



Tumour banking as part of routine clinical practice

The promise of molecular-based therapy for cancer is now well established. Currently, there is routine use of *targeted* therapies for specific tumour-related proteins such as anti-HER2 (Herceptin, Genentech, USA), anti-EGFR (Cetuximab Bristol-Myers Squibb, USA), anti-VEGFR (Avastin, Genentech, USA) and tyrosine kinase inhibitors (Gleevec Novartis Pharmaceutical Corporation, USA). Further, the genetic-based markers such as *K-ras* and HER2 have increased the precision of treatment in patients receiving chemotherapy. The availability of tissue specimens linked to clinical treatment and outcome data is an essential requirement for these developments.

Gaining access to these clinical specimens for research purposes can be difficult for a number of reasons. These include the identification of suitable patients, obtaining patient consent, coordination of the collection of specimens from theatre, processing and storage of specimens, as well as data linkage to relevant clinical information. A variety of strategies have been employed in Australia to address these requirements, and while many have been successful when measured by the number of cases collected and made available to researchers, there are significant threats to their ongoing existence through a lack of secure recurrent funding.

In Australia, as with other developed nations, tumour banking activities are conducted by or aligned with research institutions. While these institutions may be associated with clinical service delivery, they are typically run independently and must liaise with clinical staff to obtain specimens. Unfortunately, the priorities of the clinical work tend to override those of the tumour banks, and indeed sensitivities with regard to compromising a diagnosis or invading a person's privacy means that access to samples or clinical information is often less than optimal. However, the routine pathology services responsible for the daily management of patients have been providing banking of processed specimens for more than 100 years. They have huge banks of paraffin-embedded tissue. Yet while pathology services are generally supportive of cancer research, in practice, very few have taken the opportunity to become directly involved in translational research because of the cost implications.

Our group's initial attempts to establish a tissue bank (i.e. bio-bank) emerged from a joint translational research programme operating between an academic research unit (School of Surgery, University of Western Australia) and a research group associated with a clinical department (Radiation Oncology, QEII Medical Centre). This led to the establishment of the first statewide tissue bank in Australia, the WA Research Tissue Network. This employed specific staff to liaise with clinical services and arranged (on a case-by-case basis) for a pathologist to separately process the samples. However, as is common, surgeons relegated banking to an afterthought unless they had a specific interest in the projects that

used the samples. Moreover, while pathology services were not obstructive, there was some resistance to the incorporation of anything more than very occasional tissue banking episodes because of perceived workforce restraints. Furthermore, this process was viewed as a separate pathology activity and was associated with substantial financial charges.

Having established that tissue banking was possible in WA, ongoing funding became a problem. This was because it was not acknowledged as a priority by the WA health department. This led the group to explore an alternative approach. A collaboration was created between St John of God Pathology (a private pathology service) and the St John of God Colorectal Service (a multidisciplinary team who had developed a number of clinical databases and wished to become involved in translational research and tissue banking). The group extended the conventional pathology service paradigm, that provides for formalin specimen banking, to include the routine taking of an additional specimen for 'fresh tissue' banking. This subtle procedure change was found to be easily implemented and lead to clinically relevant information being immediately available.

The creation of this bio-bank was underpinned by three core principles. Firstly, the group only targeted common tumour types that were linked to a clinical database. This enabled us to perform outcome assessment. This also avoided the banking of large amounts of tissue that will never be used. Secondly, we adjusted the 'routine' pathology processing procedure to include an additional step to isolate tissue for the banking process (in itself a very minor procedure). This enabled 100% coverage and avoided 'lost' specimens, which are an ongoing problem with conventional banking. By collecting all relevant specimens you avoid the inherent bias involved in collecting only a fraction of the target group. Finally, we modified the routine surgical consent form to include consent for access to tissue and blood samples and linkage of these to clinical information.

This model has enabled us to avoid some of the limitations that currently exist in establishing and maintaining bio-banks. These include the time-consuming liaison with clinical services that frequently results in missed cases. Similarly, the bio-bank consent process is different from standard and may involve many different clinical staff. This can be very labour intensive and represents perhaps one of the biggest costs of running a tissue bank. With our current model, over the last 2 years the majority of cases are consented prior to surgery. For about 10% of cases, consent is requested after surgery. A 99.7% positive consent rate from 650 cases collected clearly demonstrates the enormous patient support for this endeavour.¹ Our group also found that by integrating specimen collection into routine pathology services, we avoided the issues of not having a pathologist available to perform a review of the material.

There are high costs associated with running bio-banks outside of routine pathology services. These costs relate to the requirement for dedicated staff, transport and payment for external pathology services. By integrating the two activities, these costs are shared between existing staff and transport costs are minimized. Further, there are numerous privacy and confidentiality issues related to third-party access to clinical information. These issues can make it difficult for clinicians to access relevant data stored in these stand-alone bio-banks. In our proposed model, the clinical information is maintained and accessed by the treating doctors. Finally, independent bio-banks are expensive units to establish and maintain and are highly vulnerable to loss of funding. By using an established pathology service, start-up costs are minimized and the whole programme is less vulnerable to funding cuts.

Based on our earlier translational work,^{2,3} the pathology department was persuaded by the colorectal service to incorporate two molecular tests into its routine processing of colorectal cancer specimens. The first, microsatellite instability testing, allows patients to be screened for a molecular phenotype that is an indicator of the presence of a familial bowel cancer condition referred to as Lynch syndrome.⁴ The second, *K-ras* mutation screening, allows predictive testing for response to anti-EGFR treatment.⁵ Analysis of the high-quality DNA extracted from frozen tissue samples avoids many of the technical limitations inherent with the use of much lower-quality DNA derived from routinely fixed and paraffin-embedded archival tissue samples. This is a significant problem faced by the rest of the oncology community. Both tests have been validated as providing clinically important information and are performed by the molecular pathology service on a routine basis and free of charge for all consenting colorectal cancer patients.

In conclusion, by changing the specimen collection paradigm and making bio-banking a 'routine' part of clinical services, our group simultaneously achieved almost 100% coverage and very substantially cut costs. We have shown that samples collected may also be utilized immediately for patient benefit through the facilitation of molecular diagnostics. We believe that this model is best suited to relatively high-volume tumours (e.g. colorectal, breast and prostate). Other models will be needed for more rare tumours where insufficient cases may be present at any one location. In these instances, networking with other tumour banking activities will probably be

required.⁶ Our group is currently a member of the Australasian Bio-specimen Network and shares the goal of greater national and international cooperation. We are presently initiating the collection for gynaecological, upper gastrointestinal and haematological malignancies with the long-term intention that all cancers treated within the institution will ultimately be available for research into cancer prevention and treatment.

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Cameron Platell,*§ FRACS

Nikolajs Zeps,†‡§¶ PhD

David Joseph,‡ FRANZCR

Nigel Spry,‡ FRANZCR

Barry Iacopetta,§ PhD

Vince Caruso,† FCMSA

**St John of God Hospital Colorectal Service,*

†*St John of God Pathology,*

‡*Radiation Oncology, Sir Charles Gairdner Hospital,*

§*School of Surgery, University of Western Australia, and*

¶*School of Pathology and Laboratory Medicine, University of Western Australia, Western Australia, Australia*

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