

Cancer Stem Cell Workshop

Toronto, Ontario
April 17 – 18, 2008



GenomeCanada



Canada Foundation for Innovation
Fondation canadienne pour l'innovation



CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Stem Cell
Network  **Réseau de**
cellules souches

GLOSSARY

CCSIP	Canada-California Strategic Innovation Partnership
CDA/MTA	Confidential Disclosure Agreement/Material Transfer Agreement
ChipSEQ	Chromatin immunoprecipitation assay for sequencing
CIHR	Canadian Institutes of Health Research
CIRM	California Institute for Regenerative Medicine
CFI	Canada Foundation for Innovation
CML	Chronic myelogenous leukemia
CpG	DNA region where a cytosine nucleotide occurs next to a guanine nucleotide
CSC	Cancer Stem Cells
CSC/TIC lines	Cancer Stem Cell/Tumor-Initiating Cell Lines
EXOME	All exons of the genome
FDA	Food and Drug Administration
IP	Intellectual Property
LOH	Loss of Heterozygosity
miRNA	Micro RNA
NOD/SCID	Non-obese Diabetic/Severe Combined Immunodeficiency
OICR	Ontario Institute for Cancer Research
RFA	Request for Applications
RT-qPCR	Real-time quantitative polymerase chain reaction
SAGE	Serial Analysis of Gene Expression
SCN	Stem Cell Network
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedures

INTRODUCTION

April 17/18th marked the Cancer Stem Cell (CSC) Workshop sponsored by Genome Canada, the Canada Foundation for Innovation (CFI), the Canadian Institutes of Health Research (CIHR) and the Stem Cell Network (SCN), with contributions from McMaster University and Dalhousie University. The planning committee brought together 115 participants, from Canada and California, comprised of researchers prominent in the field of stem cells and cancer stem cells (CSCs), and of representatives from funding agencies and industry.

A number of key events set the stage for the CSC Workshop. The first was the Summit of the Canada-California Strategic Innovation Partnership (CCSIP) in Los Angeles in 2005 when the notion of a collaborative effort between CSC researchers in Canada and California was initially conceived. The second was the CCSIP CSC Workshop that brought together over 35 participants in Stanford in January 2007. The participants explored the challenges and opportunities inherent in stem and cancer stem cell programs, considered various mechanisms of collaboration, and concluded the meeting by forming a working group to move the project forward. The third was a proposal, submitted to the Deputy Minister of Health Canada in May of 2007, in which the working group outlined the overall importance, opportunity and proposed governance plan for the first five years of a CSC Consortium.

The 'raison d'être' for the current CSC Workshop was to consult more widely with the interested parties in the hope that they would delineate the important areas in the emerging field of cancer stem cell research, and suggest the means of governing and funding a major Canada-California initiative. To this end, the workshop was divided into plenary sessions (see Agenda: Appendix 1 and Participants List: Appendix 2) which explored a range of pertinent issues, and breakout sessions which provided an opportunity for more in depth discussions of how to advance the cancer stem cell field. This report will highlight the key messages thought by participants to be required to galvanize the Cancer Stem Cell Consortium into being.

MESSAGE FROM THE FUNDING AGENCIES

During the first plenary session, and also peppered throughout the workshop, representatives from various funding agencies conveyed their perspectives, potential monetary contributions, and expectations. Taken together, their ideas helped provide a context for the requirements for funding a CSC Consortium, and provided ample food for thought for the participants to consider during the workshop discussions.

Perspectives

- There is money available from the Canadian funding agencies for a coherent plan that highlights the need for Canada and California to work together on an exceptional cancer stem cell research initiative.
- The project would be funded for 4-5 years with an opportunity for renewal based on progress.
- Keep the funding process simple and have joint calls for applications with single RFAs to ensure that the ethos of the Consortium is the same for both regions.
- Scientists have identified the needs, but the question now is how to reduce these in practice and how to get complex science into a written format.
- The California Institute for Regenerative Medicine (CIRM) has funding mechanisms that are different from those in Canada (e.g., CIRM funds research only in California and requires a competitive process) but has RFA frameworks that cancer stem cell research could fit into.
- There is a deadline for funding a CSC Consortium.

Potential Contributions to the CSC Consortium

- Genome Canada (GC) → \$30M available, conditional upon delivery of a first class strategic plan and subsequent research proposal

- CFI→ substantial monetary contribution on the table for research equipment and infrastructure, conditional upon delivery of a first class strategic plan and subsequent proposal for enabling leading edge national research infrastructure
- CIHR→ substantial monetary contribution for research and training on the table, conditional upon delivery of a first class strategic plan
- Ontario Institute for Cancer Research (OICR) → \$30M confirmed
- SCN→ substantial monetary contribution in the long term; \$100,000 in the short term to spring-board groups together through workshops
- CIRM→ would consider potential monetary contributions to provide funding for researchers in California to partner with researchers in Canada on CSC research, subject to applicable policies and regulations.

Expectations

- Joint application and review process where appropriate
- Coalescence of multidisciplinary teams to address cancer stem cell research
- Justification for a Canada-California collaboration (Is Canada-California a contrived entity or should it be pushed forward because the leadership exists? How will cancer stem cell research directed through a Consortium make a difference, as compared to cancer stem cell research projects that can be funded through existing mechanisms?)
- Plan for governance and accountability based on a flexible structure
- Plan of what would be accomplished through a comprehensive research plan with defined milestones
- Cohesive vision for how to move the Consortium forward
- Comprehensive application in terms of infrastructure and projected costs
- Plan for how the Consortium will bring the private sector to the table

Questions/comments

Participants voiced concern about going to the effort of setting up an altered paradigm of cancer stem cell research and the downstream implications of the funding not being renewed.

SETTING THE STAGE FOR THE CSC WORKSHOP

During the plenary sessions, three invited speakers presented background talks that set the stage for later discussions during the workshop. Collectively, their presentations touched on the various issues confronting the field of cancer stem cells and the potential benefits of forming a CSC Consortium.

Rational for pursuit of CSC

- Existence of tumor heterogeneity and evidence of hierarchy in experimental systems
- Unique properties of CSCs may have prognostic, diagnostic and/or therapeutic potential
- Desire to deliver right therapy to right patient at right time

Key questions

- Does every cell in a cancer have equal ability to keep the cancer going?
- Are CSCs relevant beyond the experimental system?
- Do the number, proportion or biological properties of CSC within a tumor correlate with patient prognosis?

CSC minimal toolkit

- Markers for prospective purification
- Functional assays (xenotransplantation, in particular NOD/SCID repopulating cell assay; *in vitro* surrogate)

Challenges

- Current methods to assess clinical efficacy may not predict activity against CSCs.
- Major obstacles to detect clinical assessment of anti-CSC activity include identification of new markers for tracking CSCs; validation of surrogate endpoints of drug efficacy; improved resolution of molecular imaging.
- Greater emphasis on preclinical development (e.g., novel drug discovery platforms using relevant cell populations; functional validation of activity of *in vivo* models) will result in a better chance of predicting what therapies will work.
- Experimental outcomes have not been translated into improved survival outcomes for patients.

Barriers to success

- Combination chemotherapy and combination immunotherapy to several different molecular targets may be required for curative therapies
- Barriers to new combination therapies include companies, FDA and its equivalents, and oncology community
- Redesign of preclinical studies to test combination therapies and to find ways to move from single agent phase I trials to multi-agent approaches
- Switching from spirit of competition to one of cooperation
- Encouraging surgeons and pathologists to share tissue samples, best practices protocols, permissions, etc.
- Need to overcome tendency to deny publication of perceived competition
- Development of new molecular technologies
- Cost sharing (e.g., immunodeficient mouse colonies)
- Optimization of guidelines for CSC studies using animals
- Selective targeting of aberrant cancer stem cell differentiation, survival, self-renewal, homing
- Paucity of patient samples
- Rarity of CSC
- Lack of skilled researchers
- Cost of equipment/reagents
- Clinical trials implementation

Benefits of a CSC Consortium

Potential for scale-up to address:

- Does the fraction of CSC correlate with patient prognosis?
- Are CSC properties functionally equivalent from patient tumor to patient tumor?
- Are there CSC properties that will better predict patient outcome?
- What are differences between primary and recurrent CSCs?
- Will CSC signatures result in improved stratification of patients for treatment compared to analysis of bulk tumor cells?
- Is there variation in CSC signatures (e.g., gene expression and cell surface markers) for different patients with the same cancer type?

Potential to build networks to:

- Increase patient sample size;
- Overcome rarity of CSC;
- Train skilled researchers;
- Share costs of equipment/reagents;
- Collaborate on clinical trials implementation;
- Bring together pathologists, CSC biologists, medicinal chemists, imagers, etc.;
- Create parallel networks to study normal stem cells.

Questions/comments

How will Canada and California work collectively without duplicating their efforts?

In order to magnify the scale of what is happening in Ontario, we need a consortium approach but each region does have its particular strengths. For example, biorepositories and patient collection are easier to organize in Ontario, and California is unsurpassed in terms of its ability to create new technologies. The ability of these two groups to communicate and interact within the framework of a consortium would accelerate CSC research.

Immediate collaboration could be achieved through CIRM-sponsored courses. What topics would be most useful as an intensive workshop course?

Facilitating reliable SOPs for xenograft assays would be one of the biggest benefits to CSC research.

Different tumors will vary among individuals, so isn't the idea of looking at 1,2,3, tumors and xenografts insufficient?

Yes, it is. It is so much work to get the cells, markers etc. and there are so many different pathways that one would have to analyze many different tumors from the same malignancy. The power comes from looking at many samples of a given tumor type.

EMERGING TECHNOLOGY PLATFORMS

Seven speakers presented rapid-fire talks that spoke to a variety of emerging technology platforms that could be employed to advance cancer stem cell research. The technologies and their potential applications to the cancer stem cell field are listed below.

Technology	Potential Applications
Live Cell Biorepositories	Biomarkers/characterization of CSCs CSC expansion, models/assays Pre-clinical validation of new agents
Next Gen Sequencing	Whole genome shotgun sequencing Mapping transcription factor binding sites and regions associated with histone modifications using CHIP-Seq Gene expression via whole transcriptome shotgun sequencing; miRNA profiling; Tag-Seq (SAGE-like) Profiling DNA methylation
Live Cell Mouse MR imaging	Localization and function of CSCs in animals Therapies can be tested on many mice Single cell detection
Microfluidics	Scalable and dynamic cell culture; rapid and inexpensive Microfluidic RT-qPCR (cost and time savings) Digital PCR (transcription factor profiling in individual hematopoietic progenitors) Potential for cost effective miRNA profiling and single cell miRNA profiling Combining Next Gen sequencer with microfluidics
Drug Screening	Targeting tumor initiating cells using high throughput strategies Bringing drug therapies rapidly to the clinic (from target drug to mouse model to patients in months) Determine if hits can kill other stem cell populations Identify 'stemness' of drugs
Animal Models	Can get tumors from single cell transplantation Mouse phenocopy similar to human disease Test whether epigenetic events are major determinant of clinical outcomes
Clinical Correlations	Integrate live cell banking into clinical trials protocols Looking at clinical correlations, natural history, response to therapy

ADVANCING THE FIELD

Workshop attendees dispersed into one of six breakout groups, each charged with addressing a number of major questions. The outcomes, presented in the plenary session that followed, contributed to myriad ways of advancing the cancer stem cell field.

Group 1 CSC Initiative: An Overview

What are the big biological questions that will make a difference?

- Do cancer stem cells provide a route to improved health outcome?

What are the key items to success?

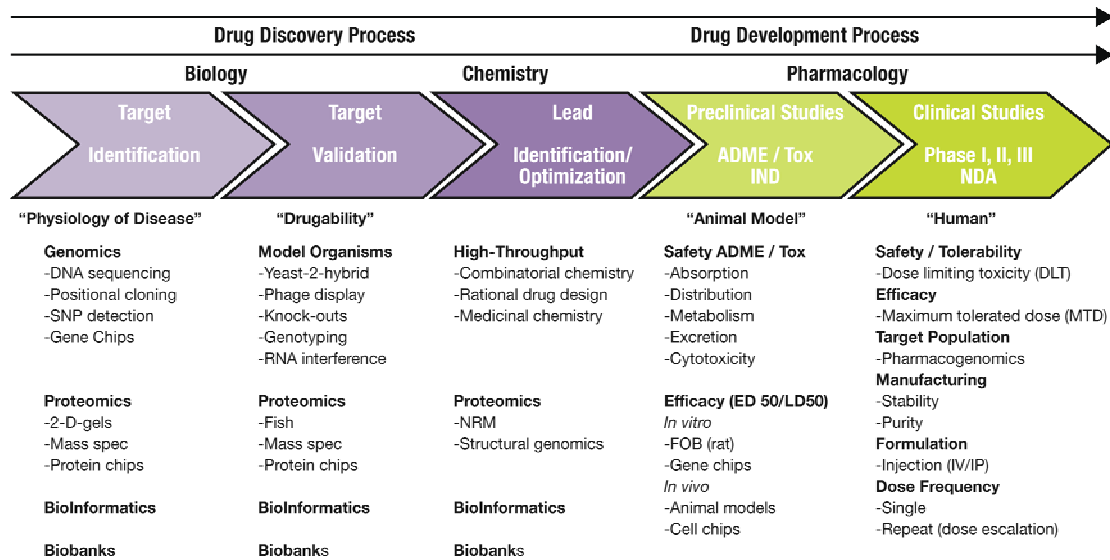
- Prove concept in a focused fashion by:
 - choosing an agreed upon objective and succeeding;
 - addressing stakeholder and funder related issues;
 - encompassing science, ethics, business;
 - providing the broadest benefits, knowing that time is of the essence.

How to accelerate a cancer cure for large-scale projects

- Vary approach based on differences in tumors of brain, breast colon, AHL, head and neck, solid tumors
- Develop common science and technology platforms, and standards and methods to evaluate the projects from discovery through to development and clinical outcomes
- Establish communication networks among groups

Drug discovery and development process

- Parameters that influence drug performance include subtle interactions among:
 - targets (molecular structure and physical properties);
 - targeted patient population;
 - manufacturing process;
 - formulation of the dose.



Project risks (How do consortia fail?)

- Poor management
- Conflicting objectives
- Size of project (from operating room to lab to commercialization to clinic)

- How to measure success is not clear but needs to be defined at the outset
- Time management (i.e., some projects feed into day jobs but others will demand extra time)
- Management of timelines and expectations (i.e., don't over-promise results; do celebrate minor outcomes)
- Rapid access to biological materials

How to ensure the success of the CSC Consortium?

- Effective oversight and management
- Start with defined projects, with specific objectives and timelines
- Answer questions who, what, when
- Next steps include:
 - establishing governance;
 - securing dedicated resources;
 - selecting key projects;
 - building the team;
 - measuring progress with definable metrics;
 - communicating our success;
 - getting the job done.

Group 2 Clinical Implications of CSCs

What are the important research questions and deliverables in this area where large-scale collaboration will be crucial to rapidly advancing the field?

- Diagnostic and prognostic applications of CSCs, i.e., determining number and characteristics of CSCs before and after treatment may lead to:
 - improved distinction of disease entities;
 - progression from dysplasia to malignancy;
 - steering patients to most appropriate current treatment (e.g., tyrosine kinase inhibitor therapy, or bone marrow transplantation in CML);
 - treatment outcome;
 - screening high risk groups/situations.
- Targeting CSCs to improve cancer outcomes
- Chose one to two initial near term settings to test CSC targeted therapies
 - change the paradigm of Phase 2 studies (may need to combine targeted therapies with existing “debulking therapies” to see clinical effects)
 - extensive correlative science studies (i.e. “ultra-high content clinical trials”)
 - creates a logistical and scientific paradigm for subsequent “ultra high content clinical trials”
- Extremely valuable in even a single clinical setting to prove the hypothesis that targeting CSCs improves outcome

What are the challenges associated with using CSCs as diagnostic/prognostic tools?

- Need to validate existing potential CSC measurements
- Need for more refined markers and characteristics of CSCs
- Inter-tumor variations in CSCs
- Need for large populations of study patients coupled with extensive correlative science
- Need for long-term follow-up in prospective clinical studies because existing tumor repositories may not contain specimens appropriate for CSC measurements

What are the potential solutions?

- Do prospective rather than retrospective studies
- Survey landscape and identify small number of promising diagnostic/prognostic CSC markers to validate in clinical trials (if such a trial could be designed and carried out in timely fashion, it would be a valuable effort and meaningful to patients)

- Survey landscape for low hanging fruit that are ready to be tested in larger studies and that would provide a paradigm for subsequent studies
- Change paradigm of Phase 2 studies
- Validate the diagnostic/predictive value of CSC measurements in even a single situation

What is the role of the Consortium in facilitating these clinical studies?

- Clinical trials/correlative science design and performance using complementary expertise and technologies
- Incorporating a number of unique resources and expertise that do not exist elsewhere
- Shared expertise, SOPs to improve consistency across multiple centers
- Common and consistent approach to ethics, IP, data sharing, tissue sample archiving
- Advocate to government, patient groups regarding need and value for these studies
- Maintain paradigm for subsequent generations of studies
- Even one study would provide valuable paradigm for higher hanging fruit

What local and/or national infrastructure would best address the goals of the Consortium?

- Live cell banking: capitalize on existing efforts
 - leukemia cell banks (in Quebec and many other places) provide valuable expertise
 - unique challenges in preparing solid tumor samples as single cell suspensions
- Sustainability: high cost of tissue collections
 - Can collection become part of reasonable medical costs?
 - Can the Consortium become an advocate to policy makers about funding this in a long-term fashion?
 - Demonstrate the value to payees of investing in a late stage development of tests into consistent and reproducible “standards of care” (i.e., Her2neu example of faults in current “ad hoc” approach to developing new cancer tests)

What are the commercial issues?

- Two way street between companies and academia (nothing is going to make an impact in patients without commercialization)
- Examples: new agents, tests
- Role of Consortium
 - industry as an essential partner in correlative science in ultra-high content clinical trials
 - deliverables: universal CDA/MTA, approach to IP, data sharing/mining agreements
 - generic consents
 - consistent reporting issues to industry and Consortium board
 - training for academic researchers in the company environment
 - facilitate training of academic researchers by industry experts in SOPs regulatory affairs, tox/manufacturing, other
- Could the Consortium address these issues with companies and patient advocacy groups through expert personnel/office?

Are there any major ethical, legal, social and/or regulatory impediments to moving forward, and if so, what are they?

- Yes, there are numerous challenges, but they could be mitigated if the Consortium were to provide expert personnel/office that could facilitate the “journey” through the regulatory/legal landscape.

Group 3 CSC Biology

Why do we need a CSC Consortium?

- No single group can capture all the major tumor types that are needed for study
- Standardization and common methodology are needed to address many of the issues in CSC biology

What is the CSC biology mandate?

- Tissue accrual network (does not preclude originality)
 - resources for samples and staff
 - collection of normal and neoplastic tissue
- Rapid assessment of CSCs
 - molecular signatures
- Common resources (i.e., what we think are common and for what we could establish SOPs and guidelines)
- Mice
- mAbs
- Pathologists
- Meeting/training (even internet contact can move things to more common and optimized structure)

What are the important research questions and deliverables in this area where large-scale collaboration will be crucial to rapidly advancing the field?

- Derive prognostic indicators
- Develop paradigm relevant to many other diseases
- Interdisciplinary approach to biological process
- New HQP (highly qualified personnel)

What are the bottlenecks?

- Shortage of HQP (e.g., pathologists)
- Excessive clinical workload (e.g., pathologists overwhelmed)

What is the role of the Consortium?

- To fund dedicated pathologists
- To standardize collecting and storing of tissues (cancerous and normal counterparts)

Group 4 CSC Genomics

What are the important research questions and deliverables in this area where large-scale collaboration will be crucial to rapidly advancing the field?

- Diagnostic, prognostic and therapeutic targets
- Provide insight on phenotypes of CSCs (renewal, differentiation, evolution from primary through to secondary)
- Understand the genetic and epigenetic programs that are fundamental to self-renewal
- Determine the origins of CSCs
- Understand heterogeneity among individuals/tumors, early vs advanced tumors, responders/non-responders (i.e., clinical importance)

What are the specific research approaches/plans that would best address these questions and generate these deliverables, and what local and/or national infrastructure would be required to support these goals?

- Approaches and outcomes are dependent on experimental questions, and availability, purity and quality of the samples; looked at nucleic acids, proteins, not just genomics
- DNA
 - Next Gen sequencing is the way to go!
 - whole genome sequence (too costly)
 - copy number changes/LOH (essential, inexpensive using SNP arrays)
 - exon resequencing EXOME (important information to identify somatic events that may correlate with clinical response; getting to affordable range)
 - paired end reads (yields translocations; getting to affordable range)
- Epigenome (important approach for biological and clinical questions)

- Methylation (CpG island/arrays are inexpensive but need 1-10k cells; bisulfite sequencing too costly)
- Chromatin Marks (profiling of histone modifications using ChipSEQ)
- RNA (important for biological and clinical questions and target identification)
 - expression levels
 - splicing
 - mutations
 - fusions
 - microRNAs
- Proteomics
 - phosphorylations
 - quantitative (new technologies)
 - quantitative (antibody arrays – Uhlen methods)
- Minor enthusiasm for glycomics and metabolomics

What would be the most appropriate funding mechanism to support these plans, and what would be the best mechanism to manage and co-ordinate the research efforts?

- Funding to teams and facilities that provide access to CSC biologists
- Some facilities will likely be unique (e.g., microfluidics)
- Some facilities will likely be hosted at a few sites (e.g., those that have Next Gen sequencers, in which case there will be a need for standardization, quality control (QC), etc.)
- Technology development is essential along with the mechanisms to support such teams

What are the potential commercial outcomes and who are the likely partners?

- Outcomes include:
 - prognostic target;
 - biomarkers;
 - imaging probes;
 - targets for drug development;
 - technologies;
 - instruments.
- Partners include:
 - biotechs, pharmas etc.

Are there any major ethical, legal, social and/or regulatory impediments to moving forward, and if so, what are they?

- Yes, but they are not specific to the CSC field, and they are not impediments but rather concerns that include:
 - Ethical concerns;
 - Consent;
 - Data sharing (internal vs the world; open vs controlled data types);
 - IP owned by inventors and institutions (need for cross-licensing among members [a benefit]);
 - Publication policy.

Group 5 CSC Therapeutics

What are the important research questions and deliverables in this area where large-scale collaboration will be crucial to rapidly advancing the field?

- Can we identify compounds and/or target signaling pathways modulated by those compounds that are effective against CSCs in culture, in animal models, and in patients?
- How can we best engage pharmaceutical companies in the academic CSC drug discovery process?

Bottlenecks

- Sharing of information, CSC/TIC lines

- Quality of libraries for screening
- Lack of medicinal chemistry expertise and collaborations
- Access and subsidizing of costs for drug testing in animal models

What is the goal of the CSC Consortium?

- To identify novel therapeutics and identify CSC self-renewal, survival, resistance to chemotherapy, and differentiation pathways using small molecules

How will the Consortium attain that goal?

- By developing a chemical library that can be used to probe the function for all known signaling pathways important in oncogenesis and stem cell biology (for chemogenomics and target identification)
- By creating platforms for information and CSC exchange for all Consortium members (identify best assays, develop common screening platforms and methodology)
- By identifying medicinal chemists to work with and who can advise the Consortium on prioritization and generation of drugs

Commercial interest

- Value is platforms and knowledge to determine how drugs might work, and validating drugs in more relevant cancer models
- Identification of novel signaling pathways that might be targeted by companies

Issues

- IP (institutional and company blocks)

Group 6 Data Management

What are the important research questions and deliverables in this area where large-scale collaboration will be crucial to rapidly advancing the field?

- Characterization of cancer stem cells leading to novel therapeutics
- Whole is greater than the sum of the parts (i.e., ability to ask deeper questions; no single technology is sufficient)
- As pair-wise early data sharing defines a collaboration, large-scale data sharing defines a consortium (demands the ultimate sacrifice to our competitive instincts along with sample sharing)
- Need to integrate all data types with well defined formats
- Need algorithms for data mining

What are the specific research approaches/plans that would best address these questions and generate these deliverables, and what local and/or national infrastructure would be required to support these goals?

- Computing infrastructure
 - local database management
 - bandwidth, firewalls
 - access to high performance computing capabilities and data storage
- Data coordinating and analysis center(s)
 - centralized or federated database models
 - common formats
 - complete records
- Bioinformatics development and training
 - need definition of minimal amount of data to be transferred

What would be the most appropriate funding mechanism to support these plans, and what would be the best mechanism to manage and co-ordinate the research efforts?

- Data coordinating and analysis centers (probably would not be a single center, regardless of different borders)
 - initial investment
 - operating costs
 - external scientific advisory board
- Access to data
 - controlled consortium access
 - open community release as quickly as possible (data well quality controlled prior to that)

What are the potential commercial outcomes and who are the likely partners?

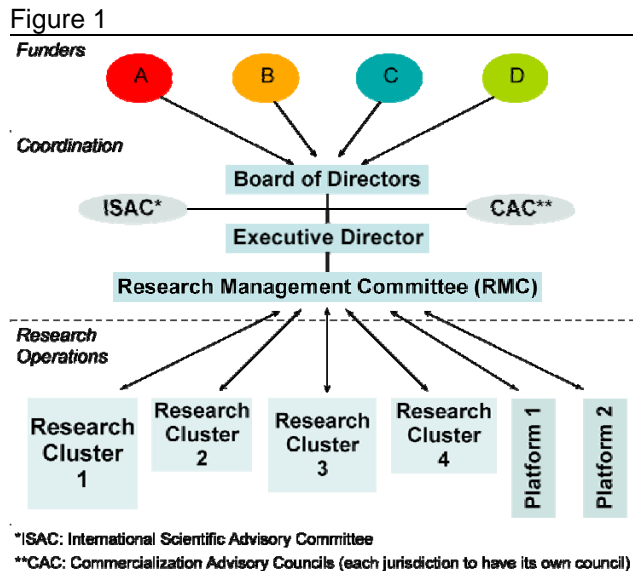
- External data analysis tool development opportunities
 - clinical tools for large-scale data handling associated with predictive medicine
- High performance computing platforms and manufacturers
 - Hewlett Packard, IBM, etc.

Are there any major ethical, legal, social and/or regulatory impediments to moving forward, and if so, what are they?

- Database security and public release
- Clinical data
- Sequence data
- Intellectual property
- Data ownership
- Trust
- Authorship and scholarly integrity

PROPOSED GOVERNANCE STRUCTURE

A model for the governance structure of the Consortium was put to the participants for their consideration. Underpinning the model is the premise that the funding would not flow through the Consortium, but in most cases from the funder directly to the research cluster or platform, thus maximizing its flexibility and autonomy. The intent of the governing body is not to be prescriptive but rather to provide a reference for accountability for the Consortium. Scientists would maintain full control but would be required to provide regular progress reports to the governing body. Figure 1 depicts the proposed organizational structure, with the salient points detailed below.



- CSC Consortium is a not-for-profit organization
- Board of Directors is composed of funders and international leaders from research and business communities
- Board of Directors is responsible for overseeing overall scientific direction, setting specific goals and milestones, fiscal management, development of policies (confidentiality, conflict of interest, IP, data release, resource sharing)
- International Scientific Advisory Committee (ISAC) is independently constituted to provide scientific direction to the board
- Executive Director is responsible for overall coordination between the research clusters and the platforms; small Secretariat will provide administrative and communications support
- Research Management Committee (RMC) is comprised of representatives from research and technology platforms to ensure coordination of projects across centers and milestones achieved
- Research Clusters are to be regional or thematic and to consist of a leader and team of researchers (biologists, bioinformaticians, clinician scientists, surgeons, pathologists and technical experts)
- Technology Platforms are to be headed by leaders and closely linked to research programs and to focus on technology development and automation in order to develop increased capacity for research activities; funding based on scientific peer review by funders and inter-agency participation
- Commercialization Advisory Councils to be established in each jurisdiction to provide recommendations for developing commercial opportunities; commercialization managers in Canada and California would coordinate the process

RECOMMENDATIONS FOR THE WAY FORWARD

By the end of the workshop, participants reached a consensus on the way forward for developing the CSC Consortium. A natural division of labour fell into place where the researchers agreed to spearhead the development of the strategic plan, and the Canadian funders to secure funding and co-develop the RFAs, upon receipt of a strategic plan. The particular tasks for each group and the overarching recommendations from the workshop follow below.

Steering Committee Membership

- John Hassell was chosen as Interim Chair of the Steering Committee.
- Members of the Steering Committee will be chosen via a nomination process, facilitated by John Hassell. Workshop participants may nominate candidates from either Canada or California by April 23/08.

Initial Tasks of the Steering Committee

- Choose a leader of the Cancer Stem Cell Consortium Steering Committee.
- Review the proposed governance structure.
- Develop a strategic plan for September 2008 (consult background documents: Cancer Stem Cell Consortium paper submitted to Morris Rosenberg; Report on Canada-California Strategic Innovation Partnership Cancer Stem Cell Workshop; OICR templates; strategic plan to be used as basis for the RFA.)
- Provide clarity on the nature of the proposal (e.g., themes, single, multiple, program-like; tissue accrual as infrastructure, scientific method as matrix?).
- Develop working groups and schedule meetings.

Strategic Plan to Encompass

- Guidelines and principles of the Consortium
- Disease teams (five to seven biological nodes, both in Canada and California, responsible for live cell banking, genomics, screening, technologies etc.)
- Infrastructure, sample collection, data sharing policy

- Multi-year vision for how the Consortium would work together
- Plan for follow-up meetings

Offers of Assistance

Volunteers to help write the proposal

- Rhavi Bhatia City of Hope
- Connie Eaves British Columbia Cancer Research Agency
- Allen Eaves StemCell Technologies, Inc/BC Cancer Agency
- Peter Geary Canadian Tumour Repository Network
- Tom Hudson Ontario Institute for Cancer Research
- Jeanne Loring The Scripps Research Institute
- Thea Tlsty UC San Francisco

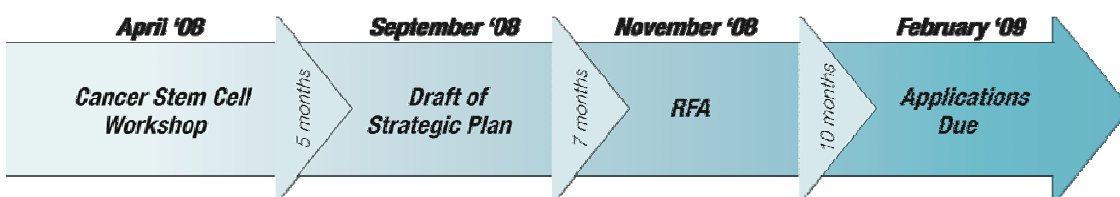
Organizations to help with training and administration

- CIRM (funding courses [e.g., growing ES cells])
- StemCell Technologies, Inc/BC Cancer Agency (software programs that keeps track of all procedures, SOPs, inventory system etc.)
- Health Canada (assistance with ethical and legal aspects of issues arising from emerging technologies [e.g., ethics, IP and biobanking])

Next Steps for the Funders

- Cindy Bell will coordinate with funders to move the project forward.
- Upon receipt of a first class strategic plan the Canadian funders will seek approval from their Boards to fund the CSC Consortium.
- Funders from Canada and California will meet and exchange memorandum of understanding, and clarify governance or other structures and mechanisms to advance collaborative research in the area of cancer stem cells.
- Funders will discuss a funding framework and elements of RFA, and finalize the details of the RFA once they have received the Strategic Plan.
- Funders will explore mechanisms to establish a joint peer-review process, and a process to monitor and report on progress once projects are funded. The initial opportunity to work collaboratively could be through CIRM's Disease Team Competition

Proposed Timelines



Topics for Inclusion in a Cancer Stem Cell Consortium

- Infrastructure
- Tissue accrual (annotated; include rapid autopsy)
- Personnel (pathologists, surgeons, medicinal chemists, etc.)
- Trainee exchanges among collaborating centers
- Specificity around tumor types
- Technology platforms
- Data management
- Assays/models (immunodeficient mice)
- Antibodies
- Resources
- Policies (publication; IP [e.g., OICR model])
- Generic consent that can be modulated

- SOPs
- Clinical outcomes
- Drug development
- Validation of molecular targets implicated in growth of cancer stem cells

Low Hanging Fruit

- Trainee exchanges between Canada-California postdocs
- CD44 very prognostic and proven to some extent but not yet in big cohorts
- Prognostic signatures in terms of tumor progression

Challenges and Concerns

- Convincing the funders that Canada and California can work together and that the collaboration is not 'contrived'
- Linking the funders from California and Canada
- Scale-up required for prognostic signatures (e.g., racial issues across populations)
- Working out governance system and funding mechanism that will work for both Canada and California
- Distinguish between short term deliverables (e.g., tissue accrual) and long term objectives
- Facilitate tissue accrual among best groups (avoid setting up 'silos')
- Address lack of resources that would facilitate connections among participants (those who do consenting and tissue collecting with those motivated to work on CSCs)

How to Ensure Success

- Develop common goals, infrastructure, objectives, IP, policy, consent, etc.
- Initially hone expertise and limit number of tumor types under investigation
- Build infrastructure for live cell banking (win-win situation)
- Guarantee open access of data
- Identify areas that cannot be tackled in either Canada or California alone
- Justify Canada-California collaboration
- Ensure that public funds are well spent (accountability)
- Focus on core activities that will have broader benefits (avoid short-term goals as milestones)
- Involve funders early on to liaise with government, raise funds, manage project, protect against complaints of partisan funding
- Concentrate on a few focused areas that are quantifiable and have the broadest impact
- Identify areas that can only be coordinated by large groups
- Take advantage of the scientific work already done when writing proposal (see background documents cited above)
- Ensure that RFA process invites full participation
- Promote sustainability within the Consortium
- Keep the momentum going!

CONCLUSION

John Hassell thanked the participants for their attendance and the organizing committee for their tireless efforts to push this stem cell initiative forward. He assured the funders that 'out of chaos comes clarity' and that in no way should they interpret the discourse during the workshop as lack of enthusiasm on the part of the scientists. The fact that a significant fraction of the published literature on cancer stem cells emanates from Canada and California bears witness to the pioneering spirit and solid commitment to stem cell research in these communities. As well, the technologies presented during the workshop had the participants 'positively salivating' over the potential for such innovative buttressing of the project.

Equally enthusiastic were the funders, eager for participants to choose a leader to drive the project forward, and counseling some speed with regards to the next steps given that the funding earmarked for the Consortium could not be held indefinitely. All in attendance agreed that

building a Cancer Stem Cell Consortium, which would facilitate and enhance collaborations between Canadian and Californian scientists, would be a unique opportunity that could not afford to be missed, that could significantly advance the field of stem cell research, and that could have far-reaching public health and economic benefits.

APPENDIX 1 – WORKSHOP AGENDA

**Cancer Stem Cell Workshop
April 17 – 18, 2008
Sheraton Gateway, Pearson Airport
Toronto, Ontario**

AGENDA

OVERALL GOALS

The principal goals of the workshop are to bring together all interested parties, including researchers, and representatives from funding agencies and industry, to identify important areas in the field of cancer stem cell research for investigation, and to discuss means of governing and funding a major initiative in this emerging field. Expected outcomes of the workshop are: the definition of priority research areas and the tools and resources required; clarity regarding the governance structure of a proposed Cancer Stem Cell Consortium; and possible mechanisms whereby funding for cancer stem cell research might be solicited, reviewed and granted.

CANCER STEM CELLS: A STATUS REPORT

DAY 1: THURSDAY, APRIL 17, 2008

The session will set the stage for the discussions to take place on Day 2. It will include a brief overview of the history leading up to the Workshop, a discussion of the goals of the Workshop, and an overview of the cancer stem cell field, including a description of the outstanding issues confronting the field and current barriers to research progress. The session will conclude with presentations on potential funding opportunities made possible through a Cancer Stem Cell Consortium.

- | | | |
|-------|---|---|
| 18:00 | Dinner
Welcome | John Hassell |
| 19:00 | Plenary Presentations <ul style="list-style-type: none"> • Rationale & Goals of the Workshop (10 min) • State of the Cancer Stem Cell Field (20 min) • Challenges Confronting the CSC Field (20 min) • Funding Mechanisms & Governance (30 min) | John Hassell (Moderator)
John Hassell
Irv Weismann
Catriona Jamieson
Martin Godbout, GC
Eliot Phillipson, CFI
Pierre Chartrand, CIHR
Patricia Olson, CIRM
Tom Hudson, OICR
Michael Rudnicki, SCN |

DAY 2: FRIDAY, APRIL 18, 2008

CANCER STEM CELLS: THE CHALLENGES AND OPPORTUNITIES

In this session participants will learn about the history of the cancer stem cell field, as well as some of the challenges and opportunities facing the cancer stem cell researcher. The emphasis of the presentations in this session will be on emerging technology platforms that could advance research progress in the cancer stem cell field.

- | | | |
|------|---------------------|--------------|
| 7:00 | Breakfast | |
| 8:00 | Outline for the Day | John Hassell |

8:05	History of the CSC Field and the Opportunities	John Dick
8:35	Short Presentations (10 min each)	Tom Hudson (Moderator)
	a. Live tumour cell banks	Clay Smith
	b. New tools in genomics	Marco Marra
	c. New tools in imaging in vivo	Mark Henkelman
	d. New tools in microfluidics	Carl Hansen
	e. Drug screening	David Kaplan
	f. Animal models	Robert Cardiff
	g. Clinical correlations	David Huntsman

CANCER STEM CELLS: POTENTIAL SOLUTIONS

Participants will join breakout groups to discuss cancer stem cell research topics with the objective of proposing means by which the field can be advanced. Each group will be charged with addressing the following questions:

1. What are the important research questions and deliverables in this area where large scale collaboration will be crucial to rapidly advancing the field?
2. What are the specific research approaches/plans that would best address these questions and generate these deliverables, and what local and/or national infrastructure would be required to support these goals?
3. What would be the most appropriate funding mechanism to support these plans, and what would be the best mechanism to manage and co-ordinate the research efforts?
4. What are the potential commercial outcomes and who are the likely partners?
5. Are there any major ethical, legal, social and/or regulatory impediments to moving forward, and if so, what are they?

9:50	Break-Out Groups: Charge for the Groups	Aled Edwards (Facilitator)
10:00	Health Break	
10:15	Break-Out Groups	
	Group 1 Clinical implications of CSC	Clay Smith
	Group 2 CSC Biology	Connie Eaves
	Group 3 CSC Genomics	Tom Hudson
	Group 4 CSC Therapeutics	John Hassell
	Group 5 Data Management	John McPherson
12:15	Lunch (Working if needed)	
13:00	Reports from Group Leaders (10 minutes each)	
14:00	Discussion	Aled Edwards (Facilitator)
16:00	Summary: Recommendations and Next Steps	John Hassell
16:30	Workshop Adjourns	

APPENDIX 2 – PARTICIPANT LIST

Cancer Stem Cell Workshop
April 17 – 18, 2008
 Sheraton Gateway, Pearson Airport
 Toronto, Ontario

PARTICIPANTS LIST

NAME	AFFILIATION
John Hassell – Workshop Chair	McMaster University
Laurie Ailles	University Health Network
David Andrews	McMaster University
Sam Aparicio	BCCA/UBC
Alain Beaudet	Fonds de la Recherche en Santé du Québec
Angela Beckett	British Columbia Cancer Research Agency
Cindy Bell	Genome Canada
Mickie Bhatia	McMaster University
Rhavi Bhatia	City of Hope
Alexander Borowsky	UC Davis
Josh Bowie	Industry Canada
Phil Branton	Canadian Institutes for Health Research / McGill University
Glenn Brimacombe	Association of Canadian Academic Healthcare Organizations
Ryan Brinkman	BCCA/UBC
Robert Cardiff	UC Davis
Maya Chaddah	Scientific Writing and Illustration
Pierre Chartrand	Canadian Institutes of Health Research
Melissa Cooper	University Health Network
John Dick	University Health Network
Peter Dirks	The Toronto Hospital for Sick Children
Allen Eaves	StemCell Technologies, Inc/BC Cancer Agency
Connie Eaves	British Columbia Cancer Research Agency

Aled Edwards	University of Toronto
Jian-Bing Fan	Illumina, Inc
Pasan Fernando	MDS Nordion
Jacques Galipeau	McGill University
Peter Geary	Canadian Tumour Repository Network
Carman Giacomantonio	Dalhousie University
John Gillard	Aegera
Martin Godbout	Genome Canada
Robin Hallett	McMaster University
Carl Hansen	University of British Columbia
Cal Harley	Geron
Chuck Hasel	Genome Canada
Mark Henkelmann	Hospital for Sick Children
Donna Hogge	BCCA/UBC
Cheryl Holden	Foreign Affairs and International Trade Canada
Thomas Hudson	Ontario Institute for Cancer Research
Keith Humphries	BCCA/UBC
David Huntsman	BCCA/UBC
Norman Iscove	University Health Network - Ontario Cancer Institute
Erica Jackson	Genentech
Kim Janda	The Scripps Research Institute
Catriona Jamieson	Moore's UCSD Cancer Center
Xiaoyan Jiang	BCCA/UBC
Steve Jones	BCCA/UBC
Michael Kahn	Keck School of Medicine, USC
David Kaplan	The Hospital for Sick Children
Melanie Kardel	British Columbia Cancer Research Agency
Aly Karsan	BCCA/UBC
Karen Kennedy	Genome Canada

Agnes V. Klein	Health Canada
Bartha Maria Knoppers	Université de Montréal
Antonija Kreso	University Health Network
Peter Lansdorp	BCCA/UBC
Patrick Lee	Dalhousie University
Stephane Lessard	Health Canada
Angus Livingstone	University-Industry Liaison Office, University of British Columbia
Jeanne Loring	The Scripps Research Institute
Drew Lyall	The Stem Cell Network
Jacques Magnan	Alberta Heritage Foundation for Medical Research
Marco Marra	BCCA/UBC
Sean McDermott	University Health Network
John McPherson	Ontario Institute for Cancer Research
Mark Minden	University Health Network - Ontario Cancer Institute
Jason Moffat	University of Toronto
Michael Morgan	Genome Canada
William Muller	McGill University
Ben Neel	University Health Network - Ontario Cancer Institute
Catherine O'Brien	University Health Network
Patricia Olson	California Institute for Regenerative Medicine
Francis Ouellette	Ontario Institute for Cancer Research
Morag Park	McGill University
Eliot Phillipson	Canada Foundation for Innovation
Lali Reddy	Consulate General of Canada in San Francisco
Michael Rudnicki	Sprott Centre for Stem Cell Research Ottawa Health Research Institute / Stem Cell Network
Guy Sauvageau	Université de Montréal
Babette Schade	McGill University
Carrie Shemanko	University of Calgary

Marianna Sikorska	National Research Council of Canada
Sheila Singh	McMaster University
Clay Smith	BCCA/UBC
Kristen Smith	The Hospital for Sick Children
Jocelyn Stewart	University Health Network - Ontario Cancer Institute
Bob Sutherland	Ontario Institute for Cancer Research
Dr. Alexey Terskikh	Burnham Institute for Medical Research
James Till	University of Toronto
Thea Tlsty	UC San Francisco
Alan Trounson	California Institute for Regenerative Medicine
Jac van Beek	Canada Foundation for Innovation
Peter Watson	BC Cancer Agency
Dan Wayner	National Research Council of Canada
Irv Weissman	Stanford University
Christine Williams	National Cancer Institute of Canada
Richard Wintle	The Hospital for Sick Children
Eldad Zacksenhaus	University Health Network