



ACADEMIC DEVELOPMENT MODEL FOR THE UNIVERSITY OF TORONTO BRAIN TUMOUR BANK

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1.0 Executive Summary



The University of Toronto Brain Tumour Bank (UofT BTB) is a new biobanking initiative made possible through the generous donation of \$2M by Dr Michael Dan. The UofT BTB will enable researchers in the U of T health sciences network to make more rapid progress towards effective treatment for people with brain cancer—progress



that will prolong and save tens of thousands of lives in Canada and around the world in the years ahead.

We are in an era of advances in

genomics, proteomics, diagnostic technologies, surgical techniques and pharmacology, leading to personalized therapies. The rapid and precise characterization of patient tumour tissue samples and individual patient tumour cells will soon be the new standard of diagnosis. Treatment plans based on this characterization will define the standard of care. We envision individualized molecular diagnosis and drug screening of every patient's brain tumour based on banking and systematic tissue analysis. The establishment of the UofT BTB—a coordinated, multi-institutional tumour tissue and cell resource—will be an important step in the development of these personalized therapies for brain cancer.

Personnel involved with this initiative will collect, store and study brain tumour tissue and cells from

every patient operated upon in the fully affiliated University Hospitals where Neurosurgery is performed. It is estimated that more than 1500 brain tumour specimens and related samples and cells will be banked making this the largest BTB effort of its kind in North America, and one of the most comprehensive in the world.

Brain tumours will be banked as frozen tissue, fresh live cell suspensions and primary patient tumour cell cultures. Through blood samples, we will also bank the patients' normal constitutional DNA, essential for defining true tumour driver alterations using next-generation sequencing. Data will be recorded in state-of-the-art databases using software programs that allow for seamless migration of data to the other investigators in the affiliated hospitals under research protocol driven, and research ethics board approved projects.

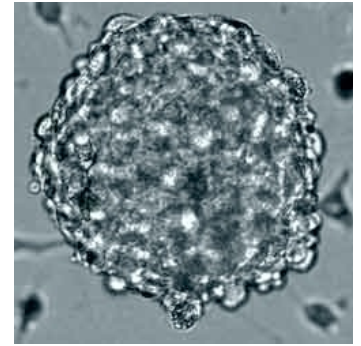


The generous gift from Dr Michael Dan will enable the UofT BTB to operationalize its activities over 5 years following which time, it is anticipated

that the effort will be fully fiscally sustainable through application of support from government research grants, and further private, philanthropic contributions and partnerships.

Executive summary (continued)

We will also explore commercial opportunities for revenue generation including the patenting of discoveries from brain tumour tissues, sales and delivery of specimens to academic health sciences centres where neuro-oncology research is performed, and the use of high-throughput chemical/drug screening of well characterized brain tumour cell lines or neurospheres/stem cells.



In addition to advancing research and the treatment of brain cancer, the establishment of the UofT BTB will be a major step towards the creation of a comprehensive and concerted biobank effort at UofT. As such, it represents a leading-edge initiative that will propel the Toronto Academic Health Sciences Network (TAHSN)—nine fully affiliated academic hospitals and research institutes and 18 community affiliated healthcare institutions, with the University at its centre—to the forefront of the biomedical sciences internationally.

2.0 Background and Situation Analysis

The number of cases of brain tumours treated at the U of T-affiliated hospitals represents an unparalleled opportunity to collect and study tissue samples. The volume of tumour specimens available to Toronto researchers through a single medical school and university exceeds that in other large cities where samples are divided among several schools and institutions. In the past year alone, more than 1500 patients underwent neurosurgical procedures for brain tumours at UofT making it the largest single institution in which brain tumour surgery is performed in North America. The opportunity to harness the magnitude of this resource and to implement change in neuro-oncology patient management provides the rationale for the creation of the UofT Brain Tumour Bank (BTB).

Although two Toronto hospitals, the Hospital for Sick Children (Sick Kids) and the Toronto Western Hospital (TWH) at the University Health Network (UHN), have created brain tumour banks to serve a select group of researchers, these efforts have not been systematic and have not been structured to advance personalized diagnosis and treatment. A city-wide, multi-institutional bank is therefore essential to realizing the goal of personalized molecular diagnosis and therapy for patients with brain tumours.

The proposed UofT BTB will build on the current repositories at Sick Kids and TWH and will also encompass samples collected from Sunnybrook Health Sciences Centre (SHSC) and St Michael's Hospital (SMH). Tissue and blood samples collected at the participating hospitals will be stored at those hospitals in their Department of Laboratory Medicine and Pathobiology (Division of Neuropathology) and logged into a common bio-informatics platform that is accessible to all institutions. Tissue samples will be made available to researchers at each site for inter-institutional studies following basic science and clinically-driven protocols approved by the Research Ethics Boards of each of the participating hospitals. Data collected from the research involving individual samples will be stored on the network with a communications system for researchers in labs across the Toronto network and beyond.

Background and Situation Analysis (continued)

The UofT BTB will provide research specimens to the the Arthur and Sonia Labatt Brain Tumour Research Centre at Sick Kids where state-of-the-art research laboratories exist for the study of the molecular biology of human brain tumours. The Labatt Centre is a joint academic venture between Sick Kids and the University UHN within UofT. The bank will provide investigators with frozen tissue for DNA and RNA analysis, and live

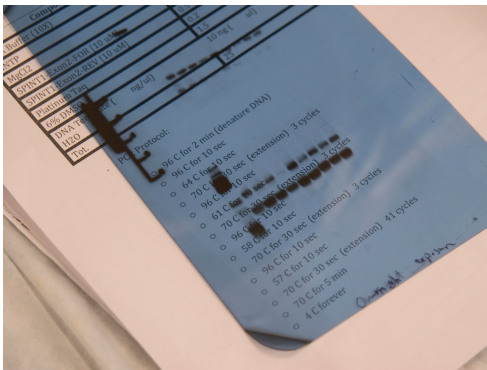


cell banking for cancer stem cell analysis and cell line establishment, with links to data on patient treatments and outcomes. In addition, where possible, blood for DNA analyses, cerebrospinal fluid, and other brain specimens may be banked at each affiliate hospital site. The UofT BTB will also enable specimens to be transferred between centres for clinicopathological research studies including tissue microarray (TMA) studies, immunohistochemical analyses, and cytogenetic testing using flourescein in situ hybridization, and comparative genomic hybridization analyses techniques.

Over time, as the number of samples grows, researchers will be able to determine the molecular differences between tumours that appear otherwise identical under the microscope. Based on this characterization, the most effective post-surgical drug therapies can be developed, tested and applied. With this knowledge clinicians will be able to biopsy or remove brain tumours, characterize them at the molecular level and ascertain the best treatment for that tumour. Ultimately, the patient's therapy will then be tailored to treatments targeted to the specific molecular and cellular attributes of their tumour.

There is agreement from each of the neurosurgery and neuropathology units at the four teaching hospitals where brain tumour surgeries are performed (SMH, SHSC, TWH and Sick Kids) to participate in and support this initiative. In addition, support is being provided by the Vice-Presidents Medical (VP-Medical) and Research Institute (RI) Directors at each partner hospital to co-operate in the management of tissue banking and transfer of materials for co-operative research studies.

Once established, the UofT BTB will become a resource for researchers and clinicians around the world,



providing a diagnostic characterization service for physicians seeking this information and recommendations for treatment of their patients. In the long term, as new knowledge, techniques and approaches emerge, the bank will serve as an invaluable source of well-characterized tumour samples, cell lines, stem cells, and molecular reagents (DNA, RNA, and protein) on which to conduct transformative research. Emerging therapies will then be tested against existing or conventional therapies to demonstrate superior efficacy. We are in an era where “personalized medicine” has become a reality for several cancer types. The UofT BTB has the distinct opportunity to extend this reality to patients with brain

tumours.

3.0 Project Outcome

3.1 Vision: Within five years, the UofT BTB will be the world's leading repository of highly annotated brain tumour and related specimens to drive precision diagnostics and personalized treatment for best outcomes in neuro-oncology.

3.2 Mission Statement: We are an academic community of physicians, surgeons, and researchers who are dedicated to working together towards identifying novel and improved treatments for patients with brain tumours. This can only be accomplished through the meticulous study of large numbers of specimens from various brain tumour types. The UofT BTB offers the unique opportunity for multi-disciplinary, and multi-institutional collaboration to achieve this goal.

3.3 Goals, Objectives and Outcomes: The overarching goal of the UofT BTB is to co-ordinate the efforts of banking of brain tumour and related specimens at each of the University affiliated institutions where neurosurgery is performed so that state-of-the-art research can be performed on these specimens leading to new discoveries, and potentially new treatments for patients with brain tumours. The main Objective is to capture data and specimens from every patient undergoing brain tumour surgery within the University of Toronto – some 1500 or more occurrences each year. Metrics will include: 1) Number of patients entered into the UofT BTB database annually; 2) Number of REB-driven research proposals for which shared specimens are required annually; 3) Number of signed TAHSN material transfer agreements related to the UofT BTB annually; 4) Number of UofT BTB specimens requested by institutions outside the UofT TAHSN system annually; 5) Number of peer-reviewed scientific research studies published annually in which specimens from the UofT BTB were utilized; 6) Number and funding amounts of operating grants received annually which are dependent on UofT BTB specimens; 7) Annual number of grants and scientific publications which demonstrate evidence of collaboration of investigators across the TAHSN hospitals as a direct result of the UofT BTB initiative; 8) Number of commercialization and patent opportunities that arise as a direct result of materials housed within the UofT BTB annually; 9) Revenues derived from commercialization and patent opportunities at 5 years; 10) Establishment of viable BTB repositories at all sites complete with capital equipment and personnel to maintain each site; and 11) Transition to sustainable business model for the UofT BTB at 5 years.

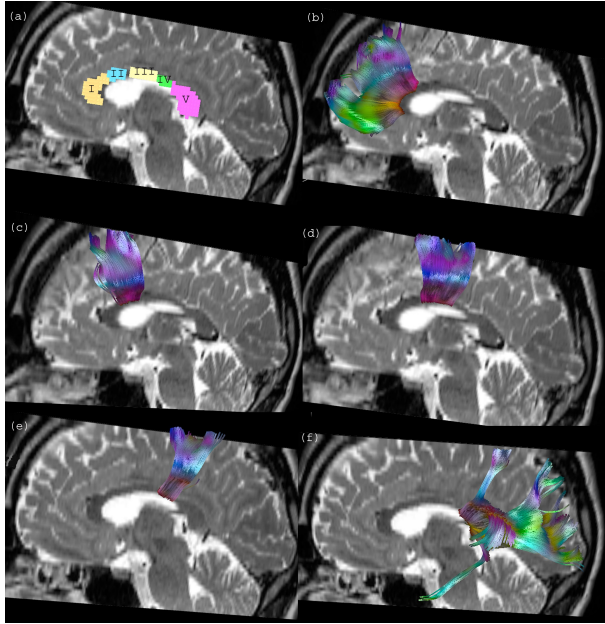
3.4 Scope of Project: The UofT BTB is a two phase project. In Phase I, lasting 5 years, funds from the initial \$2 Million endowment will be used to streamline cross-hospital collaborations, purchase liquid nitrogen storage tanks and freezers, develop and implement a robust data banking computational platform for storing patient/tissue information, and to hire personnel to operationalize the banking system across the TAHSN system. In Phase II, the UofT BTB will evolve to a sustainable business model in which core operating grants, support from industry and commercialization efforts, and assistance from each of the TAHSN institutions (Sick Kids, TWH, SMH, and SHSC) will ensure the longterm viability of this unique and invaluable resource for UofT and the world.

Banking of specimens will be accompanied by advanced database capabilities that allow for longitudinal tracking of key patient demographics including age, gender, date of surgery, neuropathological diagnosis, neuroimaging data, adjuvant treatments such as chemotherapy and radiation therapy, disease free and overall survival data points.



Project Outcome (continued)

The database software platform will be uniform across all institutions facilitating the ease of merging information and generating reports. Banked specimens will be made available to research investigators at a given institution upon request from other institutions following ethics approval of the proposed research studies.



A unified ethics approved Toronto Academic Health Sciences Network (TAHSN) Materials Transfer Agreement (MTA) [Appendix] will facilitate the transfer of specimens between institutions. Patient confidentiality will be strictly guarded through de-identification of data within the database, and coding practices that protect patient rights and preserve anonymity. Such patient confidentiality protection will be standardized across all institutions.

Ultimately, the scope of the UofT BTB will be to set the goal of capturing data and relevant tumours specimens from all patients (approximately 1500 patients annually) undergoing surgery at the four main affiliated hospitals where neurosurgery is performed. This tremendous resource will be the catalyst for cross-institutional collaboration, and shared authorship on and credit for scholarly publications and grants that arise through this effort.

3.5 Project Management: Inherent in the hiring process will be the recruitment of Project Manager (PM) whose role will be to co-ordinate all aspects of the management of the UofT BTB, and to assist the physicians, surgeons, research investigators and technicians in raising the requisite funds through peer-reviewed grants, application to industry, and commercialization opportunities to ensure the fiscal viability of the initiative at 5 years.

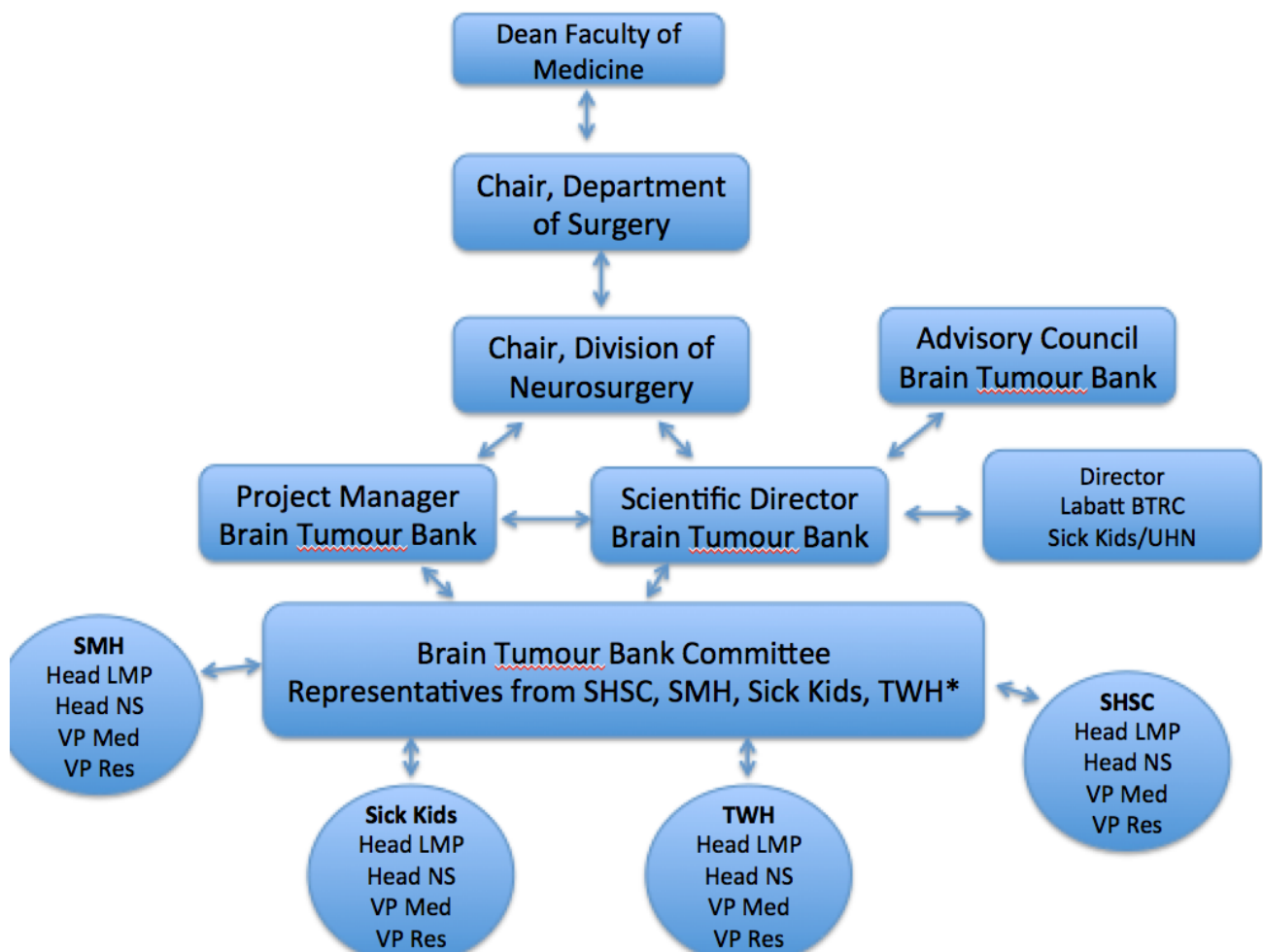
A Scientific Director (SD) will be appointed to provide oversight of the UofT BTB and to spearhead numerous investigator-driven studies based on reports from the BTB database enumerating the tumours available for study. The SD will also be responsible for biobanking best practices, and quality control at each site through frequent review of reports from each institution.

The PM and SD will meet monthly to review the goals of the UofT BTB, and to identify opportunities, as they arise, for grant applications, commercialization of products, and ease of transfer of specimens between TAHSN institutions and beyond.

Project Outcome (continued)

3.6 Governance Structure (also see Appendix):

There will be a UofT BTB Committee comprised of representatives (neurosurgeons and neuropathologists) from SMH, Sick Kids, TWH, and SBHSC. They will be supported by Heads of the Neuropathology Divisions, the VP Medical Affairs and the VP of the Research Institutes (RI's) at each partner hospital. An Advisory Council will provide timely information and suggestions to the UofT BTB Committee, and to the SD. The SD and PM will have frequent exchanges, and will report directly to the Chair of the Division of Neurosurgery, who will report to the Chair of the Department of Surgery, who will report to the Dean of the Faculty of Medicine at UofT.



*1 Neurosurgeon + 1 Neuropathologist/site

4.0 Financial Analysis

4.1 Infrastructure Analysis: BTB's already exist at Sick Kids in the Labatt Centre, and at TWH. These are funded through the Division of Neurosurgery at TWH, and the Cancer Program and the Labatt BTRC at Sick Kids. These two BTB's are characterized by state-of-the-art storage facilities in liquid nitrogen, and -80 C freezer space. Liquid nitrogen replenishment costs are currently provided by these two institutions. These two biobanks have separate information technology (IT) databank software systems. Currently, there are no BTB's at SMH or SHSC; however, each of these institutions has the capacity to house frozen tissues with liquid nitrogen in a vicinity close to the Departments of Laboratory Medicine and Pathobiology at these sites.



The UofT BTB proposal has been capitalized through the generous \$2M gift by Dr Michael Dan. This \$2M fund will be kept in an account in the Department of Surgery in the Faculty of Medicine at UofT. UofT BTB institutions will make purchases through hospital cost centres, and then invoice the amount to the UofT BTB fund held in the Department of Surgery, through the PM for subsequent reimbursement. In addition, salaries paid to individuals who are hired to manage the various BTBs will be paid for by the account in the FoM upon receipt of an invoice. These individuals will be hospital (institutional) employees, and will accrue benefits according to the practices and rates at that hospital.

4.2 Cost and Benefit Analysis (see detailed budget below): As the infrastructure for the BTB already exists at two sites (TWH and Sick Kids), the establishment of two further BTB's at SMH and SHSC will now be established. These two new BTB's will use the Standard Operating Procedures (SOPs) already established at TWH and Sick Kids to process brain tumour specimens, and to log new entries into a database system. There will be a cost to the purchase of a robust database system that is all inclusive enabling entry of clinicopathological data, storage information, neuroimaging data, and patient follow-up information including disease free and overall survival data. Each site will use the same database system, but information will be kept on site for future usage by other group members in other institutions through agreed upon research protocols. All clinical information will be de-identified to protect patient safety and health issues.



The true benefit of the UofT BTB proposal is the opportunity to capture virtually every brain tumour specimen for storage in state-of-the-art facilities for subsequent analysis by UofT researchers and investigators. In this model, the separate institutions have the autonomy to store their own specimens, track specimens and patient data in their own institutions and under their own IT domains, and yet have the opportunity to share specimens as required for research-driven ethics approved proposals.

Financial Analysis (continued)

Other benefits include the opportunities to collaborate with investigators from other UofT Hospital Affiliated Institutions in a manner which has not yet been accomplished, and to share in authorship on peer-reviewed publications and grants. Additional benefits include the opportunity to provide high quality brain tumour tissues to investigators and collaborators outside of Toronto, Canada, and North America.

4.3 Costs: The main costs of the UofT BTB proposal include the purchase of start-up equipment at different sites, the acquisition of a state-of-the-art brain tumour banking database program that permits multi-user applications, the processing of tissues and cell lines, and other molecular genetic tests as needed. In addition, salaries will be paid to the local brain tumour bank managers, as well as to the PM. Accordingly, the costs of the UofT BTB proposal can be estimated as follows, remembering that two sites, Sick Kids and TWH, already have BTB's in existence and functioning very well.

4.4 Summary of Costs

Revenues	Year 1	Year 2	Year 3	Year 4	Year 5
Dr. Michael Dan Gift	526,000	400,000	400,000	400,000	200,000
Total Revenue*	526,000	400,000*	400,000*	400,000*	200,000*

* - Additional Revenue streams will be developed and will include sources such as Patents; Commercialization IP/ copyright; and Advancement.

Expenses

Human Resources *

Citywide Manager	62,608	63,547	64,500	65,468	66,450
Research Technicians	110,000	112,750	115,569	118,458	60,710
Benefits (@24.75%)	42,720	43,633	44,567	45,521	31,472
Total HR Costs	215,328	219,930	224,636	229,447	158,632

Equipment

2 X -80°C freezers	24,000	0	0	0	0
2 X Biosafety cabinets	30,000	0	0	0	0
Robotic dispensers	50,000	0	0	0	0
Computer hardware	22,000	0	0	0	0
Warranties and Repairs	15,120	15,271	15,424	15,578	7,867
Total Equipment Costs	141,120	15,271	15,424	15,578	7,867

Expendables **

Liquid Nitrogen Storage	13,000	13,130	13,261	13,394	6,765
Blood Collection and processing	20,000	20,200	20,402	20,606	10,406
Tumour Collection and processing	20,000	20,200	20,402	20,606	10,406
Reagents	30,000	30,300	30,603	30,909	15,609
SNP arrays	57,000	57,570	58,146	58,727	29,657
Gene expression arrays	60,000	60,600	61,206	61,818	31,219
Total Expendables Costs	200,000	202,000	204,020	206,060	104,060

TOTAL EXPENSES

556,448 437,201 444,080 451,085 270,559

Revenues - Expenses	(30,448)	(37,201)	(44,080)	(51,085)	(70,559)
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* - HR adjusted to Inflation and Cost of Living at 2.5% per annum ** - Expendables adjusted for inflation at 1.0% per annum

5.0 Implementation Strategy

The gift from the Donor for the UofT BTB, and the presence of infrastructure with standard operating procedures at two sites (Sick Kids and TWH) will ensure a swift implementation of the UofT BTB vision and goals at the other two sites (SMH and SHSC) to establish the initiative. The following individuals will be involved in the implementation strategy:

Project Sponsor = Dr Michael Dan

Change Champion = SD, Dr Peter Dirks, Sick Kids Hospital, Division of Neurosurgery; Gelareh Zadeh, Toronto Western Hospital, Division of Neurosurgery

Project Manager = PM, Mr. James Loukides, Sick Kids employee, with an office in the Labatt Centre.

UofT BTB Committee = Dr Todd Mainprize (Neurosurgery, SHSC) and Julia Keith (Neuropathology SHSC); Sunit Das (Neurosurgery, SMH) and David Munoz (Neuropathology, SMH); Gelareh Zadeh (Neurosurgery, TWH) and Sidney Croul (Neuropathology); and Michael Taylor (Neurosurgery, Sick Kids) and Cynthia Hawkins (Neuropathology).

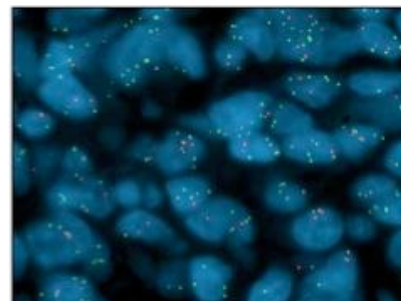
Research Technicians = James Loukides (Labatt BTRC/Sick Kids); Jennifer Glenn (TWH); To be named, SMH; and to be named, SBHSC.

UofT Division Chair of Neurosurgery = Dr Andres Lozano

Department of Surgery Chair = Dr James Rutka

Dean Faculty of Medicine = Dean Catharine Whiteside

Advisory Board = Dr Michael Dan, Dr Alan Hudson, Dr John Wedge, Mr Joe Wiley (Birch Hill Equity), Dr Charles Tator, Ms Elizabeth Peeters (BRAINchild), Dr Richard Hegele (UofT), Dr. Peter Dirks (ex-officio); and Dr Gelareh Zadeh (ex-officio).



5.1 *Organizational Structure* (see Governance Structure):

The UofT BTB Committee members will receive site-specific advice regarding best practices of tissue/tumor banking from the VPs Medical, VPs Research, and the Heads of the Neuropathology Divisions. This Committee will meet quarterly to review data in each BTB, and to suggest possible research projects of interest depending on the accrual of specific brain tumour specimens.

Implementation Strategy (continued)

The SD will be an ex-officio member of the UofT BTB Committee, and will be the change agent to identify opportunities for peer-reviewed grant submissions as a core facility (e.g. Terry Fox New Frontiers grants), provide insight into new research proposals, and to work with the ED towards commercialization of patents or discoveries that emanate from the banked specimens, cell lines, or neurospheres. The SD will report to the Chair of the Division of Neurosurgery (Andres Lozano), and will receive advice and input from the Advisory Board of the UofT BTB on a semi-annual basis.



The PM will provide day-to-day oversight of the UofT BTB, and will be responsible for ensuring that best practices of tumor banking are being followed at each site; that the funds from the account in the FoM at UofT to support the infrastructure and personnel in the institutions are being used judiciously and discriminately; that the REB approvals at each site are kept up-to-date along with the MTA's for exchange of tissues; and that efforts are made to ensure the financial sustainability of the UofT BTB beyond the first 5 years. The PM will report to the SD, and to the Chair of the Division of Neurosurgery.

5.2 Project Metrics: Items to be accounted for each year of the first 5 years will include, but not be limited to, the following:

- a) Number of brain tumour and other specimens banked each year
- b) Number of peer reviewed publications in which banked specimens were used
- c) Number of funded grants on which UofT BTB specimens are used
- d) Number of patents derived from materials within the UofT BTB system
- e) Amount of funding through commercialization or discovery projects
- f) Amount of funding through sales of UofT BTB materials to other centres

5.3 Project Budget: As described above under “Costs” of the UofT BTB initiative, the budget for the project is approximately \$400K/year for each of the first 5 years with upfront costs of purchasing storage facility equipment, computers and software programs the first year. This budget is an estimate of revenues and expenditures from the initial capitalization of \$2M by the Donor. The intent of this project, however, is to become a self sustaining BTB within 5 years (see below).

Implementation Strategy (continued)

5.4 Stakeholders Communications and Recognition Plan: The Stakeholders for the UofT BTB can be listed as follows: i) the Donor; ii) the Neuro-oncology community at UofT, and at large; iii) TAHSN biobanking initiative personnel; iv) VPs Medical, VPs Research, and Division Heads Neuropathology at each hospital site; v) UofT BTB Advisory Board.

An annual report delineating the progress and milestones of the UofT BTB will be generated, and distributed to the Stakeholders listed above. The largest constituency will be the Neuro-Oncology community at large, and these individuals (approximately 500 persons) have already been identified through the list-serv of the Labatt Centre.

Recognition for the Donor will be accomplished at each site with a plaque commemorating the onset and location of the individual UofT BTB's. In addition, a Donor-specific Annual Report will be prepared by the Chair of the Division of Neurosurgery.

5.5 Risk Management: Risk management issues relate to the transfer of human specimens and clinical data on these patients between institutions. Fortunately, there is already a system in place to exchange tissues between Sick Kids, TWH, and SMH. Therefore, there is a precedent in place, and an opportunity to use this to incorporate SBHSC in the process. A generic TAHSN material transfer agreement form has been generated to be used to facilitate the transfer of the aforementioned specimens. In general terms, any clinical data transferred between sites will be de-identified so as to maintain patient confidentiality. All exchange of specimens between sites will be research project-driven, and ethics approved.

It is the intention of this proposal that the UofT BTB be fully sustainable by the end of the 5th year. It is our strong belief that the U of T BTB will also provide increasing value over time. Once established, the bank will be sustained in the long term by government research grants and new philanthropic support. We will also explore the implementation of revenue-generating services, including:

- Fees charged to external investigators for retrieval and usage of specimens;
- Revenue from contracts with specific external academic institutions;
- High-throughput drug and chemical screens of tumour samples sent from outside institutions; and
- Provision of tissue and cell culture samples to industry partners.
- Creation of a digital library of brain tumours for education and teaching purposes.

Researchers and pharmaceutical companies will be able to purchase cell lines, vectors, reagents, neurosphere cultures and tissue micro-arrays linked to clinical data. Other commercial opportunities are likely to emerge as the number of samples grows and more data become available. These services will be a source of revenue to help sustain the bank in perpetuity.



6.0 APPENDICES

- 1) Governance Reporting Structure
- 2) Glossary of Terms
- 3) Timeline, with milestones
- 4) TAHSN Generic biospecimen material transfer agreement form
- 5) Research Ethics Board Application form (e.g. Sick Kids) to support brain tumour banking
- 6) Brain tumour tissue assent and consent forms (Sick Kids)