Practical Aspects of Tumour Banking

Challenges, issues and Potential solutions

Workshop #9

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Objectives:

- To understand the nature of biobanks, their governance and required operating procedures
- To understand and find solutions for problems encountered in tumour banking associated with clinical trials

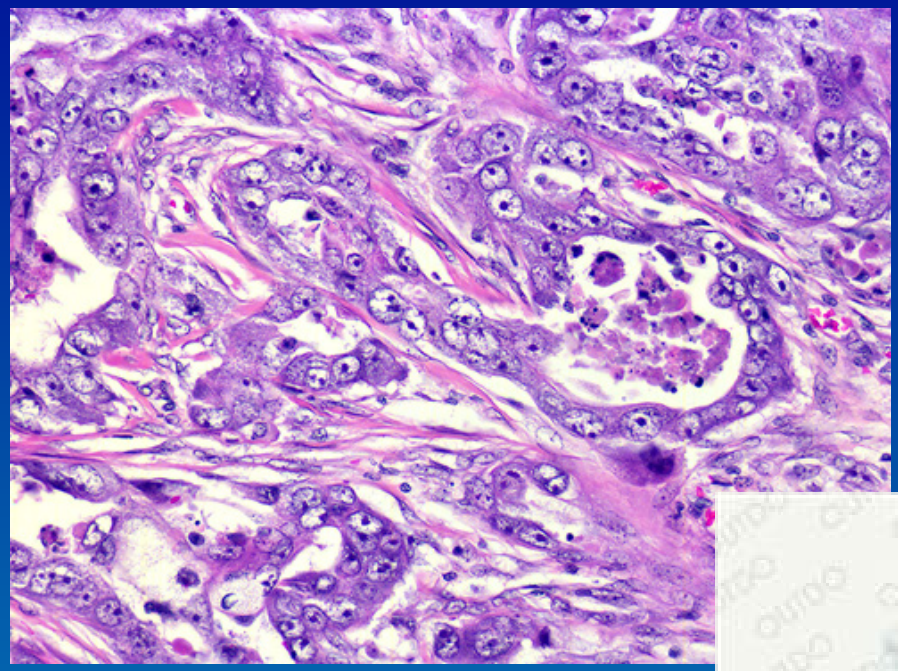
A Little History…

- 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, bone marrow on a growing number of studies



Growing number of Derivatives:

-TMAs

-DNA

-RNA

Material collected since 1997

Specimen type	Number patients	Number samples
Blocks/slides	13640	26480/71098
Whole blood	5362	14232
Plasma	4201	38694
Serum	10931	46405
Urine	533	3513

Required Operational Practices for a Tumour Bank ... ROPs

Areas which must be addressed include:

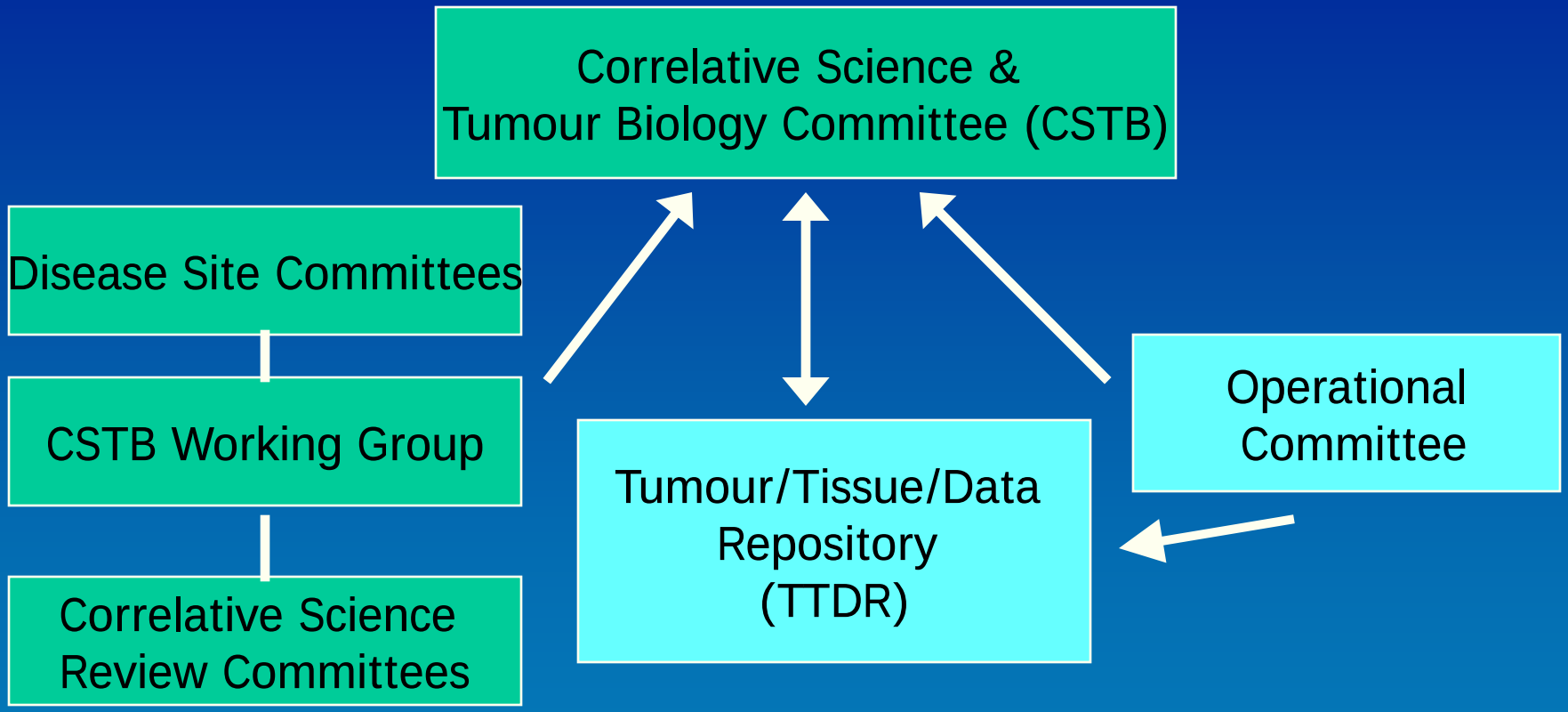
- Ethics
- Privacy and Security
- Consent
- Governance
- Access and Release
- Quality management system and process improvement
- Education and Training
- Data systems and Record management
- Biospecimen collection and Processing

ROPs continued:

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

Organizational Chart

CSTB TTDR



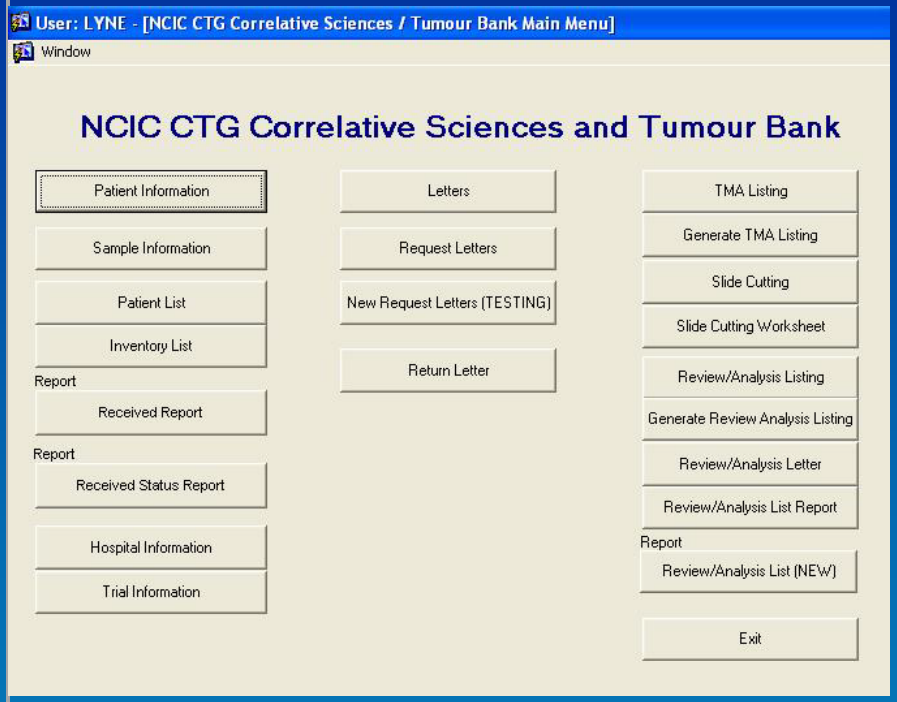
External
Scientific Agenda

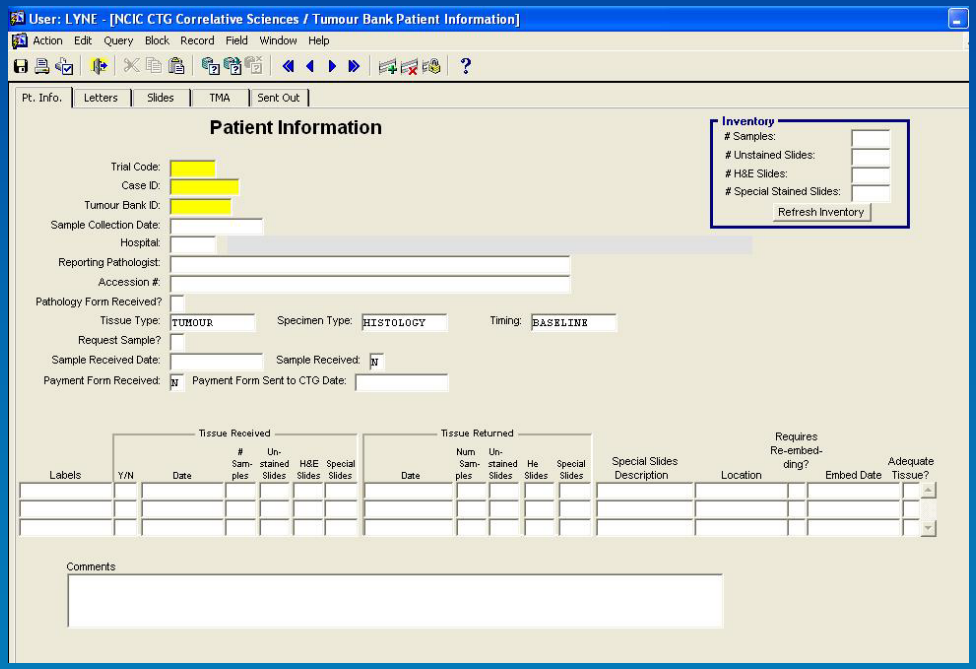
Internal Central Office
Ethics/Regulatory
Data Management/Operational

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

TTDR Database





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
- Automated Immunohistochemistry Qualitative and Quantitative - AQUA

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
- 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, processing, shipping, and storage conditions
- Inventory management and tracking systems

Confidentiality

De-identification of tissue

- All samples received are assigned a unique Tumour Bank ID
- Database creates sequential codes
- Link is in the TTDR/PCO/Statistical support
- Samples released to investigators are only identified by the unique TBID
- Clinical database remains with the NCIC CTG

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

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

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Evaluation Forms returned to NCIC CTG with reviewer comments

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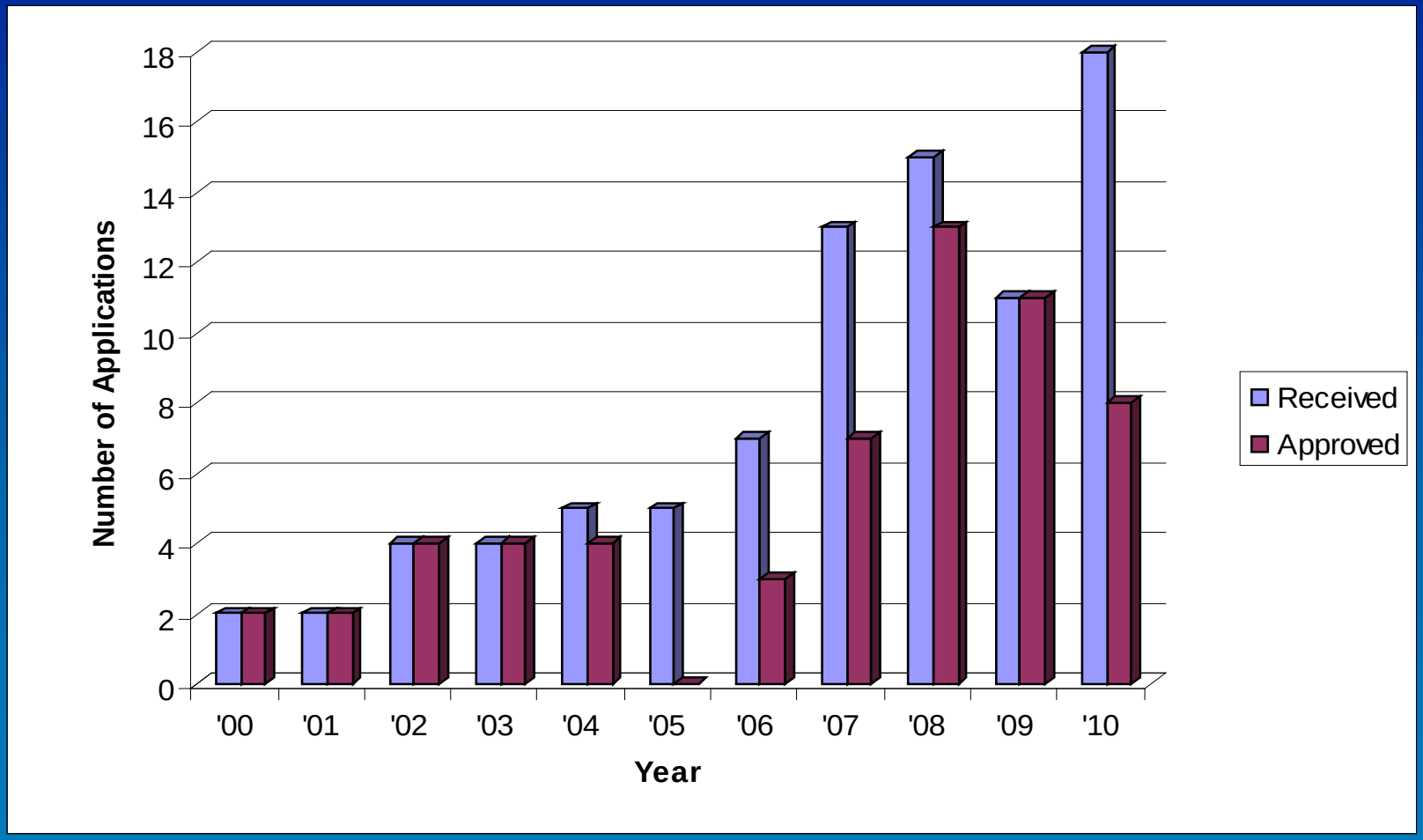
Possible Committee Discussion outcomes:

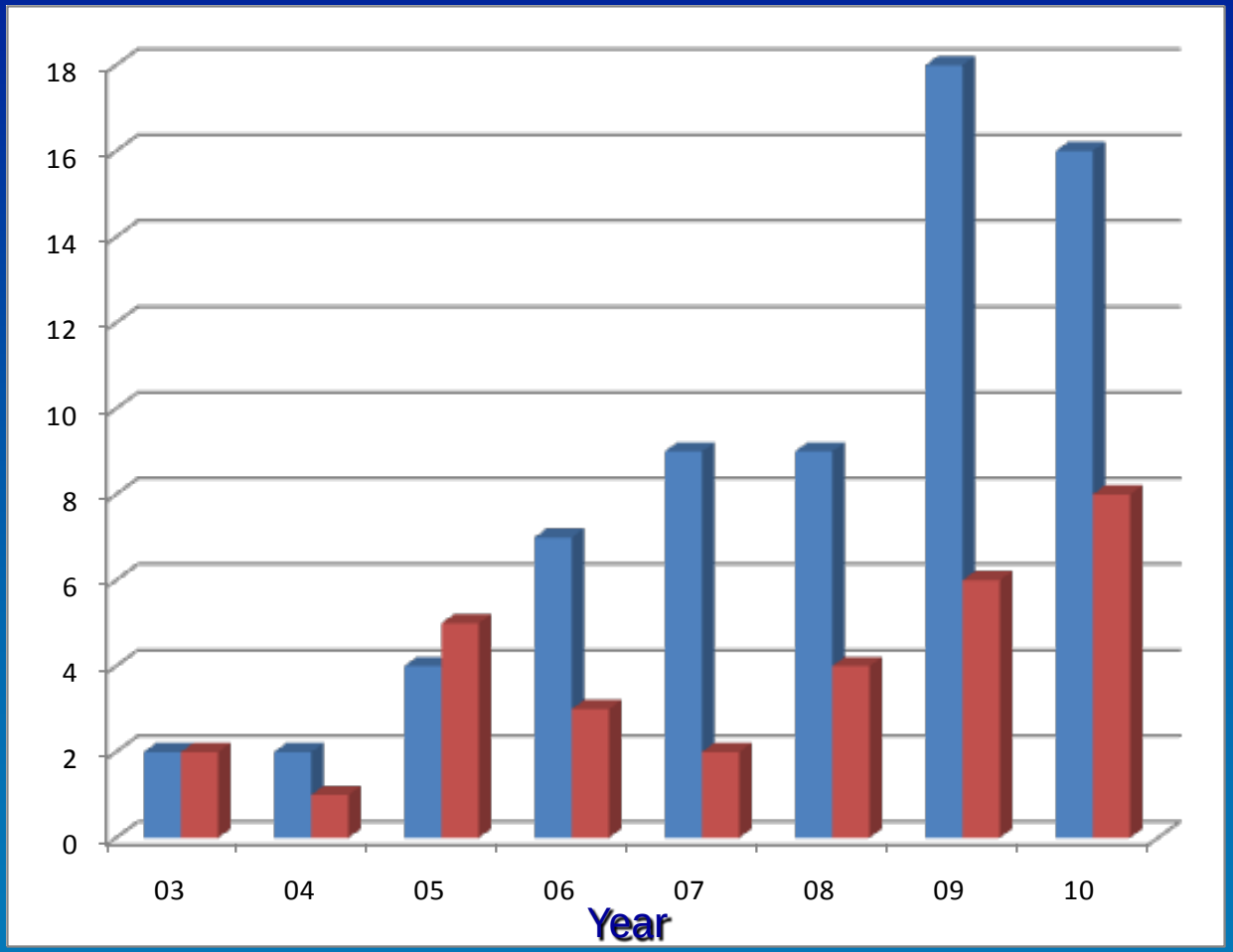
- **Approval**
- **Approval following implementation of suggested changes, presenting further evidence, adjusting amount of tissues requested**
- **Disapproval**

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

Applications to the Correlative Science Committees



Group Publications and Abstracts



Overall Process / Safeguards for NCIC CTG Collections

- Supervision by the CSTB committee and operational subcommittee
- Patient consent must be signed before requests for tissue to be sent to the bank are made
- Material is received, catalogued, de-identified and appropriately stored
- Database is maintained, secure, and regularly updated
- Defined procedures for approval of release of tissue to investigators
- Standardized SOPs are followed consistent with national and international guidelines

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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.

MA20 Details

Status: Closed
Activation Date: 1999DEC14
Closing Date: 2007FEB02
Phase: III

Description: A Phase III Study of Regional Radiation Therapy in Early Breast Cancer

Eligibility: Pre or post menopausal women with node positive and high risk node-negative breast cancer treated by breast conserving therapy and currently accepted adjuvant chemotherapy and/or hormonal therapy.

Objective: To determine if regional radiation therapy (to the ipsilateral supraclavicular, axillary and internal mammary nodes) in addition to breast radiation prolongs survival in women with early breast cancer compared with breast radiation alone. To compare disease free survival, isolated local regional disease-free survival, and distant disease free survival. To evaluate toxicity. To evaluate quality of life. To determine the cosmetic outcome of these two treatment approaches.

Participation: Not limited.

Lay Description: The purpose of the study is to find out whether it is better to receive breast radiation or the breast radiation plus radiation to the surrounding lymph glands or nodes (regional radiation). This will determine if regional radiation will prevent distant spread of the cancer and cause women to live longer by keeping the cancer from coming back.

Publications
Coming Soon

Current Projects
Coming Soon

Inventory

Hide **Tissue Samples**

Disease Site	Trial Code	Patients Accrued	Patients - Blocks	Patients - Slides	Patients - Blocks and/or Slides
BREAST	MA20	1832	960	187	1093

Hide **TMA Samples**
(Core size is 0.6 mm)

Current Issues and Challenges facing multi institutional Clinical Trial Tissue Banks

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

WHY?

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

In the past…

- Concern over adequate patient consent
- $$$
- Pathologist's time and clinical service demands
- Amalgamation of laboratory services
- Concern over block return if needed for clinical management decisions

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, future 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!!!

Solutions…

- Informed consent must be obtained and should describe the purpose of releasing a diagnostic tumour block
- There should be an assurance that adequate tissue is retained at the referring institution for the potential benefit to the patient in the future
- The tissue will only be used in an REB approved protocol
- Confidentiality will be maintained
- Informed consent should include the assurance that tissue submitted will not be totally exhausted but insure that the consenting patient understands this is a risk that however unlikely, may occur

Why are blocks the preferred material?

- Quality assurance – H&E sections, digitalization for review, annotation, archiving, assessment of tumour size, heterogeneity
- TMA construction- block preservation, standardized procedures, cost effective
- Appropriate material identified for DNA/RNA extraction
- Slides provide limited resources with issues related to storage, loss of antigenicity

Solutions - Potential alternatives to blocks…

- Bisection of a diagnostic block and re-embedding by the referring centre (costly and time consuming)
- Coring of a diagnostic area of a representative block with the potential to ship the core, or re-embed the core creating a "mini" block
- Creation of TMA by referring institution

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

SOLUTIONS…

- **Engagement** of the research community – clinical trialists, academic and research pathologists, clinical and basic scientists to find solutions
- Increase dialogue and academic return for pathology community
- **Advocacy**
- Adequate funding and infrastructure support: $$$
- Prioritization of academic research groups outside of one's own institution
- **Trust** – Tumour banks consider themselves stewards for the tissue they receive: Biobank certification

Tumour banking is a collaborative endeavour… to provide a national resource for the research community to advance the care of our patients, now and in the future