Cancer Stem Cell Consortium

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CANCER STEM CELL CONSORTIUM

Executive Summary

The discovery of a rare subpopulation of tumour cells termed **cancer stem cells (CSC)** in many common malignancies has profound implications for treating cancer patients. Most current anticancer therapies were developed to kill the major tumour cell population that makes up the bulk tumour mass; however, these cells are not responsible for the growth and dissemination of tumours. CSC are at the root of cancer and account for tumour growth and metastases. CSC are resistant to the toxic effects of radiation therapy and perhaps current chemotherapies. Hence it is not surprising that tumours often recur leading to relapse of cancer patients treated with these agents. By developing new therapies targeting CSC long-lasting cures should be achieved.

According to a recent economic report, a 1% reduction in mortality from cancer would save nearly $500 billion to current and future Canadians and Americans. A “war on cancer”, which would cost an additional $500 million for CSC research and treatment over the next 5 years, would clearly be an excellent return on investment.

Both Canadian and Californian researchers pioneered the discovery of CSC giving them a powerful historical lead in this rapidly expanding field. Moreover, a significant percentage of the world’s CSC researchers are located in Canada and California. Hence there is a natural alignment of research prowess and critical mass of researchers in both jurisdictions to surmount the challenges posed by CSC.

The CSC Consortium’s research programs will focus on identifying CSC biomarkers and therapeutic molecular targets. State-of-the-art infrastructure will provide live CSC for study. We also propose developing a number of high-throughput technologies. We believe that progress will occur more rapidly by supporting several large-scale efforts involving multiple Research Teams, who will share cutting-edge Technology Platforms and common research goals thus generating new knowledge. The CSC Consortium will be a not-for-profit corporation with a strong governance and management structure.

The CSC Consortium will invest significantly in translational activities that will accelerate the evaluation of CSC-specific biomarkers and the discovery of anti-CSC therapies. Both Canada and California host Comprehensive Cancer Centres, which will provide the appropriate infrastructure to validate CSC biomarkers and to clinically evaluate new anticancer therapies targeting CSC, including “First-in-Man” studies.

This overview of the CSC Consortium describes the activities and an organizational structure to secure sustained and stable funding of $500 million (CDN) for an initial five-year period, which will be provided by funding sources in Canada and California. Sustained funding is the key to the success of the CSC Consortium because of the unique nature of the expertise and the technologies required for this research, and the imperative for rapidly moving discoveries to the clinic.

The CSC Consortium will provide a structure to coordinate the two strongest scientific domains in CSC biology, which will be bolstered by world-leading business expertise and newly created early-stage funding mechanisms to build an exciting wave of new biotechnology companies based on CSC discoveries.

1. Identifying and Meeting the Challenges of Curing Cancer

The discovery of a rare class of tumour cells called **cancer stem cells (CSC)** has profound implications for treating cancer patients. Most current anti-cancer therapies are aimed at killing cells that comprise the bulk of the tumour mass, but are not responsible for the primary growth of tumours. CSC in many common malignancies are the major culprits at the root of cancer accounting for tumour growth and metastases. For reasons that are not yet understood, CSC are resistant to the toxic effects of current anticancer therapies including radiation and chemotherapeutic drugs; consequently tumours often recur leading to relapse of cancer patients treated with these agents. By specifically targeting CSC, new cancer treatments and potential cures will be within reach.

There are clear health benefits to be gained from a strategic investment in CSC research that is focussed toward finding a cure for cancer. The unacceptably high rates of deaths caused by cancer (2007 estimates: Canada: 72,700 (Canadian Cancer Society); California: 54,890; USA: 559,650 (American Cancer Society), in addition to the increase in the incidence of cancer associated with our aging populations, justify the need to harness the scientific power of our cancer biologists, combined with rapidly evolving technologies in genomics, proteomics, imaging, and chemical biology. Application of these technologies to CSC research will result in the discovery of CSC biomarkers and new anti-cancer agents that specifically target these cells.

To accomplish this plan, we propose forming a **CSC Consortium**, a non-profit corporation, comprising world-class CSC researchers, funding agencies and the bio-pharmaceutical industry based in **Canada and California.** The funding agencies and the researchers involved in founding this Consortium include many of the research pioneers in CSC research and have earned global recognition.

The **Canada-California Strategic Innovation Partnership (CCSIP)** initiative represents a collaborative exchange between the two jurisdictions and involves academic, private sector, financial and public sector organizations. Its purpose is to champion the development of new partnerships, and to promote commercialization, in strategic priority innovation-intensive areas including CSC, transportation & energy, integrated circuit technology, nanotechnology, and infectious diseases. The framework for this CSC proposal emerged from a series of joint meetings including a major workshop of Canadian and Californian scientific leaders held at Stanford in January 2007 (please see the appendix for the attendee list).

Together, Canadian and Californian CSC investigators constitute a significant number of researchers worldwide involved in this rapidly expanding field and have published the vast majority of the groundbreaking papers around CSC. In addition, more than 70% of patents referring to CSC have been published in the last two years, providing evidence that this field is accelerating towards opportunities in industry. Combined with the drug development expertise of the bio-pharmaceutical industry, the CSC Consortium will provide a rich environment for innovation, commercialization, and training the next generation of cancer researchers.

Understanding CSC biology and developing therapeutic interventions will require a sustained effort combined with technological advances. One of the greatest challenges that we face is the small number of CSC in tumours, which is compounded by the broad heterogeneity of tumours. There is significant variation in tumours originating from different organs and tumour subtypes which occur in the same organ. We believe that progress will occur more rapidly by supporting several large-scale efforts involving multiple teams of researchers who will access cutting-edge technologies and resources (Technology Platforms), and share new knowledge through collaboration.

The goal of this document is to describe the activities and structure of the Consortium in order to secure sustained funding of $500 million (CDN), to be ramped up over five years, and to be equally divided between Canada and California. Long-term funding is the key to the success of the CSC Consortium because of the unique nature of the CSC problem and the need to develop new technologies.

The CSC Consortium will actively manage, direct, coordinate, and take all steps necessary to ensure that we move quickly and effectively from discoveries to application in the clinic. The Consortium will have well-defined research and technology development programs, organized in Research Clusters and Platforms. A Research Cluster will either be a regional or thematic grouping of investigators. Platforms will be closely linked to the research programs, and will focus on the technology development and automation leading to increased capacity for the research activities. The Consortium will have a strong governance structure, commercialization strategy and a small directorate for coordination and communication. This structure will foster focussed fundamental understanding of the origins and control of CSC and will provide a clearer path to durable anticancer treatments for the benefit of citizens everywhere.

2. The Benefits of Investing in CSC Research in Canada and California

A natural alignment between Canada and California is possible to surmount the challenges inherent in understanding and eventually controlling CSC.

The leading research laboratories in the CSC field are located in California and Canada. California is host to superb scientists involved in CSC biology. Some of the leading CSC laboratories in California's research-intensive universities are led by the following researchers:

- Dr. Irv Weissman, who pioneered the field of "adult" stem cells
- Dr. Owen Witte, whose laboratory research laid the groundwork developing the targeted leukemia therapy Gleevec
- Dr. Michael Clarke, whose team led the discovery of breast CSC
- Dr. Harley Kornblum, who devised means of propagating brain CSC *in vitro*
- Drs. Phil Beachy and Catriona Jamieson, who identified signalling pathways in CSC

Canada is the historic home of CSC research including the discoveries made by the following researchers:

- Drs. James Till and Dr. Ernest McCulloch, who are generally considered the founders of modern stem cell research, demonstrated the existence of adult stem cells that give rise to all blood cell types over 40 years ago
- Dr. John Dick, who discovered CSC in leukemia and colon cancers
- Dr. Peter Dirks, who identified CSC in brain tumours
- Drs. Allen and Connie Eaves, Keith Humphries, Norman Iscove and Guy Savaugeau have all led research studies of the properties of leukemic CSC, laying the groundwork for this field.

This pioneering research has led to unique strengths and shared interests in cancer stem cell research for Canada and California, revealed by the rise of larger projects sponsored by various sources in both Canada and California. In 2005, California voters approved a funding mechanism to establish the California Institute for Regenerative Medicine (CIRM), a $3 billion initiative to support stem cell research, research facilities and training. In Canada, several approaches are underway to maintain the lead for Canada and include the following:

- Larger projects sponsored by the Canadian Institutes of Health Research (CIHR), Genome Canada, the Canada Foundation for Innovation (CFI), and the National Cancer Institute of Canada (NCIC)
- Innovative research models have been established, for example, the Networks of Centres of Excellence's "Stem Cell Network", which funds multi-institutional collaborative stem cell projects, including a CSC project
- The newly launched Ontario Institute for Cancer Research (OICR) has committed $30 million, over five years, to study CSC biology and develop high-throughput technologies

As the population increases, as incomes grow, as health improves and as the baby-boomer generation approaches the primary ages of disease-related death, the social value of improvements in health will continue to rise. Prospectively, even modest progress against diseases such as cancer would have enormous social values. A 1% reduction in mortality from cancer would be worth nearly $500 billion ($89,300 per life saved) to current and future Canadians and Americans (Kevin Murphy, University of Chicago and Robert Topel, US National Bureau of Economic Research: Journal of Political Economy, 2006, vol. 114, no.5). A "war on cancer" that would spend an additional $500 million on CSC research and treatment over the next 5 years, would be worthwhile if it has just a one-in-hundred chance of reducing mortality by 1%. The social value of even modest progress against diseases such as cancer would be enormous.

The CSC Consortium will promote the commercialization of intellectual property (IP) (please see Section 5: Commercialization Strategy) to ensure economic benefits to Canada and California. California is home to the largest concentration of biotechnology firms in the world and Canada is home to the third largest. Canada, a strong biotech player, ranks third in the world for life science commercialization. Fortunately, the outlook for near-term commercialization in Canada is strong because of new federal and provincial initiatives in IP development and commercialization. At the Federal level, the Government is in the final stages of preparing a revised Science & Technology policy, which is anticipated to have a strong focus on commercialization. And recently, the Federal government announced Centres of Excellence in Commercialization and Research (Budget 2007). At the provincial level, a life-science commercialization development fund has recently been announced in Quebec. Similar funding vehicles are close to being launched in Ontario and Alberta.

With strong science and coordination between the two principal domains in CSC biology, coupled with world-leading business expertise and newly created early stage funding mechanisms, the prospects are excellent for an exciting wave of company creation based upon new CSC technologies and therapeutic interventions. There are already CSC patents for therapeutic claims in 9 cancer types and diagnostic claims for 17 cancer types.

3. Cancer Stem Cell Research Program

There is overwhelming evidence that CSC initiate many malignancies, maintain progression and define metastatic potential. We propose goal-oriented research programs involving Research Teams from Canada and California working together at world-renowned institutions. The overall goals will be to discover CSC biomarkers and to develop new anticancer therapies that target CSC. We will build on existing infrastructure and where required develop new shared infrastructure and technology cores (Technology Platforms), including live tumour cell repositories, cancer cell stem cell expansion and purification facilities, and genomic, proteomic and high throughput screening centers.

3.1. Overview

Cancer arises from the accumulation of multiple alterations to the genome. These genetic and epigenetic changes affect genes involved in cell division, DNA repair and metastasis. Tumors are known to be clonal; all the cells comprising tumours are the descendants of a single cell. A spate of recent discoveries suggests that the cell of origin of cancer is a malignant adult tissue-specific stem cell (**Figure 1)**. Adult stem cells are present in tissues and organs such as blood and muscle to replenish damaged or dead cells arising from injury and normal tissue turnover. For example, hematopoietic stem cells are needed to replace the many millions of mature blood cells that are lost each day. Unlike embryonic stem cells, which are capable of producing all the cells in every organ of our body, adult stem cells are more restricted in their developmental potential and give rise to specialized cells of particular tissues and organs.

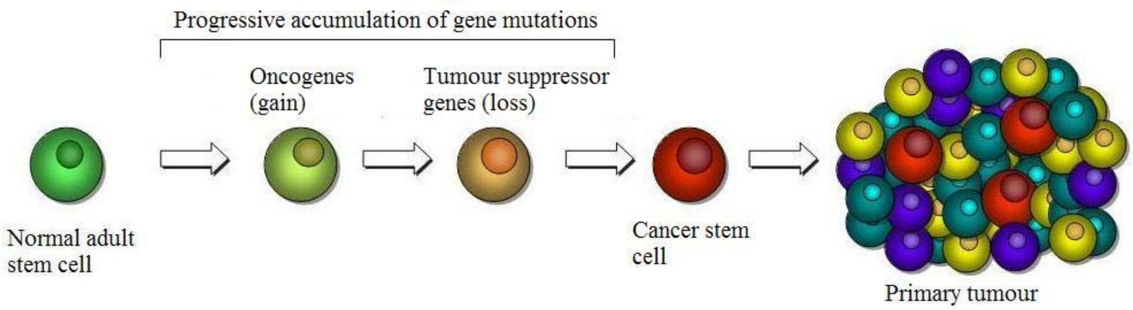


Figure 1: Origin of CSC

Adult stem cells and their cancer stem cell counterparts possess two hallmark properties, the capacity for self-renewal and differentiation. Normal adult stem cell self-renewal and differentiation are finely regulated to ensure tissue homeostasis. Cancer arises as a result of the dysregulation of these stem cell processes of self-renewal and differentiation. Self-renewal is increased in CSC, whereas differentiation is arrested at particular stages in the cellular hierarchy resulting in the accumulation of abnormal cells that make up the bulk of the tumour.

Current strategies for cancer drug development are based on the assumption that the cells comprising tumours are the same, and consequently the most successful cancer treatments are those that kill the largest number of cells in the tumour. And, the most powerful and least toxic treatments will be those that exploit the molecular differences between tumour cells and their normal adult stem cell counterparts.

However, recent experiments, much of it led by Canadian and Californian researchers, strongly suggest that tumours are not in fact a homogeneous cell population, and that only a very small percentage of tumour cells (CSC) are endowed with tumourigenic potential fuelling tumour growth, seeding metastases and accounting for resistance to current cancer therapies and hence the relapse of cancer patients after treatment.

The Importance of Cancer Stem Cell Research

The implication of the stem cell model for treating cancer is profound. The tide of experimental evidence supporting the stem cell origin of cancer suggests that our current therapies target the bulk of the tumour cells in tumours—the pawns—but not the real culprits at the root of cancer—

the king—the rare CSC in tumours. To win the cancer game we have to reorient our energies to eradicate CSC.

The evidence continues to accumulate that our current therapies fail to achieve long-lasting cancer cures because they do not eliminate CSC. Indeed new findings demonstrate that CSC have a heightened ability to repair damaged DNA and hence are resistant to radiation, which is commonly used to treat cancer patients **(Figure 2)**. Moreover, unpublished reports presented at recent scientific meetings suggest that these cells also evade chemotherapeutic agents.

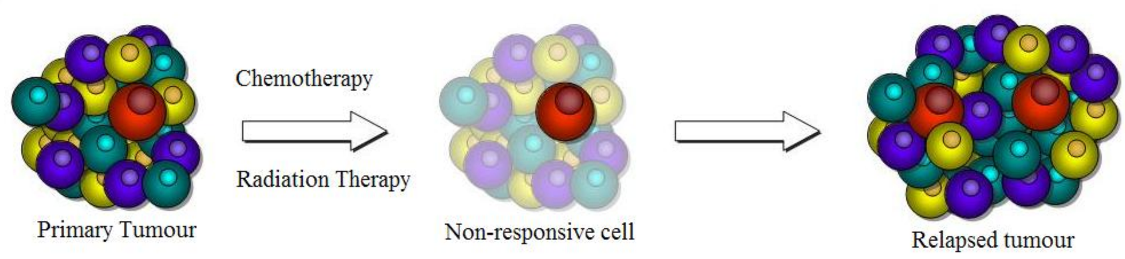


Figure 2: CSC May Be Non-Responsive to Current Anti-Cancer Agents

Therefore there is a critical need to develop new anti-cancer agents that selectively target CSC. Ideal anti-cancer drugs will kill CSC, but not their normal adult stem cell counterparts and hence would have few side effects. The path to this end hinges on characterizing the molecular differences between adult stem cells and CSC, and then exploiting these biological and biochemical differences to purify and subsequently characterize these cells in intimate detail using state-of-the-art genomic bioinformatics tools. The ultimate goal of this exercise would be to understand what makes CSC different from adult stem cells, but also to use this information to design drugs that target CSC by disrupting molecular pathways active in CSC.

To achieve the goal of developing selective anti-cancer stem cell therapies we suggest a research and discovery program outlined below, whose principal objective is to identify biomarkers of CSC and to develop novel therapies targeting CSC thereby promising the potential for achieving durable cancer cures. A key facet of our proposal is a Consortium of actively-managed, focussed research teams centered on specific malignancies (cancers of the blood, breast, brain, colon and prostate) in which we have expertise coupled with research-enabling technology platforms.

3.2. Research and Discovery Program

Understanding Cancer Stem Cell Biology

Cancer stem cell biology, especially those for solid tumours, is at the early stages of discovery. Determining how CSC work and live in their environments is critical to understanding how to find them and target them. The availability of CSC, especially CSC-enriched cell cultures, coupled with the results of genomic and proteomic analyses of these cells will provide a rich information database to launch new basic research programs. These research programs will be centered on establishing the origin of CSC, studying their progression to full-fledged malignant cells capable of metastasizing and elucidating the molecular events accompanying these processes. Identifying signalling pathways required for key stem cell processes such as self-renewal and differentiation will also be pursued.

Identifying Cancer Stem Cell Biomarkers and Molecular Therapeutic Targets

The availability of highly enriched CSC populations from multiple diverse tumours (blood, breast, brain, prostate and colon) will enable genomic and proteomic analyses of these cells, a required first step to discover CSC biomarkers and molecular therapeutic targets. Genomic studies will include identifying all the genes that are expressed in CSC and learning whether these genes differ between CSC and the non-tumourigenic cancer cells from the same tumour, and between the CSC and the normal adult stem cells of the organ of origin of the tumour.

Candidate biomarkers and molecular therapeutic targets will be validated using patient tumour samples and cell cultures derived from tumours. For example, we will study the expression of candidate biomarkers in organ-specific tumours (e.g., breast) of large numbers of cancer patients to ensure that they identify CSC. CSC biomarkers will be linked with clinical parameters such as patient prognosis and treatment outcome to firmly establish the clinical relevance of CSC.

Similarly, molecular therapeutic targets will be validated by their silencing using genome-wide libraries of interfering RNA (RNAi) or high complexity libraries of chemical antagonists in CSC cultures. Molecular targets with drugable qualities will be used to develop *in vitro* assays amenable to high-throughput screening (HTS) with compound libraries to identify candidate chemotherapeutic drugs.

We will characterize and sequence the genomes of CSC from various malignancies to identify genes whose mutation might be implicated in the genesis of CSC. The CSC genomics research program will be linked to **The Cancer Genome Atlas** (TCGA) project administered by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both part of the National Institutes of Health (NIH).

We will expand existing and develop new facilities to implement **CSC Genome and Bio-Informatics Technology Platforms**, which will be distributed among the Canada and California Research Clusters of the Consortium.

CSC High Throughput Screening

We will develop assays and implement high-throughput cell-based screens using chemical libraries from diverse commercial and academic sources. We will identify chemical hits that kill, block the proliferation or induce the differentiation of CSC thereby abrogating their tumourigenicity.

Central to the high throughput screening (HTS) activities will be the availability of CSC-enriched cell populations obtained from proposed **CSC Culture Suites**. Screening campaigns will be performed at existing **HTS Centers** supplemented with new infrastructure tailored for CSC screens.

Rapid advances in imaging technologies (Proton Emission Tomography [PET] and Magnetic Resonance Imaging [MRI]), which use labelled probes to identify specific cells and their environment will be used to study CSC. The availability of CSC biomarkers in conjunction with **Imaging Technology Platforms** will enable CSC to be identified among the various cells in the tumours of experimental animals and human subjects thus providing significant new knowledge about CSC biology and the efficacy of novel therapeutic agents targeting these cells.

3.3. Infrastructure to Enable Research and Discovery Programs

The small size of most tumours at the time of their surgical removal from cancer patients coupled with the very low frequency of CSC in these tumours is the major impediment to achieving the goals of the Consortium. We propose that new infrastructure (**Technology Platforms**) be established in Canada and California to collect and store human tumour samples under conditions that preserve the live cells in these samples (**Live-Cell Bio-Repositories**). This effort will require developing novel ways of processing fresh human tumour tissue to enable the subsequent purification of CSC.

To dramatically increase the number of cancer cells—and correspondingly CSC—for research and discovery, we propose dedicated animal facilities**—Xenotransplantation Technology Platforms**—to expand human tumour cells in immune-compromised mice as tumour xenografts. The human xenografts will provide a much richer source of tumour cells from which to purify CSC. The xenograft model will also be used as a reliable method for measuring stem cells and studying their properties.

We also propose establishing core cell culture facilities**—CSC Culture Technology Platforms**—to fine tune methods that have been established by a Canadian stem and cancer stem cell scientist (Dr. Samuel Weiss) to culture CSC in Petri dishes in the laboratory. Cell cultures enriched in CSC are crucial to identify new anti-cancer drugs in cell-based screening campaigns with chemical compound libraries, and to better understand the biology of CSC.

Whereas methods for purifying CSC from malignancies of the blood (leukemia and lymphomas) are well established, the means of purifying CSC from solid tumours are far less developed and fraught with difficulties. We will use cell sorting instrumentation dedicated to solid tumour cell fractionation to purify CSC from solid tumours.

CSC Purification Technology Platforms will be established to purify solid-tumour derived CSC. We propose a concerted effort to identify new CSC surface markers and to produce new antibodies to these surface proteins of CSC that will enable their purification.

In addition, as recounted above (3.2) existing facilities in Canada and California will need to be expanded to accommodate the technology needs of the proposed CSC Consortium.

3.4. Training of Highly Qualified Personnel (HQP) in Research

Training of HQP will be an integral component of the research programs. The expansion of CSC research will provide many opportunities for multi-disciplinary training in cancer research technologies. The CSC Consortium will provide a platform for workshops, conferences and trainee exchanges between the leading laboratories of the field, enhancing knowledge transfer and making the leading basic, translational and clinician scientists accessible to all trainees. Workshops may include instruction in new technologies, procedures, and CSC isolation. Trainees will also be exposed to hands-on training through student exchanges between laboratories. Conferences will provide opportunities to exchange ideas and keep abreast of the research that is rapidly progressing in the field. Collectively, these training opportunities and means for knowledge transfer, stemming from the Consortium, will result in enriched environments within which to train highly qualified personnel for both the academic and industrial sectors.

The CSC Consortium members have an existing outstanding record in training HQP, who include undergraduate and graduate students, post-doctoral fellows and research assistants and associates. Many of their graduates have gone on to productive careers in academia or the bio-pharmaceutical industry.

The proposed research will support training hundreds of new HQP at all levels. Where appropriate, HQP will have opportunities to train in different laboratories to learn a variety of techniques. Exchanges between laboratories in Canada and California will be fostered by travel and training scholarships. The organization of research projects along Research Clusters will foster such exchanges.

Training of HQP through research has long been known to be crucial for the development of the biotechnology industry, which will be an active partner in the growth of the Consortium.

4. Translational Clinical Programs

The CSC Consortium will invest significantly in translational activities that will investigate the clinical relevance of CSC and accelerate the evaluation of CSC-specific therapeutics. For example we will determine whether CSC account for tumour aggressiveness, metastases and relapse following therapy. The availability of validated CSC biomarkers will make this task significantly simpler than what is now possible; currently CSC can only be identified by transplanting various number of tumour cells into immune-compromised mice, an expensive and time-consuming proposition.

At this time neither current nor new anti-cancer therapeutics in clinical trials are being evaluated for their capacity to eradicate CSC. Prior to assessing new agents in cancer patients, the Consortium will work with Cancer Centres and bio-pharmaceutical companies developing new drugs and conducting clinical trials to evaluate their efficacy in targeting CSC.

Furthermore new anti-cancer agents (i.e., antibodies and small molecules) identified in the discovery and characterization phases of the proposed research program will undergo rigorous pre-clinical evaluation to obtain comprehensive absorption, distribution, metabolism, excretion (ADME) and toxicological (TOX) profiles, prior to filing for Investigational New Drug (IND) applications to the FDA.

Candidate therapeutics to be entered into clinical trials may include existing drugs now used for indications other than cancer. Indeed several CSC investigators identified with this proposal have discovered new agents and existing drugs that affect hyper-activated molecular pathways in CSC. These novel agents are investigational in nature and have not been tested in man, and hence will require detailed medicinal chemistry, manufacturing, and control information, as well as ADMET studies. Coordination among CSC laboratories, partner biotechnology firms and clinical trials centres will accelerate these processes by months, if not years.

Both Canada and California host Comprehensive Cancer Centres with world-leading expertise and infrastructure for evaluating candidate CSC biomarkers and testing new cancer therapeutics, including “First-in-Man” studies (i.e., the first introduction of a new drug in human subjects). Networking among cancer centres in university hospitals provides extensive resources, such as biomarker investigations, state-of-the-art imaging, molecular pathology, pharmacogenomics and other technologies that allow rapid monitoring of tumour response. These will provide unique opportunities to study novel CSC therapies and to understand the response of CSC in patients.

5. Commercialization Strategy

A strategic priority of the CSC Consortium is to enhance the value of intellectual property (IP), which will arise from the research programs described above. The CSC Consortium does not intend to take an ownership participation in IP arising from the research programs; IP ownership will reside with the inventor and/or his institution. Several partners in the Consortium will, however, play an active role in the development of IP by funding proof-of-principle (POP), Proof-of-Concept (POC) and validation studies.

Equally important, the CSC Consortium can position itself as a vehicle to coordinate interactions and to secure investments from the biopharmaceutical sector. We believe it would be essential to work proactively with industry and the venture community in order to promote strategic industry investments in both Canada and California. Some specific examples of initiatives that we are considering include:

- Feasibility analysis of setting up a structure for cross-border IP agglomeration (bundling)
- Development of a strategy to set up common approaches to venture capital funds
- Development of a strategy to work with business receptor networks, principally the bio-pharmaceutical sector, for primary investments and the development of clinical trials

There is already strong interest from the biopharmaceutical sector. The following companies are already involved in sponsoring CSC research or are contemplating sponsored research projects with Canadian and Californian members of the Consortium: Aggregate Therapeutics, Inc., Bristol Meyers Squibb, Pfizer, Stem Cell Therapeutics, Gemin X, Aegera Therapeutics Inc, MDS Nordion, Transgenomic, TaregeGen Inc., Becton-Dickenson, Celgene, Tegera Merck & Co., Inc., Genentech, Inc., Amgen Inc., Sanofi-aventis, ARIUS Research Inc., CSL Limited, MAT Biopharma, Geron Corporation, Five Prime Therapeutics, Inc., Alexion Pharmaceuticals Inc., and Abbott Limited. Venture capital investors, such as StemCell Ventures and Forward Ventures, are also likely to participate as discoveries mature. California is the home of the largest VC community in the world (over 500 firms) and Canada has a very active though smaller industry with many life science investors.

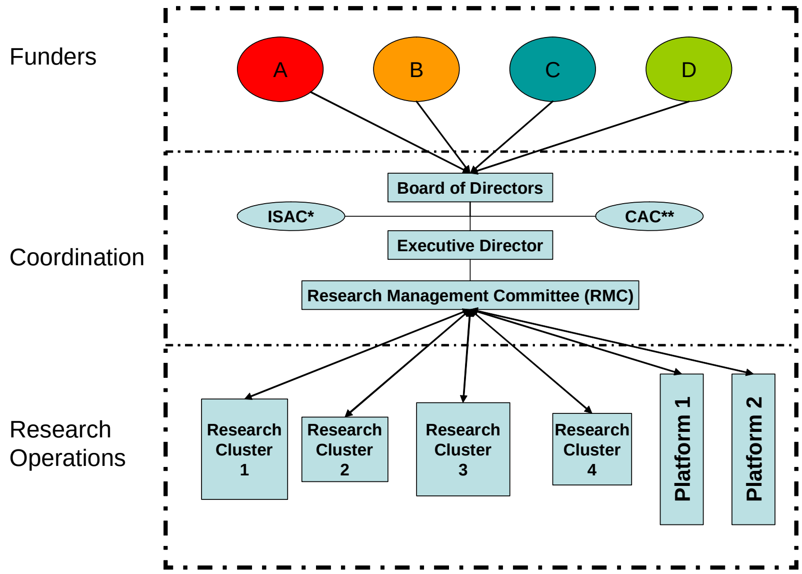
As indicated in the Translational Clinical Programs Section, the CSC Consortium will participate with the bio-pharmaceutical industry in setting up a clinical trials coordination function for CSC investigational treatment studies. This will be a considerable investment from this sector in both Canada and California.

We propose that 10% of the CSC Consortium budget will target early phases of the commercialization process. It is anticipated that this investment will yield multiples in financial benefits for both Canada and California. This is because start-up biotech firms will have to locate close to the research teams in order to take advantage of rapidly evolving biological understanding and to have access to state-of-the art research infrastructure as evidenced by the location of biotech firms in California.

In order to maximize the full value of the academic-based intellectual property, we must allow sufficient time for the development of intervention strategies targeted at CSC. Here again, the importance of sustained funding over an extended period is critical to the mission of CSC Consortium. In addition, sustained research funding, will be a pivotal factor in the attraction of industrial and venture funding in both Canada and California.

6. Governance and Management Structure

We are proposing a CSC Consortium organizational structure, to be based around world-leading Research Clusters and Platforms.



*ISAC: International Scientific Advisory Committee
**CAC: Commercialization Advisory Councils (each jurisdiction to have its own council).

Figure 3: CSC Consortium Organizational Structure

Governance model

The Consortium will be established as a not-for-profit corporation with the following management structure.

Board of Directors: The Board will comprise representatives of the major funding agencies as well as research and business leaders from the international community. The Board will be responsible for overseeing the overall scientific direction, setting specific goals and milestones and fiscal management. One of the main objectives of the scientific strategy will be the dissemination of new knowledge to ensure that new cancer therapies and improvements to existing therapies are quickly commercialized. The Board would also be responsible for overseeing the development of Consortium policies covering: confidentiality and conflict of interest, intellectual property, data release and resource sharing.

International Scientific Advisory Committee (ISAC): An ISAC will be independently constituted to provide informed, critical advice and guidance to the Board on scientific direction.

Executive Director (ED): The ED will be responsible for overall coordination between the various Research Clusters and Technology Platforms (see below) of the Consortium, and in establishing operational policies as prescribed by the Board. The ED will be supported by relatively small **Secretariat,** which will be responsible for administrative matters and communications.

Research Management Committee (RMC): A RMC will be established with representation from Research Clusters and Technology Platforms to ensure that milestones are achieved and that research projects are appropriately coordinated across projects and centres.

Research Clusters and Technology Platforms: The CSC Consortium will have well-defined research and technology development programs, organized as Research Clusters and Technology Platforms. A Research Cluster will either be a regional or thematic grouping of investigators. The Research Clusters will consist of teams of researchers, including biologists, bio-informaticians, clinician scientists, surgeons, pathologists and technical experts. Technology Platforms will be closely linked to the research programs, and will focus on technology development and automation leading to increased capacity for research activities. Each Research Cluster or Technology Platform will identify a Leader for coordination purposes with the Consortium. The Research Clusters and Technology Platforms will be funded based on scientific peer review, which will be undertaken by Consortium funders and often with inter-agency participation.

Commercialization Advisory Council: Because of the importance of commercialization for the Consortium, we propose that each jurisdiction establish a Commercialization Advisory Council (CAC) comprising leading members of their respective industrial and venture capital communities. The primary role of each CAC would be to provide recommendations on developing commercial opportunities in cooperation and proximity to the Research Clusters and Platforms. A commercialization manager would be appointed in both Canada and California for coordination.

7. Proposed Budget, North American Leveraging (2007-2012)

Sustained funding will be the key to the success of the CSC Consortium because of the unique nature of the expertise and the technology required for this research. A key operational principle for the Consortium will be that funding agencies will usually disburse funds according to their respective mandates and jurisdictions. This implies that funds may not flow through a central organization. For example, funds could flow from a particular government agency to a geographical location for a specific project. The intent is to ensure that funds flow from an agency to the desired Research Cluster or Technology Platform. Furthermore, it is anticipated that, where feasible, joint funding mechanisms will be set up between complementary funding agencies in each jurisdiction.

The Consortium will provide coordination among its funding partners to ensure that essential expertise is developed and that the use technological resources are fully used.

We anticipate that Canada and California would contribute equally to the five-year budget of $500 million (CDN) for the CSC Consortium. Whereas much remains to be discussed within the CSC Consortium regarding the specifics of the budget components, we are presenting a budget based on allocations for specific components of the Consortium (Table 1).

The Canadian funding is anticipated to be “modular,” meaning that it will be directed for specific periods of time and towards discreet components of the CSC Consortium. Overall, 50% of the funding would come from Federal sources and 50% would come from the provinces and philanthropic organizations. Several funding agencies have already begun to collaborate to create a framework for this new structure – Genome Canada, the Canadian Institutes of Health Research, the Canada Foundation for Innovation, and the Ontario Institute for Cancer Research

(OICR), to name a few. Additional public and private entities, such as provincial funding agencies, cancer NGOs and pharmaceutical and biotechnology companies, from both Canada and California are expected to join the coalition providing experience and funding in their areas of expertise. For example, Genome Canada would support initiatives such as the sequencing of the CSC genome. The Canadian Institutes for Health Research would support the CSC biology and translational clinical research and training programs. The Canada Foundation for Innovation (CFI) would play a major role with its provincial partners in supporting infrastructure needs in Canada from its existing programs. Commercialization support may come from the newly announced Centres of Excellence in Commercialization and Research.

Table 1 CSC Consortium Budget Outline (2007-2012)

Targeted sustained funds over five years - spending to be equally divided between Canada and California	**Budget Allocation**	**Million $ CDN**
1. Biology of CSC: Research Programs including technology development and HQP training	60%	300
2. Research infrastructures (space, equipment, maintenance and support costs), including tissue/live cell banking, science and technology platforms (genomics, proteomics, high-throughput screening, bioinformatics, etc.) *Spending to be concentrated in years 1 to 3.	15%*	75
3. Clinical Translational Programs **Spending to be ramped up in years 3 to 5, approaching 15%.	10% **	50
4. Commercialization Opportunities	10%	50
5. Secretariat - Administrative and Communications Hub	5%	25
Total	**100%**	**$500**

We are anticipating strong participation from several Canadian provinces. There is confirmed participation from the Ontario Institute for Cancer Research (OICR) of $30 million over five years. We are in discussions with the Alberta Heritage Foundation for Medical Research and the Fonds de Recherche en Santé du Québec (FRSQ) to explore whether support for such an undertaking fits with their priorities. In addition, we will seek support from other philanthropic organizations in Canada, such as the Terry Fox Foundation and the Michael Smith Foundation for Health Research.

It is our understanding that funds for the California participation would come from several sources including the California Institute for Regenerative Medicine (CIRM), philanthropic foundations, health charities, individual donations, patient driven research organisations, university funds and from its extensive biotechnology sector. In the November 2005 state election, California voters approved $3 billion over 10 years to support stem cell research through CIRM. Opponents to this measure filed legal appeals on constitutional grounds and the last hearing is expected in the coming months and serious funding for this sector will kick in. In the meantime, to show that California was completely committed to this initiative, Governor Schwarzenegger has advanced a loan of $150 million to start up CIRM pending a final legal decision. In addition, private foundations have provided an additional $50 million to date.

As indicated in the commercialization section, we are anticipating significant interest from the private sector in the downstream development of intellectual property and human intervention strategies.

Appendix

Canada-California Strategic Innovation Partnership
Cancer Stem Cell Workshop
January 20, 2007
Stanford University School of Medicine
Institute for Stem Cell Biology and Regenerative Medicine

List of Participants

John Hassell (Workshop Chair, McMaster University)	Phil Beachy (Stanford University)	Catriona Jamieson (University of California, San Diego)
Thomas Hudson (Ontario Institute for Cancer Research)	Phil Branton (CIHR Institute for Cancer Research)	Connie Eaves (British Columbia Cancer Research Centre)
Michael Rudnicki (Ottawa Health Research Institute)	Sam Weiss (University of Calgary)	Marc LePage (Consulate General of Canada, San Francisco)
Miguel Andrade (Ottawa Health Research Institute)	Mark Henkelman (University of Toronto)	Keith Humphries (British Columbia Cancer Research Centre)
Allen Eaves (Stem Cell Technologies, Inc.)	Peter Lansdorp (British Columbia Cancer Research Centre)	Ichiro Nakano (University of California, Los Angeles)
Chuck Hasel (Genome Canada)	Mark Bisby (Consultant)	Lali Reddy (Consulate General of Canada, San Francisco)
Clay Smith (British Columbia Cancer Agency)	Sam Aparicio (British Columbia Cancer Research Centre	"Sandy" Alexander Borowsky (University of California, Davis)
Hsing-Jien Kung (University of California, Davis)	Rhavi Bhatia (City of Hope)	Cindy Bell (Genome Canada)
Norman Iscove (University of Toronto)	Owen Witte (University of California, Los Angeles)	Luika Timmerman (University of California, San Francisco)
Arlene Chiu (California Institute for Regenerative Medicine)	Stephen Quake (Stanford University)	Irv Weissman (Stanford University)
Robert Klein (California Institute for Regenerative Medicine)	Emmannuel Passague (University of California, San Francisco)	Bob Oshima (Burnham Institute for Medical Research)
Alexey Terskikh (Burnham Institute for Medical Research)	Tia Moffat (Stem Cell Network)	John Dick (University of Toronto; teleconference)
Peter Dirks (Hospital for Sick Children; teleconference)		