

**HUMAN TISSUE
FOR
BIOMEDICAL
RESEARCH :
TUMOUR BANKS**

Position Paper from the
2001 - 2002 Chapter of Pathologists Committee,
Academy of Medicine, Singapore
for the Human Genetics Subcommittee,
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1 INTRODUCTION

- 1.1. The global **demand** for use of human tissue in research is growing rapidly and this trend is reflected clearly in Singapore where current demand far outstrips availability. Ethical and legal issues however have yet to be fully addressed.
- 1.2. At the **request** of the Human Genetics Subcommittee, National Bioethics Advisory Committee, 'tissue' will refer to small tissue samples; however, the Chapter feels that ethical issues raised in this paper would also apply to all other types of human tissue, including samples of subcellular structures like DNA to cells, tissue samples (including bone, muscle, connective tissue and skin), blood, gametes, embryos, fetal tissue, placenta, body fluids and waste (including hair and nail clippings); as well as whole organs.

2. SOURCES

- 2.1. **Human tissue** for research may be obtained from living volunteers/ research subjects, who donate their tissue for a specific project.
- 2.2. Provision for **anatomical gifts** is covered under the Medical (Therapy, Education and Research) Act where it is stated that persons over the age of 18 may donate all or part of their body (the gift to take effect upon death) for any of the specific purposes and donees stated. (Approved institutions as notified by the Minister, or specified individual for therapy or transplant.)
- 2.3. **Tissue samples** (including blood and blood products, and body fluids) left over from diagnostic or therapeutic sampling may also be harvested or archived for research purposes. Currently this category forms the largest group of archived and banked tissue.
- 2.4. **Non-coronial autopsies** may also provide a source of tissue for research. This issue has been addressed in the Chapter's Interim Guidelines : Autopsy Practice in Singapore.
- 2.5. **Human embryos, eggs and sperm** are banked in Singapore. Ethical and legal considerations for this group are not covered in this paper as they are considerably more complex.

3. CONSENT

- 3.1. The **Chapter** is of the opinion that the patient should be informed, and where possible, consent should be taken if any tissue sample is to be used for purposes other than what it was originally removed for.
- 3.2. Validity of consent is well covered in law, and the principles behind recognition of persons authorised to give consent for treatment and operation should apply to donation of 'surplus' therapeutic or diagnostic tissue for research. In the case of tissue removed in an emergency procedure where the patient is not conscious, consent for/lack of objection to donation of tissue for research could be obtained from relatives or family members. In absence of these, the advice of the hospital's ethics review board and tissue review board should be obtained.
- 3.3. For **healthy living volunteers**, the Chapter feels that the legal age of consent for donation of tissue should follow what is specified in MTERA for donation of body parts; which is persons over the age of 18. Tissue from the mentally incompetent/incapacitated or from those below this age group should preferably not be taken, especially if harvesting of tissue requires any form of surgery or anaesthesia. In exceptional cases, if tissue harvest is contemplated, researchers should ensure that the procedure does not carry any adverse on the donor. Consent must also be obtained from the legal guardians, and approval of the ethics review board of the hospital or institution involved in the study documented.
- 3.4. Where **donated** tissue, or tissue removed prospectively from volunteers is concerned, the consent is for a particular, specified approved project. In these cases, the question would be whether the initial consent extends beyond the original project. It has been common practice to store collections of tissue (including blood, blood products and body fluids) on completion of the project, with a view to using these for future yet to be specified projects. The principal investigator may also 'share' samples with other researchers. The **Chapter** recommends that these issues be addressed in the original protocol and that patient consent for, or objection to, archival of specimens and further research (on completion of the original project) be documented. Any further research project (assuming consent is given), should be treated as a new proposal and be submitted for approval by the relevant authorities. (cf Section 7, Archived Tissue)
- 3.5. In the case of **tissue** removed for therapeutic or diagnostic purposes, the consent is usually for the surgical procedure with removal of tissue,

for diagnostic or therapeutic purposes. Presently, the use of this tissue for research and other scientific purposes, though widespread, is not formally addressed.

- 3.6. The **Royal College of Pathologists, UK**, has recently issued transitional guidelines for handling of 'surplus' tissue arising from surgical procedures. Here the College recommends that 'generic' consent be taken from patients for use of surplus tissue for laboratory quality control and research work and that any research programme utilising this tissue would require the approval of an institutional ethics/review board. The Chapter fully endorses this view.
- 3.7. The Chapter **recommends** that 'consent for operation' forms should include an option whereby the patient is able to indicate lack of objection to, or donation of, 'left over' or 'surplus' tissue for medical research. For instance, a consent form may include the following sentences :
'I understand that tissue is necessarily removed and will be submitted for analysis and diagnosis.
I consent/do not consent to the donation of this tissue for research, teaching and other scientific purposes.

4. REPOSITORIES AND STORAGE

- 4.1. **Storage** : Human tissue may be stored as fresh tissue without fixative, frozen tissue or processed tissue for instance as paraffin blocks or slides. This also applies to blood and blood products, and other tissue or cell samples.
- 4.2. **Repositories**: Tissue holdings exist in many hospitals, institutional and research laboratories in Singapore. The diagnostic laboratories hold tissue samples which have been used for diagnostic purposes and may hold donated or surplus tissue. Research laboratories may hold donated tissue, or surplus archived tissue.
- 4.3. **Diagnostic Pathology Departments** : All institutions and hospitals in Singapore with service laboratories hold tissue blocks and slides, and archived samples of body fluids, blood and blood products. A few may hold wet tissue. Generally these departmental holdings are probably the largest tissue archives in Singapore.
- 4.4. **Diagnostic Departments** : archive diagnostic tissue samples in accordance with current good clinical practice guidelines, the case files

(in this case slides and blocks) can be reviewed and perhaps sent for expert opinion. The tissue is kept against the chance that there may be a medico-legal challenge regarding the diagnosis or the possibility that new prognostic and therapeutic markers may be developed, and used during the patient's lifetime. One such example is the use of Herceptin which requires evaluation of c erb B2 expression on the tumour cells. All service departments have standard procedures regarding documentation, minimum retention times, conditions of storage and use of tissue as well as cyclical laboratory audits.

- 4.5. **Research Departments** : Tissue, blood and blood product holdings in non diagnostic departments are not as well regulated, and is very much dependant on the individual researcher or principal investigator. Because of this dependance, these holdings/research banks are the source of some concern as guidelines for documentation, conditions of storage, identification of biohazards, verification and use of the tissue held are not clearly given nor audited by any professional body.
- 4.6. **Research Collections** : The fate of collections kept by individual researchers under specific grants are influenced by mundane matters such as resignation or prolonged leave of the researcher/principal investigator or lack of funding of the research programme.

5. TISSUE BANKS

- 5.1. The **concept** of establishing tissue banks to encourage biomedical research is currently very much in vogue. The Chapter however is concerned at the haste in which such banks are being set up without proper audit and due accreditation of processes. A **census** of tissue banks/collections in Singapore, and details of their holdings is highly recommended. These should be made known to the hospital or host institution where these holdings reside.
- 5.2. All **tissue banks** must be properly audited and accredited. There should be a quality programme, on a national level, to ensure "good tissue practices". The Chapter would recommend and support the formation of an ad hoc committee involving regulators, professional bodies and the biomedical industry with a view to register, inspect and accredit tissue banks in Singapore.
- 5.3. All **tissue collected** need quality assurance control, verification of tissue type and screening for biological hazards. For this, a pathologist has to

be involved. The Chapter strongly urges that all tissue banks must have a named accredited specialist pathologist in a supervisory and legally accountable role.

- 5.4. In the case of **tissue** collected purely for specific research projects, a finite end point and retention time for these specimens must be stated in the research protocol and the disposal of such tissue should be addressed. cf Section 3.4.
 - 5.5. **Collection** of surplus tissue should take place after examination of the tissue by the reporting pathologist. This is because the legal responsibility of reporting margins, adequacy and extent of resection falls on the pathologist. This is also an important tissue audit issue as the question of unnecessary surgery and excessive harvesting of tissue may arise, especially if the surgeon/clinician performing the biopsy are involved in a study that utilises this tissue. Collection of fresh tissue can be facilitated if prior arrangements are made with the reporting pathologist.
 - 5.6. If there is **chance** that these samples are to be archived after completion of the project and possibly used for subsequent projects, this intention must be stated at the time that tissue was harvested. Documentation should include conditions of storage and disposal, presence or absence of **linkage** to patient identity, and ethics committee approval for other future research projects. cf Section 3.4.
 - 5.7. **Central banking** has been mooted in several countries, but issues regarding intellectual ownership, patient consent and ultimate fate of harvested/stored tissue have arisen. This is well addressed in Livolsi's paper. Under the present circumstances, the Chapter does not support the idea of central banking. As all service departments are required to keep good documentation of the extent and type of holdings within their premises, the Chapter suggests that each individual institution be responsible for their own service holdings, but perhaps subscribe to some central data network where availability and location of tissue holdings are listed.
 - 5.8. The **tissue bank** should also be able to audit end users of the human tissue samples supplied.
- ## 6. CUSTODIANSHIP
- 6.1. The **Chapter** is of the opinion that the legal owner of the tissue is the tissue donor himself/ herself.

- 6.2. **Diagnostic Service Departments** : act as stewards or guardians of the tissue on the patient's behalf. Tissue archives in these departments are part of the hospital's medical records. The Chapter's guidelines for ethical laboratory practice states in paragraph 6.5 that as stewards of the patient's tissue, 'the laboratory providing the primary diagnostic analysis is responsible for the maintenance and integrity of archival tissue', and that while researchers should not be prevented from using this tissue, the pathologist must ensure patient confidentiality and also that there is sufficient tissue left over for diagnostic review and for the possibility of subsequent prognostic work up.
- 6.3. The **responsibility** for upkeep, maintenance, use and audit of research collections should be the responsibility of the institution/hospital/ research organisation where the original research collection was approved, or to which the tissue was donated. The institution should have proper documentation of tissue collections under its custody. Although the principal investigator may have immediate daily responsibility for the tissue, the host institution should be the formal custodian.
- 6.4. **Tissue collections** should not be allowed to be transferred between institutions or researchers without approval of the ethics and institutional boards. Collections of human tissue samples should not be regarded as the 'personal property' of any one individual investigator or team.
- 6.5. For **diagnostic tissue**, the service department has the right to refuse release of this tissue for research projects that have not been approved by the proper ethics/institutional review board, and which have not sufficiently met all the criteria as defined by that particular laboratory.
- 6.6. If **paraffin blocks** are removed from the service record files, there should be some arrangement for these to be traceable at all times, and for these to be returned to the original laboratory when the study is completed. The intellectual property and work of the pathologist/department in identifying the diagnostic tissue for these projects should be addressed satisfactorily in the study protocol.
- 6.7. '**Surplus Tissue**' : Custodianship of material left over from therapeutic or diagnostic procedures rightly lies with the laboratory where the initial diagnosis was made. The Chapter would emphasise that it is only after the pathologist has examined the tissue and the diagnosis made, that the remaining tissue can be considered 'surplus'. In principle, the Chapter

feels that this tissue is best managed by the pathology department as this is the very nature of that department's functions. However this is an issue for each individual institution to resolve.

7. RESEARCH ON ARCHIVED TISSUE

- 7.1. The **Chapter** has received several submissions on the definition of 'research' and whether all research projects require ethics committee approval.
- 7.2. The **Royal College of Pathologists, UK**, state that as long as the research proposal requires the performance of new or additional testing, this requires the approval of the ethics review board. However, if the 'research' proposal merely reviews and compares old slides and data on files, and has no adverse consequences to the patient, then the project can proceed with a minimum requirement that the review board is informed. The Chapter endorses these recommendations.
- 7.3. For **genetic** research, the Chapter supports the recommendations of the Medical Research Council, UK and the Advisory Committee on Genetic Testing - specifically regarding the necessity of consent for tests and that genetic testing should not be added onto an existing study without consent.

8. PATIENT CONFIDENTIALITY

- 8.1. **Tissue banks** providing samples to researchers should ensure patient confidentiality. Samples should be non-identifiable/non-linked/anonymised where possible. In all these cases, however, the original tissue bank should have a comprehensive documentation and a good tissue tracking system.
- 8.2. **Reference** is made to the Chapter's Guidelines on Ethics of Laboratory Practice where patient confidentiality is addressed. Researchers do not have automatic right of access to patient records. This must be approved by Ethics Review Boards.
- 8.3. **Researchers** should consider if donors of tissue samples/research participants wish to be informed of the results of the research project. This should be addressed in the research protocol. This is of particular importance in the case of genetic testing.

- 8.4. **If**, in the course of the project, a particular individual result reveals a finding of clinical and therapeutic importance, good clinical practice norms would require that there is a clear duty of care to inform the research participant via the clinician responsible for his or her care.

9. FINANCIAL CONSIDERATION

- 9.1. **Donation** of human tissue must be free. There should be no financial payment of the donor.
- 9.2. There should be no **commercial** exploitation of human tissue. The rights of the tissue donor with respect to potential patents and financial profit should be clearly addressed in the study protocol. Customarily, the tissue donor renounces these rights as the proportion of an individual tissue donor's contribution in a study may be impossible to quantify. This aspect however needs be explained and consent documented from the outset, especially if the purpose of the tissue collection is to establish a commercially viable product.
- 9.3. The **laboratory** providing the tissue banking service should be allowed to recover the costs of the service.

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