



Practical Aspects of Tumour Banking

Workshop #8
Lois Shepherd
August 22, 2013



Objectives

- To understand the elements of successful biobanks associated with clinical trials, their governance and required operating procedures
- To understand and find solutions for problems encountered in tumour banking associated with clinical trials
- To appreciate current challenges and opportunities in biobanking
- To be aware of current national resources for tumour banking

A Little History... Who are we?

 A Pan-Canadian Cooperative Clinical Trials Group

- Since 1980, the CTG has been conducting Phase I,II, III national, international, and intergroup trials in most adult cancers exploring:

- Novel therapies
- Comparative Effectiveness
- Adverse Event profiles
- Quality of Life
- Health economics
- Translational research

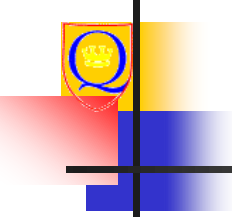
2500 - 4000 patients /year accrued



- 1991 NCIC CTG - Terry Fox Workshop
held at Far Hills Inn
- Initiative to bring together basic and clinical scientist, statisticians, epidemiologists, funders to explore the concept of tumour banking for future research purposes
- NCIC disease specific tumour bank support ultimately resulted



- 1997 the first Correlative Science/ Tumour Bank Committee was convened
- A decision taken to prospectively consider the inclusion of banking diagnostic FFPE tissue on all new Phase III trials
- Some financial support also available to retrospectively bank tissue on older studies



As a result the NCIC CTG has created...

- A national resource of clinical trial associated FFPE diagnostic material from many disease sites - breast, lung, colon, pancreas, ovary, prostate, endometrium, CNS
- A frozen tissue bank of NSCLC
- Virtual frozen breast bank
- Serum, plasma , urine, DNA, CTCs, bone marrow on a growing number of studies

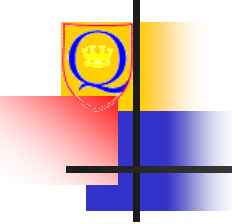


What is the TTDR?

A national resource associated with the NCIC Clinical Trials Group to facilitate research

- **Tumour** collected in the context of a clinical trial
- **Tissue** (whole blood, plasma, serum, urine, bone marrow, circulating tumour cells)
- **Data** – well described and validated clinical data including demographic information, patient and disease characteristics, therapy, outcome measures, adverse event profiles

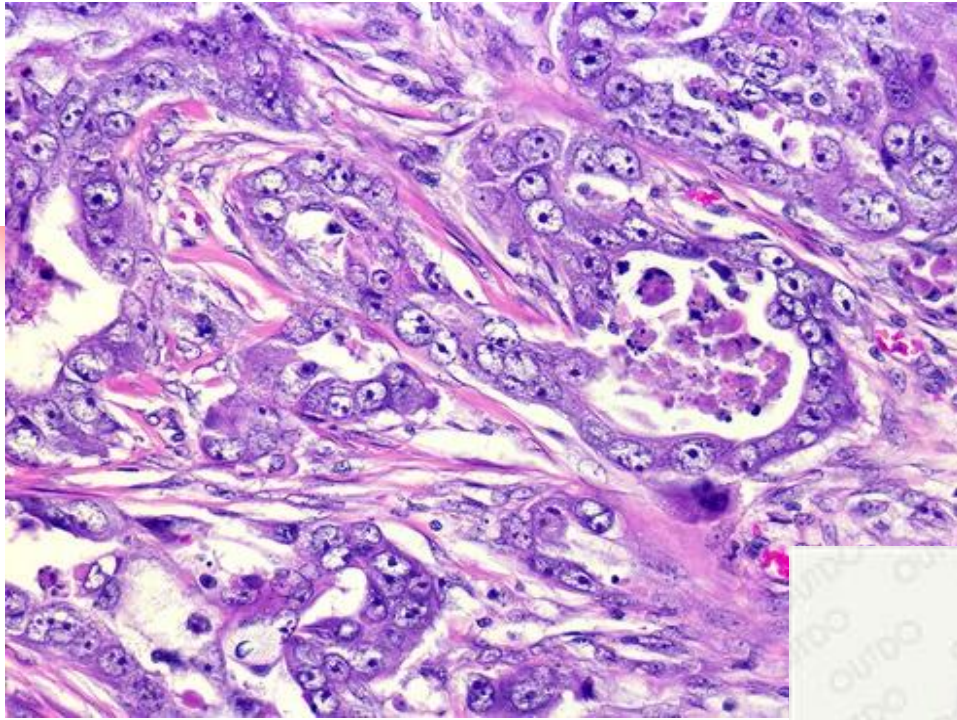
In the context of a clinical trial...

- 
- Tumour +/- or tissue is collected as an **integral** part of the study (k-ras in BR.10 for stratification, HER2 in MA.34 for eligibility)
 - Tumour +/- or tissue collection is **integrated** into a trial to answer specific study questions (insulin/glucose levels on an adjuvant metformin trial – MA.32)
 - Tumour +/- or tissue collected prospectively for **future research questions** -



Material collected since 1997

Specimen type	Number patients	Number samples
Blocks/slides	16548	31969/67803
Whole blood	9385	35356
Plasma	8594	77098
Serum	17316	82209
Urine	582	3601



Growing number of
Derivatives:

- TMAs
- DNA
- RNA
- CTCs
- Circulating DNA



Required Operational Practices for a Tumour Bank ... ROPs



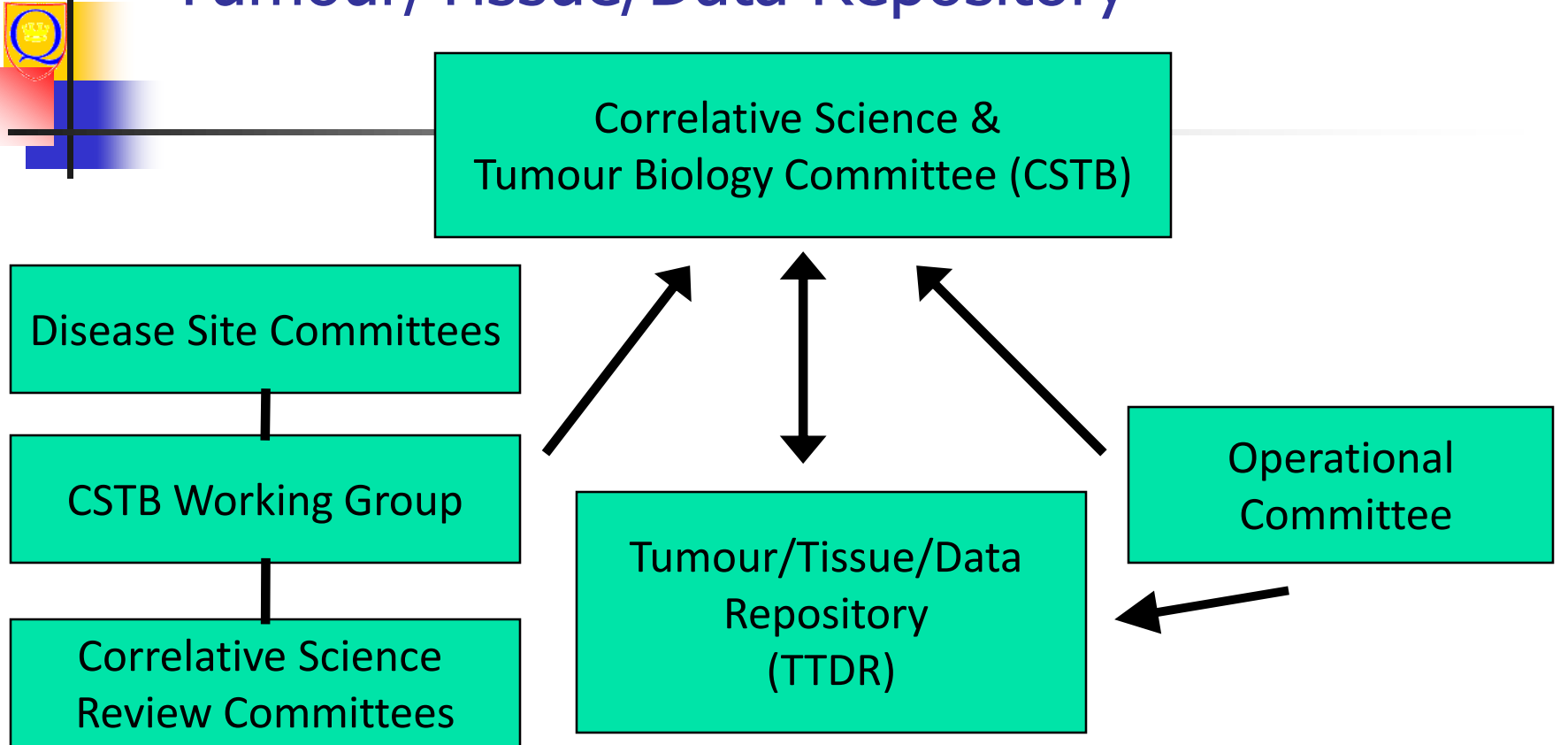
- Governance
- Privacy and Security
- Ethics
- Consent
- Access and Release
- Quality management system and process improvement
- Education and Training
- Data systems and Record management



ROPs continued:

- Biospecimen collection and Processing
- Biospecimen Storage and Retrieval
- Storage Equipment
- Facility Design and Security
- Safety and Waste disposal
- Disaster Planning

Correlative Sciences/Tumour Biology Tumour/Tissue/Data Repository



**External
Scientific Agenda**

**Internal Central Office
Ethics/Regulatory
Data Management/Operational**



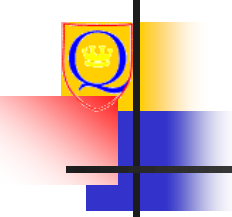
Facilities: Department of Pathology and Molecular Medicine, Queen's University

- Administrative Office, data management
- Receipt, logging and tracking of samples
- Inventory Management Tracking system
- Storage for paraffin embedded formalin fixed material
- 4°C refrigerator/cold room storage for cut sections
- -80°C freezers for plasma, serum, urines, derived products



Facilities: Department of Pathology and Molecular Medicine, Queen's University

- Histological services for cutting and routine H&E staining of sections for quality assurance and digital imaging
- Tissue microarray facility
- Whole section (Aperio) digital imaging and archival facility with web based access
 - Review on line
 - Annotations
 - Marking for TMA construction



Additional On-Site Services

- Automated Immunohistochemistry:
Qualitative and Quantitative - AQUA
- DNA/RNA extraction and associated
quality assurance
- Cytogenetics, FISH, molecular diagnostic
services
- Ariol imaging system
- Genome Sequencing
- Gene expression profiling platforms
- Laser Capture microdissection

Quality Assurance



Standard Operating Procedures/Training as per ISBER guidelines and CTRNet (CIHR funded Canadian Network of Tissue Banks)

- H&E review and annotation of material received
- Quality control on all derived products
- Digital Imaging and on-line review of whole sections and TMAs
- Well defined protocols for collection, timing, processing, shipping, and storage conditions
- Inventory management and tracking systems

TTDR Database



User: LYNE - [NCIC CTG Correlative Sciences / Tumour Bank Main Menu]

Window

NCIC CTG Correlative Sciences and Tumour Bank

Patient Information	Letters	TMA Listing
Sample Information	Request Letters	Generate TMA Listing
Patient List	New Request Letters (TESTING)	Slide Cutting
Inventory List	Return Letter	Slide Cutting Worksheet
Report		Review/Analysis Listing
Received Report		Generate Review Analysis Listing
Report		Review/Analysis Letter
Received Status Report		Review/Analysis List Report
Hospital Information		Report
Trial Information		Review/Analysis List (NEW)
		Exit

User: LYNE - [NCIC CTG Correlative Sciences / Tumour Bank Patient Information]

Action Edit Query Block Record Field Window Help

Pt. Info. Letters Slides TMA Sent Out

Patient Information

Trial Code:
 Case ID:
 Tumour Bank ID:
 Sample Collection Date:
 Hospital:
 Reporting Pathologist:
 Accession #:
 Pathology Form Received?
 Tissue Type: Specimen Type: Timing:
 Request Sample?
 Sample Received Date: Sample Received:
 Payment Form Received: Payment Form Sent to CTG Date:

Inventory

Samples:

Unstained Slides:

H&E Slides:

Special Stained Slides:

Labels	Tissue Received				Tissue Returned				Special Slides Description	Location	Requires Re-embedding?	Embed Date	Adequate Tissue?
	Y/N	Date	# Samples	Un-stained Slides	H&E Slides	Special Slides	Date	Num Samples					

Comments

Confidentiality



De-identification of tissue

- All samples received are assigned a unique Tumour Bank ID
- Link is in the TTDR/PCO/Statistical support
- Samples released to investigators are only identified by the unique TBID
- Bioassay results are returned to the CTG for correlation as specified in a predefined Statistical Analysis Plan

Design Considerations for Biomarker Studies !!



**There are 89
frozen specimens
available.**



Access to Samples for Correlative Studies

- Appropriate research hypothesis, study design and statistical consideration
- Proven investigator experience with methodology
- Budget for sample preparation, shipping and funding for research
- Ethics approval
- Statistical analyses to be conducted by the CTG or in collaboration with CTG statistical centre
- Investigator Agreement to be signed before the release of tissue - MTA



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Correlative Science / Tumour Bank

The NCIC Clinical Trials Group (NCIC CTG) established the Tumour Tissue Data Repository (TTDR) in 1997 to support Correlative Science with the assistance of Rhone Poulenc Rorer (now Sanofi-Aventis). The NCIC CTGTTDR contains unique disease specific collections which are linked to an associated clinical dataset. This represents a "real" tumour bank in that tissue is collected from institutions across Canada and the world, catalogued and housed centrally in the Department of Pathology and Molecular Medicine at Queen's University.

Our Mission

To establish a collection of specimens stored in house and linked with clinical trials dataset. Access to this tissue permits the assessment of prognostic factors in determining the outcome of disease, the assessment of predictive factors to various chemotherapeutic agents and treatment regimens, and to facilitate the understanding of the basic biological and genetic mechanisms of cancer.

Profile

The NCIC CTG TTDR has taken part in collection of tissue for over 120 clinical trials. The central coordinating office for the Bank is located in Kingston, Ontario. Participating centres include cancer care organizations, academic health science centres, community hospitals, and smaller individual practices. These centres were initially in Canada but more recently samples have been collected worldwide.



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What is the process for the release of banked tissue?

The Correlative Sciences Disease Site Specific Review Committees of the CTG have established a scientific review process for all requests. A well-defined concept and protocol describing the research project, hypothesis, underlying scientific premise, rationale for access to a particular trial material, and statistical considerations must be provided. Adequate funding must be sought or received. REB (Ethics) approval for the project at the site where the research will be conducted must be in place. Analysis of assay results is conducted by the statistical center of the NCIC CTG.

To [apply](#) for tissue access, please complete the form below:

[Application for tissue research.](#)

Who reviews application for material access?

Several Disease Site Specific Review Committees have been setup to review requests for disease site specific collections. These committees include the Central Office Physician for the disease site, the Disease Site Chair, the Chairs of Studies on which material is being requested (as needed), 1-2 Pathologists, 1-2 Clinical/Basic Scientists, a Central Office Statistician, and Tumour Banking [personnel](#).

Requests for material in the Bank are reviewed 4-6 times a year. All requests will be considered and will be evaluated on the basis of the science involved and the value inherent in the use of clinical trials related material.

Tissue de-identification

Material (tissue blocks, slides, serum, plasma etc.) is received at the NCIC CTG Tumour Bank from the originating institution labeled with pathology accession number and occasionally with other local identifiers. Upon receipt of the material, it is logged by our pathology coordinator and assigned a unique tumour bank ID number. The tumour bank maintains a database with patient information such as NCIC CTG ID number, patient initials, pathology accession number and Tumour Bank ID Number.

Local accession numbers and other unique identifiers are retained in the database at the bank to ensure that blocks can be returned to the pathology department of origin on request.

The value of the NCIC CTG tumour bank lies in our ability to link results of correlative studies to an extensive clinical database. However, in order to preserve patient confidentiality, patient identifiers are not provided to researchers accessing the material.

Material from the bank may be requested for research use, following the policy we have developed for requesting such specimens. Once a project has been approved, pathologic material is released to the researcher, and leaves the bank identified by the unique Tumour bank ID number.

Results of correlative studies are returned by the researcher to our central office for analysis, with individual patient results identified by tumour bank ID. Correlation with the clinical database can take place once the correlative study data is linked via the tumour bank ID number to data in our clinical database, by CTG biostatisticians.

What materials are available?

NCIC Clinical Trials Group - Tumour Bank

Logged in as: Public

Location: [Home](#) - [Disease Sites](#) - [BREAST](#) - MA21

MA21 Details

Status: Closed

Activation Date: 2000DEC04

Closing Date: 2005APR29

Phase: III

Description: A Phase III Adjuvant Trial of Sequenced EC + Filgrastim + Epoetin Alfa Followed by Paclitaxel Versus Sequenced AC Followed by Paclitaxel Versus CEF as Therapy for Premenopausal Women and Early Postmenopausal Women Who Have Had Potentially Curative Surgery for Node Positive or High Risk Node Negative Breast Cancer

Eligibility: Women with histologically confirmed adenocarcinoma of the breast treated with either total or partial mastectomy; node positive or high risk node negative; T0-T4, N0, N1, or N2, M0; ER status must be known; < 60 years of age; no prior chemotherapy, hormonal therapy, immunotherapy or radiotherapy for breast cancer; adequate blood counts; ECOG < 2; LVEF > institutional lower normal limit; no history of cardiac disease.

Objective: To compare disease-free survival and overall survival among the three treatment arms. To compare rate of toxicities and quality of life among the three treatment arms.

Participation: Not Limited

Lay Description: The purpose of this study is to compare the effects (on you and your breast cancer) of three different combinations of drugs which are commonly used to treat this disease. If you are randomized to Group 1 you will receive three commonly-used chemotherapy drugs called cyclophosphamide, epirubicin and 5 fluorouracil. If you are randomized to Group 2 you will receive three commonly-used chemotherapy drugs called cyclophosphamide, epirubicin and paclitaxel. If you are randomized to Group 3 you will receive three commonly-used chemotherapy drugs called doxorubicin, cyclophosphamide and paclitaxel. This research is being done because currently we do not know which of these three combinations of drugs is better than the others.

Publications [Show](#)

Inventory

[Hide Tissue Samples](#)

Disease Site	Trial Code	Patients Accrued	Patients - Blocks	Patients - Slides	Patients - Blocks and/or Slides
BREAST	MA21	2104	1186	1377	1474

[Hide TMA Samples](#)

(Core size is 0.6 mm)

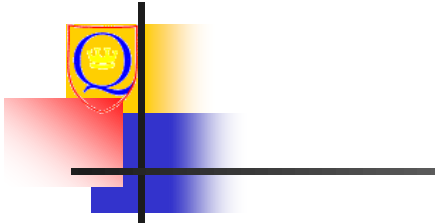
Disease Site	Trial Code	Patients Accrued	TMA Blocks	Patients on TMA Blocks
BREAST	MA21	2104	27	1079

[Hide Fluid Samples](#)

Disease Site	Trial Code	Patients Accrued	Patients - Whole Blood	Patients - Cellular Component of Blood	Patients - DNA extracted from Blood	Patients - RNA extracted from Blood	Patients - Plasma	Patients - Serum	Patients - Urine	Patients - Buccal
BREAST	MA21	2104	0	0	0	0	0	0	0	0

NCIC CTG Tumour/Tissue/Data Bank

Application for Tumour/Tissue/Serum for Research Purposes



Application Date:

Title of Proposed Project:

Principal Investigator Name:

(first, middle, last name)

Investigator's Title:

Primary Mailing Address:

Telephone:

Fax Number:

E-Mail:

Contact Person Name:

(e.g. administrative assistant)

Telephone:

E-Mail:

Summary of research proposal *(Please attach a separate 3-4 page document describing details of the following):*

- Introduction
- Hypothesis
- Study Objectives
- Background & Preliminary Data
- Methods
- Statistical Design
- Significance of Research
- Rationale for Access to clinical trial(s) materials

Type and Amount of Material Requested:

NCIC CTG Trial:

Paraffin embedded material:

Unstained sections: Number of cases:
Number per case:

Serum / Plasma Number of cases:

Fresh/frozen material (if available): DNA RNA

TMA's *(specify)*

Access to Samples for Correlative Studies



Application for Access to Banked Tissues/Fluids is submitted by investigator

- Project Title and brief Description
- Amount/Preparation/ Type of tissue/fluid required for project
- Attached CV
- Funding Details
- REB/IRB Approval

Application distributed to Correlative Science Tumor Banking Disease site specific Committee members for review

Evaluation Forms returned to NCIC CTG with reviewer comments

Possible Committee Discussion outcomes:

- Approval
- Approval following implementation of suggested changes, presenting further evidence, adjusting amount of tissues requested
- Disapproval

Specimens will be released upon verification of Funding, REB/IRB Approval, and Contract signing

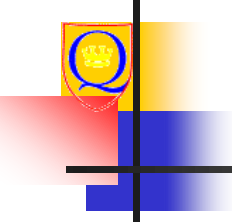


Not all trials are created equal...

- Intergroup vs NCIC CTG trials
- Discovery vs Validation
 - Requests for access to US cooperative group studies subject to Disease Site Specific CSC Review - JBR.10, JMA.17
 - Small trials or negative studies may be available for exploratory work rather than validation

What are some of the challenges -
you can't do this alone....





Current Issues and Challenges facing multi institutional Clinical Trial Tissue Banks

Collection of liquid samples is usually fairly well accepted with appropriate consent and well designed protocols and SOPs

BUT...

“a growing reluctance for Pathology Departments to release diagnostic tumour blocks” - an evolving threat to the success of clinical trial research worldwide

WHY?

Defining diagnostic tissue in the era of personalized medicine

Carol C. Cheung MD PhD, Bella R. Martin MHA LLB, Sylvia L. Asa MD PhD

Human tissue is excised for either medical care or research. Demand for excised human tissue is increasing because of the realization of personalized medicine, which relies on excised human tissue to develop innovative tests for application in patient care. However, because excised human tissue is a limited, nonrenewable resource, increasing demand has stressed current institutional infrastructures.

Excised human tissue consists of 2 classes — diagnostic and research — each with distinct rules governing collection, retention and use. Because of a dearth of published literature on the fundamental distinction between diagnostic and research tissue, there is confusion among institutions, physicians, researchers and patients regarding access to excised human tissue. Any

molecular and ultrastructural examination or other methods.

What constitutes diagnostic tissue is addressed in law.⁹ As such, diagnostic tissue includes that which is wet unfixed or fixed, frozen, formalin-fixed paraffin-embedded and derivatives of these forms, including sections mounted on glass slides cut from formalin-fixed paraffin-embedded blocks, as well as extracted materials or information (e.g., DNA, RNA, protein).

Diagnostic tissue that has undergone gross examination and is not specifically sampled and processed for further study is excess diagnostic tissue, which is retained short term (i.e., weeks) and then discarded as medical or biological waste. All sampled and processed tissue is retained as archived diagnostic tissue for a minimum of 20 years in archives of the department of

Competing interests: None declared.

This article has been peer reviewed.

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NCIC CTG Experience...



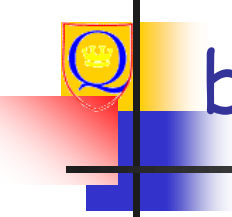
The past: 80-90% retrieval success using our system of direct requests to Pathology departments with a detailed letter outlining the trial, research question, reason for the request, the material required, the reimbursement, assurance of block return on request.

The present: 40-50% success with increasing reluctance to provide blocks and a growing trend to offer slides. Many more requests for financial support, assurance of REB approval for the bank, laboratory accreditation, copies of SOPs



More recently...

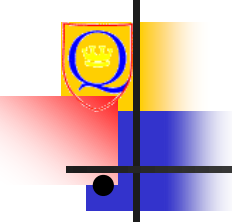
- Issues of custodianship and legal responsibility
- Liability fears over block exhaustion
- Academic return
- Litigation concerns over central review - not a real issue in Canada
- \$\$\$ and time
- Administrative decisions extending beyond the walls of a single hospital
- Institutional "protectionism"
- Policies related to retention times
- Limited amount of tissue has always been and remains problematic



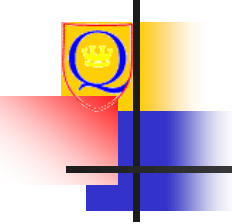
Ethics and Regulatory concerns have been largely addressed...

- Recent tri-council guidelines have clarified many of past concerns around decisions regarding level of consent eg older trials, patients who have died, nature of the research, confidentiality
- New issues: genetic testing, pharmacogenomics, data sharing - currently being addressed in consent language
- Common consent language evolving eg BCCancer Agency/OCREB
- Consistent Standard Operating Procedures, Biobank certification (CTRNeT initiative)

Pathology Issues remain real...

- 
- Pathologists are the custodians of the tissue and must remain cognizant of patient needs
 - The pathologist needs to be vested in the importance of clinical research and the importance of the submission of tissue for all consenting patients
 - Pathologists need to be partners in the research: they are critical in supplying the tissue and identifying the right tissue to send

Pathologists are your friends - talk to them!!!



Current practices in other cooperative academic groups in Europe and NA

- Mandatory block submission for centre participation (always optional for individual patients unless integral part of study) BUT punitive and potentially disadvantages the patient
- Many groups have been successful at collecting cores from diagnostic tissue blocks BUT there is an expense both to the requesting group in the provision of the biopsy core and the subsequent processing as well as extra work and cost to the referring centre
- TMA construction by referring centre BUT cost, resource and standardization remains an issue



Other Resources

- Growing number of institutional, regional, provincial banks, disease site specific collections
- Cooperative Group Banks in the US
- Trial Specific Banks
- Commercial Banks

In Canada...



CANADIAN TUMOUR
REPOSITORY NETWORK

RÉSEAU CANADIEN DE
BANQUE DE TUMEURS



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QUICK LINKS:

ATIM BIOBANKING
SOFTWARE

STANDARD OPERATING
PROCEDURES

AVAILABLE MATERIALS

POLICIES

DOCUMENTATION WIKI

The Canadian Tumour Repository Network

BIOBANK RESOURCE CENTRE ONLINE

The UBC Office of Biobank Education and Research (OBER) in collaboration with the Canadian Tumour Repository Network (CTRNet) has created an online resource for biobanks across Canada. This resource is available at www.biobanking.org

ABOUT US

CTRNet is a translational cancer research resource, funded by Canadian Institutes of Health Research, that furthers Canadian health research by linking cancer researchers with provincial tumour banks.

The benefits of working with CTRNet include:

- The ability for researchers to search for quality controlled tissue [samples](#) from Canada's leading tumour banks in one central location and for biobanks to display and make their biospecimens available for research users.
- Learning [opportunities](#) in tissue handling, research design and relevant technology training and innovations.
- Invitation to CTRNet workshops and conferences.



UPCOMING CONFERENCES/EVENTS

2013 ESBB Conference

Oct 9 2013 to Oct 11 2013 - "Biobanking for the Future". Sessions include: Global Biobanking, Ancient DNA, Biobanking for Personalised Medicine, Biobanking for Conservation, Sustainability of Biobanks and the Financial Crisis, and Innovative Biobanking.

CTRNet National Biobanking Workshop

Nov 3 2013 - CTRNet will be providing its next National Biobanking Workshop as a satellite meeting during the Canadian Cancer Research Conference. Please check back here for

Ontario Tumour Bank

OVERVIEW

The Ontario Tumour Bank is a province-wide biorepository and data bank focused on collection of tumour-related human biospecimens. It provides academic and industry cancer researchers with a diverse selection of high quality tumour-related specimens and data obtained directly by dedicated tumour bank staff, who follow a stringent set of procedures and ethical guidelines.



The biospecimens and clinical data are an important resource for scientists engaged in translational research who are developing better diagnostic tools and new drug therapies. Researchers depend on the Ontario Tumour Bank to provide research biospecimens of high quality, diversity, and integrity.

Operating at state-of-the-art hospitals and cancer centres across Ontario, the Ontario Tumour Bank coordinates the collection, storage, analysis, annotation, and distribution of tumour and peripheral blood samples. Working in collaboration with local pathologists, medical oncologists, surgeons and other hospital personnel, specially trained staff obtain patient consent, collect tissues and assemble comprehensive clinical information about each donor and the corresponding samples.

The Ontario Tumour Bank is a program of the Ontario Institute for Cancer Research (OICR). Funded by the Government of Ontario, OICR is a not-for-profit corporation

ONTARIO TUMOUR BANK

[Contact the OTB](#)

[➔ See All OICR Programs](#)



OFFICE OF BIOBANK EDUCATION AND RESEARCH (OBER)



We are pleased to announce the establishment of the **Office of Biobank Education and Research (OBER)** by the UBC Department of Pathology.

Mission:

To provide support for BC biobanks through education on biospecimen science and communication of best practices and standards for biobanking, in order to advance translational health research in BC.

Overall objective:

To establish an international centre of excellence in biobanking education and biospecimen based translational research

Specific Goals:

- create and deliver education and training for a range of stakeholders involved in biobanking
- facilitate registration/certification of biobanks in coordination with provincial and national and international biobanking organizations
- facilitate registration/certification of biobanks in coordination with provincial and national and international biobanking organizations
- develop and deploy mechanisms to communicate common protocols, standards and policies for biobanking
- promote establishment and maintenance of biobanks to support biospecimen based translational research

EDUCATIONAL RESOURCES

OBER

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Summary

- The tissue resource has its value in the association with a clinical trial
- Clinical trials often take many years to accrue with long follow-up - good and bad
- Protocol specified research has to take precedence... but sometimes the questions asked in a study are no longer relevant, technology has changed, or better research questions can be asked

Unique resource wanting to be used