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OPINION

Tumour banks: well-guarded treasures in the interest of patients

J. Wolter Oosterhuis, Jan Willem Coebergh and Evert-Ben van Veen

In order for the genomics revolution to change how we diagnose, categorize and treat cancer, scientists and clinicians must have access to tumour samples. There has therefore never been a better time to create banks of tumour tissue. Collecting and storing tumour samples and their associated data, however, creates numerous methodological, ethical, legal and technical problems. How can we leap these hurdles in a responsible manner and still make full use of the wealth of information that can be obtained from them?

It has never been more rewarding to collect and store leftover tissues from diagnostic and therapeutic procedures in tumour banks. Scientific and technical advances in genomics, proteomics and bioinformatics make it possible to do extensive analyses of very small tissue samples, and many assays can even be done on formalin-fixed and paraffin-embedded tissue. We are beginning to diagnose and treat cancer by identifying markers and critical biological targets in tumours. Information technology techniques, including telemedicine, are available to optimize the management and accessibility of stored samples. But, at the same time, the use of leftover tissue for research has never been under stricter ethical scrutiny, because of the wealth of personal, clinical and behavioural information that can be extracted from tissue samples. This type of research has therefore been the subject of legal constraints that are aimed at protecting both the interests of the tissue donor and future patients. How can we balance the needs and the rights of patients and researchers to optimize the use of this precious resource? Given the increasingly international nature of collaborative studies, a widely accepted code of conduct for research on left-over tumour and normal tissue is essential to facilitate the exchange of samples and data.

What is a tumour bank?

Tumour banks are facilities that are organized to collect, store and distribute samples of tumour and normal tissue for further use in fundamental and translational cancer research. The samples are generally obtained from histopathology and cytology laboratories, which process smears, biopsy and surgical specimens for diagnosis.

It is possible for pathologists to collect fresh tissue prospectively during their routine dissection procedures. In this way, the specimens can be optimally sampled and stored for both diagnosis and research purposes. Ideally, specimens are sampled immediately after surgery, prior to fixation, to ensure optimal preservation of proteins and nucleic acids (BOX 1). Occasionally, tumour tissue can be procured at post-mortem examination. Retrospective collection of tumour tissue for study and banking purposes is feasible because, in most countries, pathology laboratories have been legally obliged to file, for at least some years, the formalin-fixed and paraffin-embedded samples that were analysed. Both approaches — prospective and retrospective — are compatible with good laboratory practice; the tissue used in retrospective analysis is left over from the diagnostic process. Banking, therefore, does not interfere with the pathologist's priority of making an accurate diagnosis.

It is not surprising that many tumour banks are based in pathology laboratories. Pathologists receive and process most of the tissue and cell samples from patients. As guardians of these samples and also experts in tumour biology, it is natural that they have taken a leading role in the creation of tumour banks for research. Recent advances in biological targeting have modified the pathologists' roles. Part of their job now is to answer questions such as whether a patient's tumour expresses a certain drug target, such as ERBB2 (also known as HER2/neu), which is targeted by trastuzumab (Herceptin) in breast tumours[1], or c-KIT, which is targeted by imatinib (Glivec) in gastrointestinal stromal tumours[2]. The pathologist is therefore also involved in selecting the appropriate therapy for cancer patients. Pathologists can derive a large amount of information from a tumour sample, so serious harm can not only be done to scientific progress, but also to the patient when these samples are discarded.

Types of tumour bank

Many investigators who are involved in such cross-sectional and prognostic research have their own, specialized collections of tumour samples on which their research is based — so-called 'project-driven' tumour banks. Systematic collection of all available tumour tissue is much rarer. Systematic could mean collection of samples from consecutive patients, random samples or even population-based samples. Institutions might have been reluctant to invest in such efforts because specific research objectives were lacking. But this attitude is changing rapidly, and it is now widely appreciated that we have much to gain from high-throughput analytical approaches in cancer research[3]. The conditions and the equipment are now at hand for cancer researchers to embark on highly successful, hypothesis-generating 'fishing expeditions'. Moreover, the methodology for clinically and aetiologically relevant research has been explicated[4].

The usefulness of tumour banks in research depends as much on the quality and accessibility of the tissue samples as on the reliability and extent of the information that is stored with them. Exposure data (gathered in various cohorts), personal and clinical data

Box 1 | How tissue samples are processed

The goal of routine pathological processing of specimens is to describe their gross appearance and to sample all visible pathological areas (lesions) for examination. Small specimens (biopsies and small surgical specimens) are often entirely processed for embedding in one or more paraffin blocks. A paraffin block typically contains a piece of tissue not bigger than 2 mm thick and 2 cm diameter. Representative areas of tumours are sampled from larger surgical specimens for paraffin embedding, in addition to surgical margins and dissected lymph nodes to study loco-regional extension of a cancer. Paraffin embedding requires fixation (usually in buffered formalin; ethanol fixation combines acceptable morphology with good-quality RNA) and dehydration of the tissue. From a paraffin block, slices of 2–4 μm thickness can be cut for histological examination. Formalin-fixed, paraffin-embedded tissue is cheap to store and has a virtually unlimited shelf life.

Normally, only the paraffin-embedded tissue will be stored in a pathology laboratory. The rest of the dissected specimen is discarded after the diagnosis has been reported. So, only minute amounts are kept from larger specimens; the bulk of the tissue will be destroyed.

Immunohistochemistry and molecular analyses often require unfixed, fresh/frozen tissue. It is therefore becoming routine to take representative samples from unfixed tumour and normal tissue for frozen storage. For research purposes, frozen tissue is preferred over paraffin-embedded tissue. However, processing and storage is more difficult and expensive.

The paraffin-embedded and frozen tissue that is stored in pathology laboratories as 'left over' from the diagnostic process could, according to our proposal, be used for further research, if the patient does not object. In an ideal setting, pathologists would save some extra samples of normal and tumour tissue for future research. This would, of course, not be allowed if the patient objected to the secondary use of his/her tissue for research.

(collected at the time of diagnosis), tumour stage and histological classification, information on the response to treatment, and follow-up data should all be linked in a responsible way — along with samples from an appropriate control group, if possible. Investigators could then correlate their experimental findings with these data, at the level of individual patients and groups of patients. The goal of storing this type of information would be to study the effects of certain exposures, to redefine disease entities or prognostic groups, and to associate these with treatment response. Virtual tumour banks will aid in this process[5] (BOX 2).

If used in properly designed studies[4], tumour banks will undoubtedly advance cancer research, and so benefit present and future cancer patients. However, the nature of the information that can be extracted from the tissues and the linked patient data can conflict with patients' rights. What are these rights, and how can we ensure that, where tumour banks are concerned, the interests of the patient/donor and the goals of science can both be upheld?

Tumour banks and the law

The legal framework for tissue banking and research, based on secondary use of samples, is still fragmentary and confusing. Binding international treaties on this subject do not yet exist. National legislation that is specifically for tissue banking exists in very few countries, such as Iceland and Sweden. At present, the specific legal and ethical aspects of tissue banking are mainly and most comprehensively addressed by a growing number of reports from national and international advisory bodies[6–12].

These reports, however, differ on numerous aspects. Most of these reports only address the consent procedures for the use of tissue for research purposes after the tissue has been stored, but not for the storage and handling of tissue as such. In some countries, such as France, the existing safety regulations for the preparation of human tissue for medical purposes, such as allogeneic bone grafts, are applied to the handling of tissue for research purposes as well.

Other countries, such as the United States, have highly regulated consent procedures for clinical research subjects that are also applied to tissue banking[11,13]. These consent procedures apply to publicly funded institutions that perform research involving human tissues, and research protocols are carefully revised by Institutional Review Boards[13]. The latest version of the World Medical Association's Declaration of Helsinki also equates medical research using human subjects with research on identifiable tissue[14].

Research involving human tissues does, however, differ in many respects from clinical trials research[15,16]. Referring to an individual whose tissue sample is used as a 'research subject' blurs this difference between patient and sample. We therefore will avoid this term, and use instead the more neutral word 'donor' — reminding readers not to confuse this designation with organ donation. Organ donation is a completely different matter. Yet, in some countries, laws on organ donation, or laws on post-mortem examination, also apply to human tissue research[9]. In any case, if research is done with tissue that can be traced back by the tissue bank to the donor (directly identifiable tissue), data protection legislation is applicable.

Balancing competing interests

Legislation and codes of conduct regarding research on human tissues must balance the interests of science and involved donors. In this context, medical research should not be seen as an end in itself. Research studies involving banked tissue will serve the general good of society by improving our understanding of disease mechanisms, and improving treatments for current and future patients.

The patients whose tissues are used in the study — 'the donors' — have rights to autonomy and privacy. Autonomy (self-determination) is a fundamental human right. Since the late 1980s, people have become aware that tissue samples can be used to derive highly personal information. Recently, most researchers agreed that it is the patients' right to determine the final destination of their tissue samples.

Privacy is obviously also an issue because tissue research essentially tries to correlate exposure and clinical data with information that has been extracted from the tissue, such as molecular or genetic features. Violation privacy rights can result in serious harm to donors when individuals who are outside the health-care field — such as employers or health insurers — acquire sensitive information that can be used against the patient. Privacy can also be violated by letting donors themselves know about research findings when they had chosen not to be informed. Genetic information about disease risk is very sensitive. The knowledge that a certain individual has a genetic predisposition to a disabling disease can create problems for donors and their relatives in planning their future, or even when applying for a job or an insurance. What mechanisms need to be in place to safeguard the donor's interests, and at the same time promote the interests of those who might benefit from research that is facilitated by tissue banking?

Safeguards for conducting research

Safeguards for conducting research should include review and approval of the research protocol by an ethics committee, maintaining confidentiality and respecting the consent

procedure. Tissue should be used with the exclusive goal of answering the scientific questions posed. Good research practices encompass both technical and procedural measures to guarantee that these safeguards are kept. Technical measures will consist of firewalls between research data and clinical records, if these are available at the same institution. These safeguards are more easily guaranteed in European countries, where for-profit-insurers do not own health-care facilities, statutory basic health insurance is available for the whole population, and strict privacy regulation applies to commercial as well as public industries[17]. Procedural measures must guarantee that investigators will not have access to information that the patient has not consented to, and research data should never be published unless the patient remains fully anonymous. Scientific research journals should also bear part of the responsibility, by refusing to consider any manuscript that describes experiments that are conducted on human tissues, unless it includes an explicit statement from the authors regarding measures that were taken to comply with local laws and international standards for the protection of patients.

Consent procedures

Consent procedures vary between countries. The strictest laws require potential donors to consent to the storage of the tissue after it has lost its clinical utility, and donors provide separate consent for each individual research protocol that will involve their tissue. The recent Swedish law on tissue banking is an example of this approach[18]. A less strict procedure would omit the consent for storage. In 'layered' or 'multiple-choice consent' procedures, patients agree to allow their samples to be used only in certain types of research, such as research that is directly related to a specific disease. Donors can also provide blanket consent, which allows their samples to be used in any type of research. Until about 10 years ago, most countries had no consent procedures at all, and this is still the case in some countries. Iceland's Act of Tissue Banking[19] and the Dutch Code of Conduct[20] offer middle-of-the-road consent procedures for tissue research (TABLE 1).

We believe that the level of consent that is offered to a donor should depend on how his/her tissue is to be labelled and identified. Although the reports listed above all use different terminologies, they all make some sort of distinction between directly identifiable, indirectly identifiable and fully anonymous tissue. In the case of directly identifiable tissue, the researcher knows — or can easily discover — the identity of the donor. For indirectly identifiable or coded tissue, the identity of the donor remains unknown to the researcher but can be retrieved by the provider of the tissue (the physician who treats the donor, for example) by a code that identifies the tissue. The privacy of the donor is not at stake at the level of the researcher. Finally, in the case of anonymous tissue, the identity of the donor cannot be retrieved without resorting to extraordinary means.

Middle ground

Using these distinctions, the following proposal for a consent procedure combines a high level of protection for the donor and feasibility for the scientific community: indirectly identifiable or anonymous tissue samples should be made available for storage and research, as long as the donor has not objected to its research use. The storage or use of directly identifiable tissue should require the informed consent of the donor for each specific research use.

Indirectly identifiable or anonymous tissue can be collected by means of an 'opt-out' system. In this system, patients must be informed that their tissue could be stored in a tissue bank for further use in research. While the patient is in the hospital, physicians would offer patients the opportunity to opt out of the tissue storage procedure. There is ample evidence that most patients would not object to the donation of their leftover tissue samples for research if researchers are transparent about their projects and procedures and the above-mentioned safeguards have been met[21–24]. Our proposal is very much in keeping with the public opinion, but leaves ample room for those who object to the secondary use of their tissues. Of course, donors should be able to exercise their right to autonomy by withdrawing their implicit consent at any time.

Under stricter consent procedures it is difficult to prospectively and systematically bank (frozen) tumour tissue, for a number of reasons, as it becomes available during the diagnostic process. In the first place, it would rely heavily on the cooperation and interests of the treating physicians and therefore lead to strong biases in the types of tissue collected for banking. Secondly, at the time of banking, the specific research studies in which the tissue will be used cannot be foreseen. Under a strict consent protocol, researchers would have to go back to the donors to get their consent for each particular research application. This is obviously a prohibitively tedious and costly procedure. Although practical arguments like these should never be used to bypass individual rights, they can contribute to — in connection with the other interests involved — the creation of a balanced consent procedure. The balance that we and most other cancer researchers seek is not compatible with a strict consent procedure.

In our proposal, coded and anonymous tissue are similar as far as the consent procedure is concerned. However, there is a major difference between fully anonymous and coded tissue. With coded tissue, as with directly identifiable tissue, the results of research can be made available to individual patients by their treating physician. This is not the case for anonymous donors.

The option of individual feedback on research findings should, therefore, be mentioned in the opt-out procedure. As a rule, however, there is no need for individual feedback of research results, because important new research findings will eventually benefit

Box 2 | Virtual tumour banks

Virtual tumour banks are databases of microscopic images of the samples stored in a tumour bank. Databases could be set up to include a network of tumour banks from different medical centres. The images could be accompanied by an anonymous set of data, including patient sex, age, exposures, tumour site, stage and histological diagnosis, outcome of disease and response to therapy.

This application of telepathology enables authorized researchers to browse the content of a tumour bank without physically handling the samples. Virtual tumour banks make it possible to select the best specimens for a particular experiment, and simplifies planning of collaborative efforts. For example, tumour samples from a variety of databases can be screened for inclusion in large-scale studies, such as tissue microarray analysis, to determine the prognostic value of the expression patterns of certain tumour types.

A virtual tumour bank is currently under development at the data centre of the European Organisation for Research and Treatment of Cancer. This project — named Tubafrost — has been funded by the European Commission and has the goal of creating a virtual tumour bank that provides access to the collections of frozen tissue samples of ten major European cancer centres[5].

Table 1 | Variations in consent procedures for storage and research use of human tissues

	Storage			Research use			
Country	**Anonymous**	**Coded**	**Identified**	**Anonymous**	**Coded**	**Identified**	**References**
Global						Opt out	8
Global						Consent 1	14
European Union	No rules in most countries	No rules in most countries	Via data protection, ref. 17, consent 1A	No rules in most countries	No rules in most countries	Via data protection, ref. 17 consent 1A	9,17
Iceland		Opt out*	Consent?		Opt out*	Consent?	19
UK						Consent 2	12
The Netherlands	Opt out‡	Opt out‡	Consent 1‡	Opt out‡	Opt out‡	Consent 1‡	20
The Netherlands (Dutch Civil Code)				Opt out*			
Sweden		Consent 1*	Consent 1*		Consent 1*	Consent 1*	18
USA				Consent 1A	Consent 1	Consent 1	11
USA				Consent 1A§	Consent 1§	Consent 1§	13
Canada				Consent 1?	Consent 1	Consent 1	10

The Table globally compares the quoted sources, omitting specific information, such as differences at the state level in federal systems. *Laid down in legislation applicable to everyone. ‡Based on self-regulation. §Binding to specific types of institutions (such as those working with public funds). Text indicates explanation of the common law, privacy legislation or regulation of research with human subjects applied to tissue banking or a statement based on ethical considerations (as of November 2002). Blank boxes indicate that this topic is not addressed in the referenced report, or that the position is unclear. Types of consent: consent 1, specific for each research protocol; consent 1A, as 1, but consent might be waived (minimal burden, minimal risk); consent 2, multiple choice consent, such as 'disease-related but not tied to a specific protocol', 'specific for genetic research but not tied to a specific protocol' or 'blanket consent'.

the donor by means of improvements in health care. The prompt and universal acceptance of c-KIT expression as a relevant factor in the diagnosis and treatment of various tumours — in particular, gastrointestinal stromal tumours — adequately illustrates this point[2].

Existing tumour banks that were established without consent of the involved donors create a temporary problem. The practical approach that is favoured by most reports is that the banks can be preserved, and that the tissues can be used for research without retrospectively asking for consent of the donors, provided that only coded or anonymous tissue and data are used. If the data are directly identifiable, consent is required from the donors. The Swedish law requires that existing tissue banks are destroyed unless retro-active consent is obtained from the donors. Under certain circumstances can the tissue bank be preserved without retroactive consent by making the existing material fully anonymous[18].

Commercial use of human tissues

No one would deny that human cells and tissues have been exploited in commercial settings, and that progress in medicine is also due to this commercial use. Yet there is no unanimity on the ethical aspects of this. The highly debated issue of patenting of human genes[25–28] is just one example of these types of issues. In Europe, it is accepted that donors should not have financial incentives for making their leftover tissues available for secondary use[29,30]. Tissue banks should not commercially market tissue samples[20,30,31]. European researchers do not, however, exclude the possibility of commercial exploitation of inventions that are based on tissue research in industry. In cases in which academia and commercial researchers collaborate, the findings of the academic partners should be freely disseminated for the public good, thereby carefully avoiding even potential 'conflicts of interest'[32,33].

Whether donors could or even should share in the profits of commercial use of their tissues is a difficult question. This is not deemed acceptable in Europe[30]. In the United States, there are strong opinions in favour of the possibility of financial incentives for donors[34,35]. It is advisable to make tissue fully anonymous when making it available to companies. Any consent procedure should be transparent on the issue of possible commercial exploitation of donated tissue.

Conclusions and future directions

In terms of the banking and research use of leftover tumour and normal tissue samples, we propose a consent procedure that distinguishes between identifiable, coded and anonymous tissue. Identifiable tissue samples would require written informed consent from the patient for specified uses. Coded and anonymous tissues could be collected on an opt-out basis. Research discoveries would be reported to (indirectly) identifiable patients only if they so wish. Patients could be discouraged to ask for individualized information, as clinically relevant new findings will benefit the patients as a group via state-of-the-art, evidence-based medicine. Research proposals that make use of banked tumour samples of any type should require approval by protocol review board and by medical ethical committees.

Donors should agree to donate tissue for storage and research without financial incentives, and tissue banks should be operated on a not-for-profit basis. The consent procedures for potential donors should clearly outline the possibility of the use of their tissue by companies.

International collaborative efforts in translational cancer research would strongly benefit from supranational networks of tumour collections that can be accessed by means of virtual tumour banks. For this to happen, there needs to be an internationally accepted code of conduct for the banking and use of the samples, such as the one we have proposed. Strict laws on tissue banking, such as those that exist in Sweden, will slow the progress of cancer research, and, in the long term, will harm patients rather than protect them.

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Biog

James Mulshine received his clinical training in internal medicine at the Cleveland Clinic, and in medical oncology at the National Cancer Institute. He began working on lung cancer tumour biology as a post-doctoral fellow in John Minna's laboratory in 1981. He developed a variety of diagnostic and clinical applications with monoclonal antibodies for lung cancer. He has led a section since 1988 that has focused on developing clinical management tools for pre-invasive lung cancer, such as by exploiting promotion factors as targets for chemoprevention. He is the co-chair of the Aerodigestive Chemoprevention Faculty at the Center for Cancer Research, National Cancer Institute.

CancerNet

breast cancer
http://www.cancer.gov/cancerinfo/pdq/treatment/breast/patient/

cervical cancer
http://www.cancer.gov/cancerinfo/pdq/treatment/cervical/patient/

colon cancer
http://www.cancer.gov/cancerinfo/pdq/treatment/colon/patient/

lung cancer
http://www.cancer.gov/cancer_information/xml_tab.aspx?viewid=7d080f7f-585d-40e8-bd59-13fb31481b2b&expand=Lung

ovarian cancer
http://www.cancer.gov/cancerinfo/pdq/treatment/ovarianepithelial/patient/

pancreatic cancer
http://www.cancer.gov/cancerinfo/pdq/treatment/pancreatic/patient/

prostate cancer
http://www.cancer.gov/cancerinfo/pdq/treatment/prostate/patient/

FURTHER INFORMATION

Clinical screening information:
www.cancer.org

National Lung Screening Trial:
http://cancer.gov/NLST

Report of the Lung Cancer Progress Review Group:
http://prg.nci.nih.gov/lung/finalreport.html

Lung Imaging Database Resource for Imaging Research:
http://www3.cancer.gov/dip/steer_lidc.htm

State-of-the-Science Workshop for Lung Cancer:
http://www.webtie.org/sots/Meetings/Lung/June%2019%202001/Default.htm

Biogs

J. Wolter Oosterhuis is Professor of Pathology at the Josephine Nefkens Institute, The Netherlands. His main research interest is the pathobiology and therapy resistance of germ-cell tumours. As Chairman of the European Organisation for Research and Treatment of Cancer Pathology Group, and of the Federation of Medical Scientific Societies in The Netherlands, he is interested in the technical, ethical and legal aspects of tumour banking, and proposed the idea of a virtual tumour bank.

Evert-Ben van Veen was previously the Director of Legal Counsel at Rotterdam University Hospital, and is, at present, a senior consultant at MedLawConsult, The Hague. He specializes in the ethical and regulatory aspects of medical research, privacy legislation and the consequences of European law on the free movement of health-care services and patients.

Jan Willem Coebergh has been Chairman of the subcommittee on Privacy and Self-Regulation of The Netherlands Epidemiological Society since 1991 and, since 2001, has been a member of the board of the Federation of Medical Scientific Societies. This Federation harboured the multidisciplinary committee that developed the Dutch Code on secondary use of human tissue. He is a cancer epidemiologist who has worked with the Eindhoven Cancer Registry since 1982 and teaches cancer epidemiology at Erasmus MC, Rotterdam.

Databases

LocusLink

ERBB2

http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=2064

c-KIT

http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=3815

FURTHER INFORMATION

Biobank UK, a study of genes, evironment and health:
http://www.wellcome.ac.uk/en/1/biovenpop.html

Federation of Medical Scientific Societies in the Netherlands: www. fmwv. nl

Human Tissue Banking:
http://europa.eu.int/comm/secretariat_general/sgc/ethics/docs/avis11_en.pdf

NCI/National Action Plan for Breast Cancer:
http://www-cdp.ims.nci.nih.gov/legal.html

Office for Human Research Protections (ORHP) [1993] US Dept of Health and Human Services (DHHS):
http://ohrp.osophs.dhhs.gov/jan2001bu/humansubjects/guidanc/reposit.htm

Public Health Genetics, UK:
http://www.medinfo.cam.ac.uk/phgu/info_database/ELSI/genet-database.asp

University of Minnesota Cancer Center Tissue Procurement Facility:
http://www.cancer.umn.edu/page/cores/tisproc5.html