

TISSUE BANKING FOR CANCER CLINICAL TRIALS

CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA

Tissue banks linked to cancer clinical trials clearly have a vital and growing role in improving patient outcomes, maintaining Australia's international standing in medical research and enabling Australia to remain a country of choice for clinical trial conduct in an increasingly competitive international market. This paper reports on outcomes from a workshop convened by the Clinical Oncological Society of Australia (COSA) in October 2008 to facilitate a collaborative and coordinated approach to the collection, storage and distribution of biospecimens collected as part of cancer clinical trials conducted by Cooperative Cancer Clinical Trial Groups (CCTGs) in Australia.

Biological studies involve correlation of clinical outcomes with markers that predict response to treatment or that have prognostic value through analysis of samples of fixed or frozen tissue. Such studies can also provide information about markers of underlying disease. Research of this type is dependent on the appropriate collection and storage of fixed or frozen tissue and blood samples, as well as mechanisms to facilitate timely access to biospecimens for analysis.

There is considerable interest in linking biological studies with cancer clinical trials and it is increasingly common for trial protocols to include a biological sub-study. Such research has the potential to make a significant contribution to cancer care, providing the capacity for a targeted approach to treatment that is individualised to a patient's needs. Examples of biological studies with therapeutic relevance for cancer include the development of therapies targeting HER2-positive breast cancer and recent data about the influence of K-RAS mutation status on response to cetuximab in advanced colorectal cancer.¹

Biobanking of specimens from patients enrolled in cancer clinical trials in Australia is currently undertaken predominantly by the pharmaceutical industry. Most of this activity involves collection of blood samples for pharmacogenomic^a or pharmacogenetic^b research conducted exclusively by/for the sponsor company, with specimens and data often sent overseas for analysis. Tumour biobanks have been established at many sites in Australia. A number of these have started to work cooperatively – most notably the seven biobanks involved with the Australasian Biospecimen Network – Oncology (ABN), the National Leukaemia and Lymphoma Tissue Bank (NLLTB), the Breast Cancer Biospecimen Resource, the Australian Prostate Cancer Collaboration (APCC) BioResource, the Victorian Cancer Biobank (VCB), kConFab and the Australian Ovarian Cancer Study (AOCS).

a *The study of the human genome to identify genes involved in the mechanism of action or metabolism of drugs.*

b *The study of a limited number of genes involved in the mechanism of action or metabolism of drugs.*

There are currently 13 CCTGs in Australia. Trials overseen by these groups vary in size and complexity, but are typically multicentre studies recruiting patients in several states and territories, and in some cases New Zealand and other countries. While some CCTGs have been actively involved in biobanking, each group typically collects specimens only for a particular trial and there is currently no standardised or systematic approach to biobanking for multisite clinical trials. COSA is ideally placed to facilitate a collaborative and coordinated approach to biobanking of specimens collected as part of cancer clinical trials conducted by CCTGs in Australia.

Workshop overview

COSA convened a one-day workshop of key stakeholders in October 2008, with the aim of exploring a coordinated approach to the collection, storage and efficient utilisation of clinical trial specimens, as well as appropriate mechanisms for funding tissue banking and access within the CCTGs in Australia. The workshop was attended by 50 participants from biobanks, CCTGs and cancer registries, as well as consumers and representatives from relevant cancer organisations such as Cancer Australia.

Workshop presentations

Presentations from international and national experts provided valuable context to guide workshop discussion and included:

- an overview of key statistical considerations to be factored into the design of trials examining biomarkers (Professor John Simes, Director, National Health and Medical Research Council (NHMRC) Clinical Trials Centre and Dr Chee Lee, Researcher, University of Sydney, New South Wales (NSW))
- a summary of the importance of tissue banking in clinical trials, including regulatory and logistical implications of different trial designs (Professor Paul Waring, Professor of Pathology and Laboratory Medicine, University of Western Australia, Western Australia (WA))
- an overview of the development of the National Leukaemia and Lymphoma Tissue Bank (Dr Paula Marlton, Head of Leukaemia and Lymphoma Services, Princess Alexandra Hospital, Queensland)
- an update on the current status of tissue banking in Australia (Ms Heather Thorne, kConFab Manager, Peter MacCallum Cancer Centre, Victoria)
- a summary of outcomes from a review of tissue banks in NSW undertaken by the Cancer Institute NSW (Dr Parisa Glass, Research & Information Advisor, Cancer Institute NSW)

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■ a suggested list of questions and issues for consideration by workshop participants in relation to the role COSA could play in facilitating a more streamlined, uniform and cost-effective approach to tissue banking for oncology clinical trials conducted by the CCTGs in Australia (Dr Nik Zeps, Research Manager, St John of God Pathology and Radiation Oncology, Sir Charles Gairdner Hospital, WA; incoming Chair of the COSA Research Group).

Recommendations

Participants were asked to consider four issues in relation to tissue banking for CCTGs in Australia:

1. minimum data elements
2. standardised consent/ethics
3. collection and storage of samples
4. distribution of samples and sustainability.

Issues and recommendations were identified through discussion by four self-appointed multidisciplinary groups. Time limitations precluded a full consensus approach and the outcomes reported below summarise key outcomes reported back to the plenary group. All groups recognised the importance of avoiding duplication and building on existing national and international initiatives.

Minimum data elements for a tissue bank linked to cancer clinical trials

The minimum data elements identified for a tissue bank linked to cancer clinical trials related to demographic identification of the trial and specimen, with specific data elements identified for the trial and the specimen itself (table 1).

Standardised consent/ethics

Current issues identified in relation to consent and ethics approval for the collection and storage of tissue samples as part of cancer clinical trials included the need for:

- increased awareness and application of national guidelines for consent and ethics developed by the Australian Health Ethics Committee (AHEC) and issued by the NHMRC,³ as well as the Harmonisation of Multi-centre Ethical Review (HoMER) project⁴

- public engagement about the benefits of tissue collection and the importance of information collected from specimens held in biobanks.

It was suggested that the ultimate goal in Australia should be to obtain consent for the collection and storage of tissue samples for the purposes of research from all patients at the point of diagnosis. One possibility would be an opt-out rather than an opt-in policy and would ideally include storage of samples for germ line sampling and assessment of somatic mutations. However, there are major health consumer concerns with such an approach and much would need to be done to gain wide acceptability. The need for a streamlined, efficient process that could be applied beyond cancer was identified.

In developing a standardised approach to consent, questions to be considered included the timing of obtaining consent (at diagnosis versus on entry to the clinical trial), as well as who should obtain consent. Other questions included:

- Process for informing the patient or family members about the implications of the information obtained from sample analysis.
- Implications of use of tissue after death.
- Sampling considerations (for example, collection of normal tissue, blood samples and relapse tissue).

A number of possible roles for COSA in facilitating a standardised approach to consent and ethics were identified. This included lobbying for legislation around the process of consent for tissue banking although there was some debate about whether such an approach is appropriate. Other possible roles include liaison with the Royal College of Pathologists of Australasia (RCPA), and undertaking a review of international and national consent procedures. It was also suggested that COSA could be involved in the development of common guidelines, templates and procedures, as well as in public engagement about the altruistic benefits of tissue collection and storage.

Collection and storage of samples

A number of obstacles to the collection and storage of tissue samples by CCTGs were identified, including the

Table 1: Minimum data elements for a tissue bank linked to cancer clinical trials

Minimum data elements for the trial*	Minimum data elements for the specimen
Primary questions for the tissue sub-study	Trial name/identifier
Contact details of the trial group/principal investigator	Patient identifier
Type of specimen collected (as defined by the trial protocol)	Tumour type
Type of consent (generic or specific to the trial)	Type of tissue (tumour, blood, plasma, serum, DNA etc)
Potential availability for collaborative research (Y/N/qualified)	Collection method (fresh, frozen, paraffin-embedded etc)
	Date of collection
	Storage location
	Type of consent

*To be based on the World Health Organisation minimum data set for clinical trials.²

lack of pathology contact before trial initiation and lack of standardised approaches to sampling and storage. The absence of financial incentives for pathologists to be involved in the collection, storage and release to third parties of tissue for research purposes was also seen as a barrier. Other identified issues related to the range and complexity of approaches to tissue collection and storage. For example, difficulties associated with certain techniques, such as obtaining frozen samples and limitations of paraffin-embedded samples, can influence the quality of samples. However, despite these issues, there was a view that funders and policy makers are currently unaware of the complexities of tissue collection and storage.

A number of possible solutions to encourage a consistent approach to the storage of tissue samples were identified. Several solutions focused on the need for greater involvement of pathology from the trial outset, including:

- inclusion of a pathologist on trial management committees and, where possible, at each participating site
- scientific acknowledgement of pathology input
- consideration of reimbursement options for pathologists involved in tissue sampling, with the option of a Medicare item number for collection and preparation of tissue by pathologists for the purposes of research.

It was also suggested that pre-definition of a biological or translational research question with a clinical trial that has a clear clinical objective was important to promote clinician engagement and to encourage the collection of a sufficient quantity of tissue of appropriate quality for testing. Other solutions included creation of a virtual network to allow samples to be collected and stored locally, but accessed nationally and a future goal of collecting a second block of tissue to be stored locally for future studies as standard.

Possible roles identified for COSA included collaborating with the RCPA to centralise coordination of pathology input, as well as with appropriate partners to lobby government for a Medicare number to reimburse pathologists for collection of tissue for research purposes. It was also suggested that COSA could be involved in tendering for activities to support localised collection and storage of tissue samples.

Distribution of samples

The heterogeneity of existing tissue banks was identified as a key issue in limiting the distribution of tissue samples for the purposes of clinical research. It was suggested that additional tissue samples collected in relation to a specific clinical trial should be quarantined from translational research samples. Such clinical trial samples should remain under the governance of the Trial Management Committee. In contrast, access to 'open collection' samples for biomarker discovery, pre-clinical studies and translational research should be managed by the respective tissue bank.

The sustainability of tissue banks was considered to be dependent on: international best practice and standard operating procedures;⁵ database management and clinical linkages; long-term funding through a range of avenues, including federal and state government, grants and philanthropic groups; and the amalgamation of consortiums to maximise efforts.

The potential role of COSA in advocating for funding was discussed.

Opportunities for funding

A range of potential sources of funding were identified to support the collection, storage and distribution of tissue for oncology clinical trials and translational research in Australia (table 2).

Table 2: Potential funding sources for tissue banking linked to cancer clinical trials in Australia

Category	Examples
Government/government bodies	<ul style="list-style-type: none"> □ Enabling grants/infrastructure grants (eg. NHMRC, Cancer Australia) □ Tax revenue □ Medicare items for sample collection
Trial sponsors/commercial entities	<ul style="list-style-type: none"> □ Pharmaceutical companies □ Health instrument/consumable suppliers
Philanthropic donations	<ul style="list-style-type: none"> □ Banks □ Health insurance companies □ Disease-specific charitable foundations (eg. Leukaemia Foundation)
Non-government organisations	<ul style="list-style-type: none"> □ Cancer Councils □ Australian Cancer Research Foundation
Overseas funding sources	<ul style="list-style-type: none"> □ National Institutes of Health (US) □ National Cancer Institute (US) □ Department of Defence (US)
Other potential sources	<ul style="list-style-type: none"> □ Private hospital associations

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Questions to be considered in relation to funding of tissue banks included:

- Who should receive funding – clinical investigators/tissue bank groups/research scientists/health departments/hospitals?
- Who ‘owns’ the tissue/specimen?
- What is the long-term cost-effectiveness of targeted approaches to cancer treatment developed through analysis of biomarkers?

Various options that could be considered to ensure long-term sustainability were suggested. Many of these related to cost-efficiencies and included:

- embedding value-added research in clinical trials and making clinical questions more cost-effective
- centralisation, standardisation and linking of approaches and knowledge to improve efficiency and maximise use of available funds
- consideration of cost-efficiencies in shared approaches to infrastructure.

The potential for commercial opportunities/partnerships was highlighted, for example, the option of providing new pathology services to measure known biomarkers. It was also suggested that translational research involving tissue banks could be prioritised, with priority given to collections from randomised controlled trials with linked high-quality clinical data that allow analysis of prognostic and predictive markers. Other possible support activities included the conduct of a national audit of existing biobanks and processes to build and learn from existing initiatives, and engagement of consumer advocacy groups such as Cancer Voices Australia to assist in lobbying for change.

Specific actions to be considered by COSA in moving forward included:

- Joint submission with the RCPA to government in relation to the creation of a Medicare item number for preparation of specimens for the purposes of research.
- Coordination of a committee to seek a five-year funding grant from the Australian Cancer Research Foundation to support a tissue bank coordinating centre.
- Exploration of options for seven-year renewable funding for cancer clinical trial tissue banking.
- Building on the existing NHMRC enabling grant to facilitate new initiatives.
- Commissioning of an analysis of the cost-effectiveness of tissue banking activities, in partnership with the pharmaceutical industry and/or Pharmaceutical Benefits Advisory Committee.
- Appointment of a project officer to assist in building a business case and identifying and engaging relevant stakeholders.

- Consideration of approaches to capture and promote the international value of the Australian situation to international bodies such as the Wellcome Foundation.

Next steps

In closing, Professor Goldstein outlined the following priorities for action by COSA:

- development of a health economic model to support the need for tissue banking
- scoping activities to identify options for tissue banking linked to cancer clinical trials and map existing initiatives
- identification and pursuit of potential funding sources.

Professor Goldstein indicated COSA's commitment to building a business case for tissue banking linked to cancer clinical trials in Australia and emphasised the importance of the meeting in setting a solid foundation and direction for future activities to guide a consolidated approach to tissue banking in Australia. He encouraged ongoing dialogue and collaboration to facilitate progress in this important area.

Acknowledgements

The workshop was sponsored by unrestricted educational grants from Roche Products Pty Ltd (Australia) and Novartis Pharmaceuticals Australia.

COSA gratefully acknowledges the input and support of the workshop facilitator, Professor Ian Olver, speakers and members of the Workshop Steering Committee: Professor David Goldstein (Chair), Professor Stephen Ackland, Dr Anna DeFazio, Dr Anne Thompson, Ms Heather Thorne, Dr Nik Zeps, Dr David Roder, Margaret McJannett and Kathy Ansell.

The workshop report was developed by Dr Alison Evans from Alison Evans Consulting.

References

1. Karapetis C, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008; 359(17): 1757–65.
2. World Health Organization. Technical Consultation on Clinical Trials Registration Standards. 2005. http://www.who.int/ictrp/news/ictrp_meeting_april2005_conclusions.pdf (accessed November 2008).
3. National Health and Medical Research Council and Australian Research Council Australian Vice Chancellor's Committee. National Statement on Ethical Conduct in Human Research. Canberra: Australian Government, 2nd ed, 2007.
4. National Health and Medical Research Council. Harmonisation of Multi-Centre Ethical Review (HoMER) project. http://www.nhmrc.gov.au/health_ethics/homer/index.htm (accessed December 2008)
5. International Society for Biological and Environmental Repositories. 2008 Best Practices for Repositories. Collection, Storage, Retrieval and Distribution of Biological Materials for Research. *Cell Preservation Technology* 2008;6(1).