therapy. To achieve these objectives Dr Dick and

colleagues have organised the collection of leukaemia cells and pancreatic cancer tissues in a way that they have stored viable cells from each. This enables cancer stem cell identification, preclinical tests of various therapeutic options with patient xenografts in immune deficient mice, and eventually, will be crucial for testing patient specific immune responses to their own cancer. This programme of shared tissue and viable cancer cell collection is rare, even in dedicated cancer centres. The programme has been supported by many sources of funding and the contribution of OICR in numerical terms is very small (\$3-5 million per annum out of a total of \$50 million per annum), but Dr Dick would argue that OICR was crucial in helping to create the CIRM partnership, the evaluation of NOD/SCID recipients to determine the best assay for each tumour type and the patient to mouse transplantation of 220 AML samples. The publication record of this group is excellent, with papers routinely in major journals, and its international reputation is equal to the best worldwide. The OICR has been a vital contributor to this programme.

2. Pancreatic Cancer

Pancreatic cancer continues to have some of the most dismal response rates and outcomes of all the solid tumours and hence a focus on this specific tumour within the Institute is understandable. The OICR Pancreatic Cancer Programme has taken benefit of the presence of a powerful and motivated surgical team specifically focused on this disease and the availability of samples that emerge from this programme. The focus to date has been on sequencing. However, this disease is also particularly challenging in that obtaining high quality samples of cancer tissue requires considerable manipulation and the group has ultimately resorted to laser capture micro-dissection. Because of this, the sequencing has been slow and large numbers of outputs have not yet been achieved nor have there been any major papers emerging from this programme. The Review Committee was concerned that this programme, which has been slow emerging, is now faced with substantial competition from Australia where pancreatic cancer sequencing has been done successfully for some years. If OICR retains this program it would benefit greatly from better integration with translational laboratory investigators in the province with the primary goal of supporting the strongest science.

3. Transformative Pathology

This programme reveals some of the challenges of attempting to operate a free-standing translational institute in the cancer arena when many of the challenges and opportunities exist within a more clinical setting. It is clear that creating an effective molecular pathology capability in the Province needs to be a major goal of the cancer research programme. Acquiring high quality patient samples that provide opportunities for the creation of primary cancer stage viable cell suspensions for xenotransplants into immune deficient mice, as well as for primary cell lines is an essential pre-requisite. These viable cells can be separated for sequencing using substantial quantities of high quality DNA from tumours (not stroma), and are an essential requirement for the programme today and will become increasingly important in the future. The field must also evolve to access routine samples hence capabilities in handling FFPE samples or

approaches to directly accessing high quality human samples from the operating theatre need to be developed. For this reason, a focus on establishing capable molecular pathology is imperative to support any major cancer initiative. Although there are one or two centres in the Province where molecular pathology has been developed within a hospital setting, Ontario shares with the rest of the world the fact that its pathology capabilities are poor, with little academic activity and none of the structures are in place to move this important field to take advantage of the molecular revolution. In terms of the OICR programme, there were two objectives. The first was to ensure that the handling of clinical trial and biobank samples was done capably and effectively and that appears to have been the major focus of John Bartlett, the leader the pathology programme; this has been successful. The second objective, though, was to try to transform molecular pathology in the context of a number of clinical sites around the Province; clearly, this has not happened. As a result, there appears to be no transformative change occurring around the Province and this will ultimately disable the OICR programme if not corrected. Simple issues such as access to tissue blocks have not been resolved, there appears to be no digital pathology or novel technologies such as mass-spec based pathological analysis, nor does there appear to be the development of a cadre of young, enthusiastic trainees who can help transform this academic discipline over the course of the coming years. The Committee views this as being a major problem for the programme and strongly recommends exploration of effective methods to ensure broader strategic engagement with the pathology community and a joint far sighted approach to development of internationally competitive academic and molecular pathology expertise. The focus of this programme must now be extramural but this will require not only engagement from OICR but also a willingness of Ontario hospitals to recognize the need and wholehearted support the initiative.

4. Imaging

The imaging programme, which is largely extramural, is one of the great successes of the OICR and demonstrates unambiguously how powerful the Institute can be in catalysing the collaboration between different centres in Ontario, bringing a variety of excellent scientific endeavours together to create a single integrated programme that clearly has a major impact, not just nationally, but internationally. The creation of the Centre for Probe Development and Commercialisation is an excellent example of how this has led to both translation and potential for economic development and the level of leveraged funding (5X) also indicates the widely recognised excellence of the programme. It is also clear that this programme would not have occurred without OICR's primary investment which brought together a wide range of basic probe research in Ontario with other forms of expertise. The output of this programme has also been extremely impressive in terms of applied and translated technologies.

This is OICR at its best, catalysing strong relationships amongst the excellent Ontario imaging community and producing a range of outputs that will be important in the clinical setting.

5. Health Services Research

Ontario is uniquely positioned in North America with its ICES programme that allows anonymised linking of administrative data from the healthcare system of 13 million people going back to 1991. This is hugely positive for many domains of population based research and has been used effectively by Dr Earl and his colleagues to address a number of issues in the healthcare system where population data has proved to be informative. Providing a cancer focus for the application of ICES has clearly been important and the programme is likely to yield important insights that will improve the way that healthcare is applied across Ontario. The Committee was surprised, however, to note that the health system itself had to rely on OICR scientists to observe that 30% of their colorectal cancer screening positive patients were not followed up! There will, however, be many insights that emerge from Ontario's relatively unique datasets that will continue to provide important insights as to how to more efficiently run this healthcare system and this area remains a strategic opportunity for the OICR and the Province.

6. The Ontario Health Study

The OICR has taken responsibility for the Ontario Health Study. This project, which has been part of an effort across Canada to create a substantial cohort appears to have been a major distraction for the OICR. Although online recruitment has generated more than 200,000 participants, the failure to obtain biological specimens and generate better phenotypic data at initiation is likely to considerably disable this programme. In the modern era, cohort studies without biological specimens are useful only when there is a very specific purpose and most current cohorts recruited over the past fifteen years have such biological material available, given the importance of the analysis of biological samples at scale alongside classical epidemiology. There are, however, some other fundamental issues that question whether OICR should lead this cohort study. Until recently, the leadership of this programme has been constrained, with the lead scientist having limited epidemiological experience in this research area. The recruitment of Mark Purdue has improved this position but, unfortunately, too late to easily resolve the issue of the lack of biospecimens. Similarly, whether there is benefit from a cohort of just over 200,000 individuals in the field of cancer research is not clear. Most modern cohorts trying to address cancer have at least 500,000 individuals. This is because the incident rate of most cancers is sufficiently low that one cannot obtain the large numbers needed to detect small effects with cohorts of less than 500,000 and this is likely to become more challenging as we sub-stratify cancer taxonomy. A large cohort, properly put together, would have substantially more benefits for the cardiovascular community or those interested in obesity, diabetes or neurodegeneration than it will have for cancer scientists and, as a result, it is rather perverse that the OICR has been asked to lead and fund a programme that is suboptimal for its own requirements. We recognise the political complexity of this project both within Ontario and across Canada, but we believe OICR should reconsider its role in the project.

7. Target Validation

This is largely an extramural programme which is applying new high throughput technologies to better identify and validate targets for therapeutic interventions in cancer. The programme is well led by Robert Rottapel and has had a number of notable recruits, including Sachdev Sidhu, who depended on OICR funding for salary and startup. These scientists have been focusing on breast, ovarian and pancreatic cancer, with a view of using genome wide shRNA screens, RNA-seq, SNP databases and other genome sequence public databases for the identification of exploitable targets in cancer. There is enormous merit in utilising these high throughput genome-wide methodologies for target identification and validation and their efforts, particularly in P53 mutant cancers and in the development of inhibitors in the ubiquitin cascade reveal the power and capabilities of this programme. This group has used the best of protein engineering and antibody technology to create a remarkable set of potential probes and therapeutics. Their success with reagents targeting the ubiquitin pathway is exciting and they are poised to make substantial gains with their Celgene collaboration. This external programme addresses a key challenge of identifying much better targets for cancer therapy and has established (outside the OICR) a powerful biotherapeutics platform. In keeping with its translational mission, the OICR should seek to help this programme more.

8. Drug Discovery

The OICR chose to develop a drug discovery group focused on medicinal chemistry, ADME and preclinical toxicology. These competencies were clearly not in evidence in Ontario before OICR. The wisdom of creating such programmes in academia has been questioned, given the limited productivity of much larger programmes in industry and elsewhere in Academia, despite almost unlimited resources. The group has 28 scientists, many recruited from industry. Although they have made progress in developing potential small molecule interventions for hard-to-drug targets such as BCL6 and GRK6, these programmes are still very early in their evolution (at lead-optimisation and hit-to-lead stage) and this programme, given its relatively small size, is struggling to deliver an effective drug discovery capacity for Ontario cancer scientists. Importantly, it did not seem that this programme was very well connected with the target validation programme which seemed odd given the importance of target validation before embarking on drug discovery efforts. Indeed, one of the biggest causes of failure in industry is the failure to undertake thorough target validation efforts before launching a small molecule campaign. A clear understanding of what loss of function mutants for BCL6 might look like biologically, for example, might be an important step in knowing whether it is ultimately a valid target. Similarly, this group might have added value to the biotherapeutics programme by facilitating drug conjugation studies but appear to be isolated technologically and intellectually in the Ontario environment.

There is a big philosophical question about what progress in drug discovery can be made in academia given the challenges that have confronted the pharmaceutical industry over many years attempting to do small molecule discovery at scale. In this regard, better co-ordination with other drug discovery programmes which have also

been evolving over the last ten years in the Province might achieve more. Using unique skills academic groups may be able to address particularly difficult 'hard-to-target' molecules. Interestingly, the Structural Genomics Consortium in Toronto has achieved much in this area and yet seems absent in this OICR vision. It is also not clear what the balance should be in such settings between small molecule medicinal chemistry discovery efforts and those associated with biotherapeutics, particularly antibodies, or in the current era, cell and gene therapy. In providing the capacity to move from discovery research into translation, however, it seems clear that there needs to be a coordinated effort in Ontario around at least one of these therapeutic modalities, and OICR is in a good position to facilitate that. The scale and scope of this relatively small intramural programme is unlikely to solve this problem for Ontario or deliver the kind of product that will transform the translational environment and a more interactive, outwardly focused collaboration is in our view the only sensible way forward for this program.

9. ICGC

The Director, Tom Hudson, came to his role in OICR with an outstanding international reputation in the field of genetics and genomic research, having led the Genome Centre at McGill for many years. Since his arrival, he has been the key driver in establishing the ICGC which has provided cancer research with remarkable insights into genomic variation in most common tumour types. This project is undoubtedly an international success and Dr Hudson deserves considerable credit for leading that from Toronto. More recently, Dr Hudson has continued to play an important role, in other international genome programmes. It is in these international collaborations that the OICR has had major genomic impact through its leadership role.

10. Genome Technology

The Genome Technology programme is an intramural programme and provides genome sequencing capabilities for a number of projects, particularly those in pancreas and prostate cancer and early invasive breast cancer. The Committee was surprised to find that the genome capabilities within the centre at OICR were not recognised as the major 'genome centre' for the wider community in Toronto and Ontario. This may have been beyond the intended scope of the Genome Centre in OICR, but it begs the question as to where that critical mass of genome sequencing capability exists in an increasingly centralised technology driven arena. The outsourcing of much of their sequencing to other sites suggests that OICR may not be seen as the most appropriate place to undertake such a genome centre function but it should, perhaps, play a role in identifying, supporting and ensuring such a centre exists in Ontario.

11. Bioinformatics and Biocomputing

The recruitment of Lincoln Stein was an excellent example of a high level recruit who brings remarkable expertise to Ontario. The importance of a strong informatics programme greatly exceeds the importance of having large numbers of sequencers generating sequence data. The bioinformatics programme in OICR has been steadily evolving, although it has been limited by a number of factors including space and co-

location. The programme reveals however, some of the challenges of attempting to operate a free-standing institute in a multidisciplinary clinical area which is in need of IT support for the clinical sequencing efforts in regional hospitals. It is clear that creating an effective molecular computational biology capability in the Province needs to be a major goal of the cancer research programme to support distributed sequencing activities. All surrounding hospitals will greatly benefit from the outstanding genomic, statistical and data integration skills of Lincoln Stein and his team. The strong need for such a knowledge hub was clearly expressed by various scientists. A provincial capability supporting computational systems biology provides opportunities both for the creation of valuable content that can be re-used as well as high quality (DNA) diagnostics needed for the introduction of personalised treatment strategies in the regional hospitals. This programme should ultimately be recognised alongside internationally recognised bioinformatics institutions such as NCBI and EBI and The Cancer Genome Atlas Consortium. In order to achieve its goals, however, it needs to embrace the wider Ontario community. With the scientific vision of Lincoln Stein and strong support from OICR, this programme has the potential to be globally competitive. It represents a significant 'win' for OICR.

13. Immuno and Biotherapeutics

This is an excellent example of a productive external programme partly funded by OICR and facilitated by the overall OICR structure. This programme endorses the view that OICR supported programmes can go from basic science discovery through into clinical trials, as the programme is now using an Ontario wide network to deal with the key manufacturing and CMC issues related to viral therapies, and is in the process of developing its first in man clinical trials protocols. OICR was crucial in assembling an IP portfolio for the Maraba technology, for facilitating the development of the ORBIT programme and taking this innovation into clinical development. This group has clearly obtained substantial leverage from other sources but would acknowledge the important role OICR has had in funding its programme and making available more flexible funding as well as networking facilitation around the Province. In the field of oncolytic viruses, this is clearly one of the strongest programmes globally. To its credit, OICR has supported this truly ground breaking programme, despite the very substantial risks associated with it. This is another example of the influence that OICR can have on creating an outstanding science base that can be ultimately translated and commercialised in the Province of Ontario.

The Committee discussed at length whether, in the current era, an oncolytic virus programme of this kind, excellent as it may be, provides sufficient immuno-oncology for a major cancer research programme, given the interesting results and challenges associated with developing more efficacious immunotherapies using checkpoint control antibodies or modified T cell populations. OICR and the associated programmes in Toronto have a long history of leadership in various areas of immunology, and devotion of resources only to the oncolytic program does not fully take advantage of this kind of immunology. It was our judgement that consideration needs to be given to exploring and

expanding into these additional areas of immune-oncology research where Ontario does not have a significant presence at the current time.

14. Canadian Clinical Trials Network

The evolution of the Clinical Trials programme from a high impact trials format into an infrastructure support system (3CTN) has been a positive force in Ontario clinical trials and has also had an impact nationally. Given the very low level of patient participation in clinical trials when OICR was originally created (1%), the contributions made by 3CTN and its predecessor should be noted and supported. Having created this new vehicle to improve the preparedness in Ontario for a new generation of clinical trials, those associated with molecular science components that generate high impact, it would seem that its current colocation with the NCIC Clinical Trials Group would allow it now to be absorbed within that structure, given its notable impact and success. It is important to note that the OICR resources have been used to strengthen the existing Canadian cooperative group networks and not deployed to create yet another silo and this should continue.

15. FACIT

It was clear from the original mandate that technology commercialisation was to be an important component of the OICR vision. This was, however, inevitably a very challenging objective, given the lamentable state of the biotech sector in Ontario and the near complete absence of significant sources of risk capital. Having attempted to manage this within OICR, it was agreed that a more appropriate mechanism to handle these diverse commercialisation and technology transfer issues would be to establish a for-profit business trust, FACIT, with management brought in from the venture capital community to help handle the commercialisation agenda. This appears to have created a more functional technology transfer capability and there are notable examples of successful commercialisation. The Centre for Probe Development and Commercialisation in Hamilton has addressed a significant unmet need for radioisotopes and has created a number of jobs and an apparently viable business. Similarly, the sale of the Cytof technology platform which emerged from MDS is clearly a success. While the original technology did not flow out of an OICR programme, OICR funded the Cytof programme at various stages to ensure it could be progressed, taking a significant equity stake. It is not clear that the technology would have been developed to the extent that allowed a sale to Fluidigm without OICR involvement, hence this is a significant win for the commercialisation programme. However, if Ontario had succeeded in fully developing and merchandising the Cytof in Ontario, the broad economic success generated would have had an even more significant impact on the province's economy.

The Triphase Accelerator is a rather more novel approach to facilitating early development for assets acquired not only from the OICR or Ontario pipeline, but also those brought in to Ontario from global companies. Taking responsibility for the early development programmes around these molecules may lead to a set of milestones and, ultimately, royalties if any of these compounds are successful. The commitment of

Celgene to this programme is an endorsement of its novelty and utility to pharma. However, it is unclear whether this will enhance Ontario's economic growth in any substantive way in that the CRO functions will not necessarily lead to substantial economic growth, particularly as some of this development activity will itself be done outside the Province. Using this mechanism to fuel more exploratory development and 'translation' within the Province was recognised to be important by the Director of OICR, but was clearly not part of the culture of the FACIT management team.

The remainder of the portfolio of commercialisation activities involves the creation of multiple small companies, all at a very early stage, backed by very modest amounts of risk capital in every case. In some cases, the creation of these entities required significant reorganisation of the IP portfolio (e.g. around the Maraba oncolytic virus). However, these are small, very early stage companies which at the moment are inadequately financed and extremely high-risk.

The management team of FACIT is clearly capable of small company commercialisation and has a wide range of experience. It was not clear, however, that this old model for technology commercialisation in which companies started very early require repeated rounds of risk capital funding and the decisions taken are often perverse because of the need to either exit quickly or reduce the funding requirements of these companies as they go through the valley-of-death. This experiment has been tried in many places and has only very rarely been successful and many other models are now beginning to take hold. These include

1. Maintaining programmes in the public sector much longer until they have reached clinical proof-of-concept, at which stage the possibility of commercialisation becomes much easier. This model has been exemplified by CIRM investments, including those in John Dicks' technology, but more could be done in this area.
2. Retaining a range of companies within a single portfolio and seeking much longer term funding for the portfolio either from the public equity markets or from long term investors (Imperial Innovations).
3. Seeking out sources of long term funding from other sources, be they pension funds or family investors, and creating a tax environment that makes this attractive.

The Committee was on one hand impressed by the efforts being made by OICR to make this commercialisation strategy viable through FACIT but, on the other hand, the Committee was concerned that, in the Ontario environment in particular, this was unlikely to be transformative for the regional economy. This program clearly has the right intent but the committee was uncertain whether, given the current economic climate within the province for growing small to medium size businesses, other approaches might be considered to facilitate this important part of the strategy for OICR.

OICR Seven Years On – Evolving the Model

The original mandate for the OICR emphasised a number of specific objectives. These included the creation of a strong intramural ‘institute’ within the Ontario environment that would have its own internal programme. It also was clear that a major objective of the programme should be both to deliver benefits to the Ontario healthcare system and to provide significant translation or commercialisation of components of the Ontario pipeline in the cancer area. Both these objectives were reasonable and realistic. Ontario biomedicine, however, is complex and the creation of a new government funded institute in the province was likely to produce issues that should now be considered and dealt with. Toronto has the strongest set of biomedical scientists in Ontario, although it is not alone in housing excellence. The Toronto environment has historically been challenging, given the presence of multiple competitive research institutes with limited influence from the University of Toronto. There are great strengths in cancer research, both at basic and translational levels across all the institutes in Toronto, but also excellent cancer programmes around the Province.

It was into this complex environment that the OICR was placed. The selection of Dr Hudson as a leader for the OICR created some unique opportunities. Firstly, there was an opportunity to create an institute led by a scientist who was not associated with any single institution in the Province and, secondly, Dr Hudson had a well established reputation for creating a highly effective Genome Centre at McGill. This background should have been a welcome addition to the Ontario environment where there was no single critical mass of genome science for the cancer community.

As one might have expected in this complex political environment, however, the OICR has both significant supporters and some detractors.

The Review Committee spent some time receiving inputs from the community, both before and during the review process and it is clear that it has both significant supporters and significant detractors. These views were provided, in large part, constructively as there is a universal view in Ontario that the OICR is ultimately a powerful engine for the research community. Opinions were provided by those funded and those not funded by the OICR, from those in Toronto and those outside Toronto, and from others not associated with cancer research. All those that provided feedback felt there were many outstanding scientific achievements that have emerged from the OICR programme and, for the most part, these align with the Review Committee’s position. The programmes of John Dick, John Bell, Rob Rottapel, as well as the wide imaging programme received enthusiastic support from the entire community and the judgement is that these internationally competitive programmes would be competitive with any in the rest of the world. However, there were many respondents who felt that the intramural programme had, to date, contributed little to the general environment for cancer research in Toronto and in the Province, had in part failed to meet the expected quality standard of such a programme, and was consuming significant resources without the expected outputs. It was also clear that in areas of limited impact inadequate support from the wider community was an important feature.

In general, negative opinions focused particularly on the limited impact and quality from the intramural programmes. There is also a general view amongst those concerned about the intramural programme that the standards of peer review are ultimately different, with a lower bar for funding than for external programmes. There was particular concern that these intramural programmes have not contributed to making Ontario cancer research better than the sum of its parts by providing leadership in some selected areas.

It is clear that an external review committee which relies heavily on the written paperwork provided by the OICR and then spends two days in Toronto is unlikely to resolve this apparent tension amongst the wider scientific community. It did, however, resonate that Ontario's strongest cancer hospital, the Princess Margaret Hospital, had relatively limited interaction with the OICR, despite the fact that they are only 100 yards apart. There are, of course, many reasons why the dominant institution for cancer research in Ontario might feel threatened by a new entity attempting to create more Province wide activity in this space. The Review Committee felt it was imperative for all parties to work together to ensure that the OICR continues to develop in a way that it catalyses and creates new collaborations, especially in the clinical arena. The current environment provides a unique opportunity for the OICR and the PMH to establish a productive and robust clinical research initiative. The OICR should evolve its scientific strategy, and the OCI/PMH is searching for a new research director who hopefully will see many advantages to a close association between OICR and OCI/PMH.

Our independent review also suggested that there were significant issues with the intramural programme that should be corrected. These include:

1. The molecular pathology programme lacks impact on pathology services that are needed in the major cancer hospitals to ensure an appropriate flow of good quality tissue for the new world of sequencing and primary cell lines. The current programme is unlikely to achieve the impact necessary and needs to be fully revisited.
2. The Ontario Health Study should be seen as a wider asset with perhaps more relevance to those studying cardiovascular disease, stroke and neurodegeneration. In our view, this project and OICR's role in it needs to be reconsidered as it continues to be a major distraction for the program.
3. In the emerging world of next generation sequencing, it is clear that large in-house sequencing capacity has become less important than the bioinformatics that support it and, although the recruitment of Lincoln Stein and the creation of a strong bioinformatics programme under his leadership should be broadly welcomed, it is important that these capabilities are available to strengthen the cancer research community across the province. OICR should focus on creating a programme that reaches out and helps others to improve their competitive position.
4. It was intended that the OICR should act as a catalyst to bring significant small molecule drug discovery to help with the translational objective within the Province. The intramural drug discovery unit is probably too small to have a significant impact in terms of small molecule drug discovery. Further, this

programme seems to be relatively isolated from excellent work going on in other parts of the Province including the Structural Genomics Consortium which has its own small molecule probe development programme, and the Target Discovery Programme which should be closely engaged with any drug discovery efforts to produce a more coherent whole. Opportunities are also clearly possible in the area of biotherapeutics as it is clear now that many of the major immunotherapeutic interventions come from modulated T cell therapy or therapeutic antibodies and a purely small molecule focused programme misses many of these opportunities. The panel and most of those we interviewed felt that this program needs now to be reconfigured and should be integrated in the wider efforts to create new therapies that are occurring around the province.

With regard to the peer review process that adjudicates intramural versus extramural research, there is a major challenge in attempting to evaluate entirely different types of research such as health service research or drug discovery and compare them to classical cell biology, stem cell research or imaging. This will inevitably create concerns that the bar for funding is fundamentally different, but we saw no direct evidence that the process of determining funding was biased in favour of internal programmes. Virtually all funding organisations that have both internal and external programmes have these innate tensions and it is generally true that intramural research programmes are less competitive than those in the highly competitive external environment. This provides another strong argument for moving the intramural program into one that is outward facing and requires external collaboration and input.

It is our view, therefore, that the Board should consider how to use the intramural programme to create open platforms which help bring the Ontario community together more effectively. The drug discovery programme, in our view, needs to be reconfigured to engage some of the other expertise in small molecule development around the Province (e.g. SGC and PMH) and to be more connected both to target discovery and to other approaches to drug discovery, particularly in the biotherapeutics area. The Province needs leadership in informatics and genomics and this should be a major role for an outward looking OICR programme. Pathology needs to be embedded in hospitals, not in an intramural programme. A judgement also needs to be made about the Ontario Health Study which, in our view, is a distraction for the OICR. **Our major conclusion, therefore, is that it is timely given the enormous success the OICR has had in raising the capabilities and outputs of cancer research in Ontario to now concentrate on the components of the program that are not delivering the excellence that is evident throughout much of the programme. These largely reside in the intramural program and can be readily modified to be more engaged with external institutions and collaborators. In our view, the intramural strategy can deliver a greater transformative change if it becomes more outward facing and facilitates a broad set of collaborative programs in areas that need enhancement in the province.**

Governance

The Board of OICR appears to have done an excellent job establishing the programme described in the mandate, recruiting Tom Hudson as the Director, and overseeing the development of the OICR programme over the past seven years. The Board has, however, relied largely on the advice of the Scientific Advisory Board for the independent scientific advice about the success and direction of the programme. As the Institute enters the next phase, however, we believe that it is important to distinguish between the Scientific Advisory Board of the Director which essentially provides helpful and friendly advice as to the direction of the Institute, and independent adjudication which provides truly independent reviews of the strategic direction and quality of the science funded by OICR. The latter independent science activity should either report directly to the Board or be a subcommittee of the Board. The Board itself will also require independent non-Ontario based scientific expertise to manage the feedback it obtains from this independent science committee. We believe that, were such a governance structure to exist, the Board will be positioned to help the Director alter strategic direction more effectively.

There are other elements of governance which also need consideration. It is important for OICR to recognise that it lives within a wider community of Ontario bioscience and, as a result, the salary structure it applies to its scientists needs careful consideration so as not to disrupt the compensation equivalence amongst Ontario and Toronto institutions. Similarly, we also heard concerns that the grant portfolio at OICR suffered from excessive administration and continuous review. Some thought needs to go into what is an appropriate review procedure to, on one hand provide clear accountability for the expenditure of government funding but, on the other hand to allow science not to become over bureaucratized.

Conclusion

The funding of a major cancer research institute by a Canadian province was both innovative and novel and, seven years into this project, the Province has much to be proud of. Many of the programmes funded through this mechanism are world leading and the OICR contributions to these have continued to enhance the recognition of Ontario as a major centre for biomedical research with particular expertise in cancer. As the Institute approaches its tenth anniversary, however, we believe that the time is right to look again at some aspects of the strategy that could deliver a more powerful output from the Province as a whole and that could do more to enhance the cooperation and collaboration amongst scientists and clinical researchers in Ontario. We believe that the time is right to adjust the intramural programme so that it creates platforms, needed by the wider Ontario community, to enhance the overall capabilities of Ontario cancer research, both basic and translational. The key roles of OICR should be to fill gaps in the science base in the Province (as informed by consultation with the community), to catalyse more effective collaboration and alignment to maximise the potential for innovative, creative translational medicine, and to foster and support improved health and economic gain. This could provide additional momentum to many

of the cancer programmes around the Province, and will align the interests of many of the best scientific groups by providing additional capabilities and expertise to ensure improved outputs of both drug and diagnostic discovery and translational programmes. Our sense was that the OICR has already been crucial in leading Ontario science down this path but that more can now be done. If successful, this will both deliver even greater productivity from Ontario cancer scientists and ultimately, this will not only prolong and enhance the lives of many of those suffering from cancer globally, but will also continue to help develop and expand the economy of Ontario.