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REVIEW PAPER

Standard Operating Procedures, ethical and legal regulations in BTB (Brain/Tissue/Bio) banking: what is still missing?

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Abstract The use of human biological specimens in scientific research is the focus of current international public and professional concern and a major issue in bioethics in general. Brain/Tissue/Bio banks (BTB-banks) are a rapid developing sector; each of these banks acts locally as a steering unit for the establishment of the local Standard Operating Procedures (SOPs) and the legal regulations and ethical guidelines to be followed in the procurement and dissemination of research specimens. An appropriat Code of Conduct is crucial to a successful operation of the banks and the research application they handle. What are we still missing ? (1) Adequate funding for research BTB-banks. (2) Standard evaluation protocls for audit of BTB-bank performance. (3) Internationally accepted SOP's which will facilitate exchange and sharing of specimens and data with the scientific community. (4) Internationally accepted Code of Conduct. In the present paper we review the most pressing organizational, methodological, medico-legal and ethical issues involved in BTB-banking; funding, auditing, procurement, management/handling, dissemination and sharing of specimens, confidentiality and data protection, genetic testing, "financial gain" and safety measures. Taking into consideration the huge variety of the specimens stored in different repositories and the enormous differences in medico-legal systems and ethics regulations in different countries it is strongly recommend that the health-care systems and institutions who host BTB-Banks will put more efforts in getting adequate funding for the infrastructure and daily activities. The BTB-banks should define evaluation protocols, SOPs and their Code of Conduct. This in turn will enable the banks to share the collected specimens and data with the largest possible number of researchers and aim at a maximal scientific spin-off and advance in public health research.

Keywords Brain/Tissue/Bio banking · Code of Conduct · Donors · Ethics · Financial gain · Funding · Genetic testing · Informed consent · Safety · Sharing

Abbreviations

AD	Alzhemiers disease
BTB	Banks—Brain/tissue/Bio banks
EBBN	European Brain Bank Network
SOP	Standard Operating Procedure
MTA	Material Transfer Agreement
QMS	Quality Management System
TubaFrost	European Human Frozen Tumour Tissue Bank

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Introduction

Brain/Tissue/Bio banks (BTB-banks) are essential repositories supplying basic scientists and bio-industries with human biological specimens obtained from living donors or obtained at post-mortem autopsy.

The exponential growth of modern neurobiological techniques, which can be applied on human samples increases the pressure on these banks to supply a large number of specimens to the scientific community and the bio-industry.

Rapid progress in molecular biology, genetics and pathology paves the way for elucidating disease mechanisms and subsequent development of targets and therapeutics. Biological research specimens can be obtained from several sources:

a. A traditional tissue/biobank who is connected with a local donor program at a single central facility. These banks deal with *prospective tissue procurement service* to anticipate research applications. Part of the specimens are used for diagnostics and the rest is stored for short periods until they can be shared with researchers;
b. Virtual bank in which specimens are collected, handled and stored locally with the associated specimen data centralized. Requests for specimens are handled through a central coordinating office;
c. Hospital pathology departments;
d. Coroner's office. All of the above need to have full consent/authorization from the donor or next of kin/legally authorized person (Human Tissue Act 2004, 2006).

The currently operating research BTB-banks have been established in the past decade and form at present an important link between donors, their relatives, clinicians, pathologists and scientists. These banks are confronted with a need for a consensus on legal and ethical guidelines as well as clinical and pathological criteria, which will make the specimens suitable for high quality scientific research, teaching and target development (Anderson et al. 2001; Baeyens et al. 2002; Gindro and Mordini 1998; Royal college of Pathologists 2001; The Nuffield Council on Bioethics 1995).

To facilitate the work of BTB-banks on the international level, we still have to solve the following four major structural features, which will be specified hereunder:

1. Adequate *funding* for BTB-banks, governmental or otherwise.
2. Audit/review protocols for an external auditing commity.
3. Concensus on the *methodological framework* formulated as SOP's
4. Consensus on the legal/ethical regulations formulated in a *Code of Conduct*.

Funding

The main objective of BTB-banks is retrieval and storage of human biological specimens. Due to recent developments in molecular genetics, tissue culturing, stem cell technologies and tissue manipulation techniques, there is increased pressure on BTB-banks and this sector is undergoing a major transformation.

New products and processes require a higher level of tissue manipulation, complex processing of the samples and a growing number of specimens; all these factors increase the running costs of the banks.

The funding of research BTB-banks is at present still a major problem as not all banks are government-funded or supported by the local health care system. The funding, or more often the lack of it, creates a major obstacle and will determine whether banks will make their repositories open for the scientific community, health care system and the pharmaceutical companies. Sharing of specimens often depends on the ability to obtain adequate compensation for the costs involved in recruiting, handling and preserving the specimens in the proper way, in addition to the costs of registration/documentation of the clinical and pathological data who accompany the specimens.

One possible scenario to facilitate funding on a local level is using a *Foundation or a Charitable Trust* as a model for BTB-banks. This will be based on an agreement between the host institution of the bank, the researchers and the donors. The Foundation/Charitable Trust is a flexible legal structure for stimulating potential donors and research that will eventually benefit public health. The Foundation/

Trust will have the means and experience to attract grants and funding from public foundations and patient's associations as well as private donations. The Foundation/Trust has clear legal, ethical and scientific advantages.

The mechanism of obtaining funding depends on the Bank's mission and whether the bank uses its resources and knowledge for pure basic research, public health or both? A good solution to attract more funding will be to adapt a shared cost strategy between the not for profit academic and governmental resources on one hand and the for-profit bio-industry on the other hand; this is already happening and with success in many countries in which governments, non-profit organizations and pharmaceutical companies are working together and sharing the infrastructural costs of BTB-banks.

A second scenario, on the global level, will be to establish an *international network of BTB-banks* to serve as a trustee and fund-holder.

At present the BTB-banks worldwide are not linked or represented by an international organization. Such an organisation will be able to secure funding and harmonize the methodological/legal and ethical issues and to achieve a safe, efficient and progressive BTB-bank sector.

The first collaborative effort in a pan-European context has been launched in the 90s by the European Brain bank Network (EBBN) concerted action which was a part of the Biomed-1 program funded by the European community (PL 931359). This concerted action was mainly about concordance studies and harmonisation of the clinical and neuropathological diagnostic criteria in Brain Banking (Cruz-Sanchez et al. 1995, 1997; Ravid 2002; Ravid and Swaab 1993, 1995; Ravid and Winblad 1993; Ravid et al. 1992, 1998, 2001). This network was later followed by the PF6-program-funded BrainNet Europe consortium; both networks tried to harmonise the ethical codes of conduct of the participating banks from European member states; until now without success.

Another issue is the question of 'ownership'/custody of obtained specimens and the code of conduct for collaboration with pharmaceutical companies and the bio-industry, including regulations related to the intellectual property and patenting (Womack 2002, 2006).

A genuine effort is continuously made to harmonize and standardize the broad spectrum of regulatory and ethical issues on the exchange of tissue specimens for research across Europe (Harris 2002; Malinowsky 2005; Orr 2002; Van Veen et al. 2006).

Audit procedures and standard evaluation protocols

A possible solution and support to the funding problem would be for each bank to consider criteria for assessing the effectiveness of its resource and develop a set of criteria used to determine whether it is effectively meeting a critical research/clinical needs. BTB-banks need to prove that they facilitate basic and clinical research and have regular Audits including a site visit of the review committee (Appendix 2). The evaluation/audit of the running costs of a bank is difficult but one can assess the cost recovery from the costs involved in operating the bank.

Methodological framework

Scientific research using biological samples (tissues, cells, cerebro-spinal fluid, blood, urine, proteins, RNA and DNA) has dramatically increased over the past years. The recently identified human genome, translational research and gene-expression profiling techniques have contributed to the vast possibilities of research with well-documented samples. The growing demand for well documented human specimens has served as a catalyser to the emerging of new BTB-banks, most of which operate currently with a large number of collection sites and in close collaboration between Biobanks, tissue donor banks, brain banks, nursing homes, homes for the elderly, organ transplantation national teams and surgery and pathology departments in a large number of hospitals. Various Interlaboratory concordance studies concerning SOPs and regulations have been performed in Europe. The US and Japan but there is still no consensus on a definite set of international regulations (Alafuzoff et al. 2006; Anderson 2001; Bideaut-Russel 1995; Duyckaerts et al. 1990; Ferrer et al. 2007; Matsumoto et al. 2002; Orr et al. 2002; Tenenholz-Grinberg et al. 2006). In the case of repositories who collect cells, specifically developed SOPs are used and there is at present an attempt to harmonize these protocols on European and global level. The specific legal and ethical issues attributed to the use of stem

cells, are still a topic of debate and discussion. (J. Mintzer (2007) Global bio repositories. The Coriell/BioRep experience. Available at http://www.esh.org//biobanking2007, personal communication; P. Rebulla (2007) GMP protocols for cell manipulation for cellular therapy. Available at http://www.esh.org/biobanking2007, personal communication).

The overall structure and interfaces of BTB-banks is shown in Fig. 1.

BTB-banks act as intermediaries who regulate the flow of biological specimens between donors and researchers; the banks are also the spin in the web which facilitates the availability of specimens for research and bio-industry.

BTB-banks apply various procedures stemming from validated protocols and SOPs; samples may be either frozen and stored at −80°C or fixed and embedded in paraffin blocks or kept in medium, depending on the research question. Studies using tissue specimens originating from different sources usually have to cope with huge variation and conflicting results, due to the heterogeneity of the samples and the clinical/genetic/pathological data. The establishment of the European Human Frozen Tumor Tissue Bank (TuBaFrost) took these factors into account and adapted the SOP's to be more flexible and minimize the variation between centres (Mager et al. 2007).

To guarantee specimen quality and their stability for a long period, each bank needs to have a solid quality management system (QMS) for the collection, preparation and storage of research specimens (Von Versen 1999; Von Versen et al. 2000). The pyramided structure of BTB-banks, the sample processing and data flow are shown in the schematic diagram of Fig. 2.

Research Tissue banks design factors consist of a base line including the donor system, code of conduct and rapid autopsy, ensuring the quality and ethics of the collected specimens.

The middle and upper row include the complex overall regulatory items involved.

Ethical/legal framework and Code of Conduct

The ethical, legal, and social issues arising from biomedical sciences research have not been well regulated in most countries and legislative efforts are currently arising to take care of this missing links. Bio-ethics committees are setup to review the underlying medico-legal system needed for the procurement, collection, storage and dissemination of human samples for biomedical research (Lipworth 2005; Pauwels 2007; Illes et al. 2006).

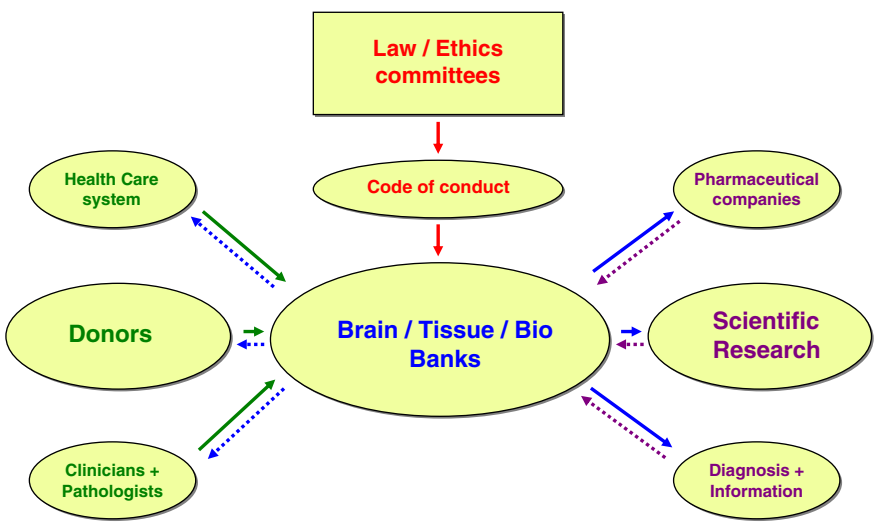

Fig. 1 *Flowchart of BTB-banks interfaces* This scheme illustrates BTB-banks as intermediaries to facilitate the availability of specimens for research. The middle line shows the three main parties who make this combination a success; the donors on the one hand, the BTB-banks and the scientific research community on the other hand. The local health care system, policy makers, clinicians, pathologists are the supporting elements and it is obvious that the main core of the banks is adherence by local legislation, ethics review committee and a solid code of conduct

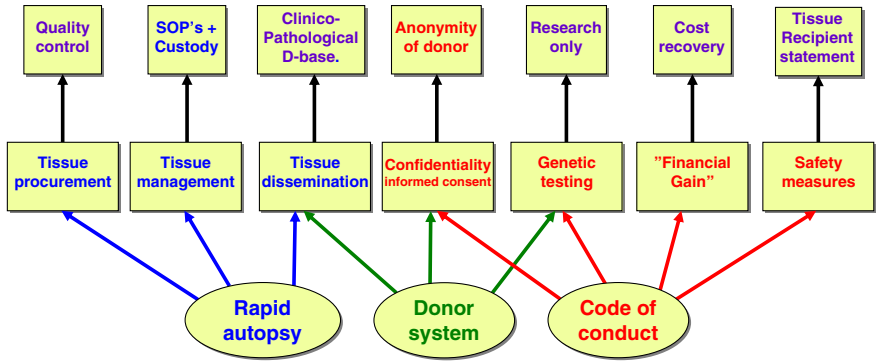

Fig. 2 *Overview of the pyramided structure of BTB-banks* The base line of the pyramided tissue banks structure consists of the donors, Code of conduct and rapid autopsies, ensuring the quality and ethics of the collected specimens. The middle row indicates the seven issues which form the Golden standard for banks collecting human specimens. The upper row illustrates the subsequent flow to regulatory and ethical guidelines for safe repositories

The concept of "bioethics" has been the centre of a long period of debate, involving experts in the filed of ethics, legal issues, science and medicine as well as governmental institutions and policy making officials and worldwide Ethics and human rights committees (Reymond et al. 2002; Snyder and Leffler 2005; Tully et al. 2000; Whitehouse 2003).

The bioethics concerning brain donation is in some respects different from other tissues/organs and requires a careful setup based on transparent information and a well defined Code of Conduct and a battery of SOP's which guarantee maximal and ethical use of the donated brain tissues for research (Mordini 1995; Ravid and Swaab 1995; Ravid et al. 1995a, b, 1998).

Characteristics inherent to the donor must be considered when recruiting donors (Human Tissue Act 2004; Human Tissue Authority; Code of Practice 2006). According to Article 6 of the convention of the Council of Europe, interventions may be carried out on mentally incompetent persons or persons who have no legal capacity to give consent and those who, though legally capable to give consent, have a reduced capacity of understanding, only for their direct benefit and under protective conditions approved by law (Clayton 2005).

This concept is important in cases of demented patients and psychiatric patients. These donors can be mentally incompetent and a relative/legally authorized person could be the active donor. However, the donor must always be informed in spite of his/her age/medical/mental condition (Fulford and Mordini 1994; Post et al. 1997; Ravid and Menon 1993; Ravid 1992a, b; Thoret and Kantin 1994; Whitehouse 2006).

Special attention should be paid to the informed consent and legal/ethical procedures for donors who are incapable of signing the consent forms themselves (Fig. 3).

Many attempts have been launched but failed to standardize and harmonize the legal and ethical guidelines in brain banking (Cruz-Sanchez and Tolosa 1993; Cruz-Sanchez et al. 1995; Ravid and Swaab 1995; Ravid et al. 1995a, b, 1998). The important issue of ownership and sharing of specimens for research is not been properly defined yet; formulating a Code of Conduct will facilitate sharing and exchange of specimens (Hakimian and Korn 2004; Knoppers 2005).

Figure 3 illustrates the extra care and attention which is given to the consent process and ethical guidelines for the use of specimens donated by demented persons, who are incapable of giving the consent (Cassel 1985, 1998; Whitehouse 2006).

Specific ethical issues also arise in the case of syndromes of impaired consciousness, such as coma, brain death, locked in syndrome and persistent vegetative state. The British medical association and the American Neurological association have both published guidelines concerning the management of patients in these conditions. (American Neurological Association 1999; British Medical Association 1996).

The concept of informed consent is different for the group of surgical patients (Jack and Womack 2003; Micke et al. 2006). In this group the consent is granted after a joint decision taken by the clinician

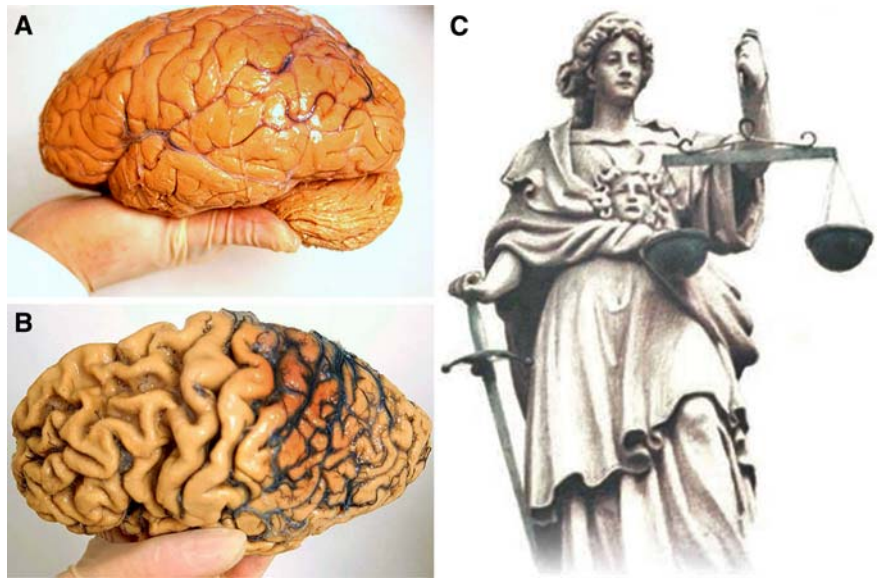

Fig. 3 *Law and ethics in Brain Banking*. This is a major issue and each bank should formulate a code of conduct specifying the legal and ethical basis underlying the daily activities of the brain bank. (**a**) Brain obtained from a deceased donor who did not have any neurological/psychiatric disorders. (**b**) Brain obtained at autopsy from a donor who died from Alzheimer's disease. (**c**) Legal/ethical guidelines for registration of living donors

with the donors or their surrogates. As clearly stated by Bernat and Peterson (2006) 'Surgical consent is not an event or a signature on a form but is an ongoing process of communication that continues throughout preoperative, operative and postoperative care'.

All biological specimens stored in BTB-banks are obtained either under consent by the donor himself or next of keen or by authorization by the legally appointed person/authority. When consent is also granted to the bank to access clinical records it includes general patient information, medical history, family history, lifestyle, education level, and medical treatment, geographic cultural and ethnic background. Some BTB-banks require separate consent for genetic testing and perform mutation analysis on the donated specimens; Informed consent, differs by definition from presumed consent and means that each donor is clearly informed of the purpose of the donation, future possible use of the specimens and his/her right to refuse/withdraw the consent at any given moment (see Appendix 1).

The seven golden standards in BTB-banking

Tissue procurement

The voluntary donation of human biological materials has been included in various international statements: Council of Europe (1994, 1997, 2006); Declaration of Helsinki (1964, 2000); European Directive (2001, 2004); Human Tissue Act (2004); Human Tissue Authority; Code of Practice (2006); Universal Declaration by UNESCO (2005); CIOMS/WHO (2003).

The rights of individuals to exercise autonomy and control in the informed consent process have been recently re-evaluated and examined in many countries (Kismodi and Hakimian 2001; Kass et al. 2003; Knoppers 2004, 2005; Mallardi 2005; Matsumoto et al. 2002; Molyneux et al. 2005; Nishimura 2005; Womack et al. 2000).

In an attempt to improve autopsy accrual of tissues for research, European countries have adopted various legal frameworks; an "opting in" system, whereby potential donors must register their wish in advance, or an "opting out" system, in which it is presumed that people give their consent for donation unless they register their objection (Jacob 2006).

Tissue management

All practical aspects in banking of human biological samples mentioned earlier, e.g. the collection, handling and subsequent storage of specimens must also adhere by ethical rules. The issue of 'ownership' of collected biological specimens is still in debate; the major issue is not the legal status of the samples or

the bank, but who has the right and control of the use of the samples, sharing with other researchers, the prioritization of distribution and the feed back of the obtained scientific results into the D-base of the bank. Therefore, the term 'custodianship' is more appropriate than ownership. This term implies that the bank will guarantee the safe and ethical handling of the specimens, as well as the proper use and optimal sharing with researchers and eventually safe disposal of specimens.

Managing the stored inventory of biological samples at −80°C in Bio banks and repositories involves several aspects. Automation helps to resolve some of the issues and another challenge is to maintain sample quality and provide reliable and efficient retrieval. This can be done by monitoring the frequency of access to samples, the size of the collection and storage conditions. The samples in BTB-banks must be suitable for long-term use in multiple user groups, bar-coded, approved and consented and stored within a compatible electronic roster.

An extensive IT component is essential to tie all factors together including a user-friendly data-base and automated processing, storage and retrieval, samples coding and web-based monitored shipment and tracking. To manage the huge amount of samples and share them with research centres world wide, BTB-banks need to have safe and transparent protocols for shipment as well as proper accompanying documentation for the handling and management of these precious and sensitive specimens.

Tissue sharing and dissemination

Sharing of collected and stored samples is one of the major aims of BTB-banks, as this is the basis for the trust relationship between donors and the banks. Genomics research has to deal with the ethical problems of sharing of stored biological material and maximize its availability for research in line with the ethical/legal restrictions (Cambon-Thomsen 2004).

BTB-banks need a quality control assurance to guarantee the quality of the collected specimens and try to ascertain future specimen need of scientists by e.g. preventing freezing/fixation artefacts, protein and m-RNA degradation and by extracting DNA from the obtained specimens.

The end-users of the specimens are subject to a form of accreditation so that a minimum set of criteria are fulfilled before use of tissue, by signing a tissue/specimen request form; this will assure following both ethical and safety guidelines requested by the bank. The scientific norms and accreditation is awarded by an independent review panel of scientists and medical experts reporting directly to the bank. The request for specimens presented to the BTB-bank should have an approval from the local ethics review committee.

The transfer of material from the Bank to the recipient should be formalized by a Material Transfer Statement (MTS) and a Material Transfer Agreement (MTA) signed by both parties. These documents specify the terms in which samples have been procured and the conditions and obligations under which the recipient will be able to use them.

The MTS and MTA free the banks from liability concerning the use of specimens and will also define the status of intellectual properties related to the obtained results and the right to file patent applications or register them.

The dissemination and quality assessment of transport of the specimens strongly rely on the time and route. Different transport times, transport media and temperature have been reported to have a severe effect on structural integrity of the specimens and gene expression levels (Micke et al. 2006).

Confidentiality and data protection

The material collected and stored in BTB-banks is usually strictly anonymized and the specimens are coded. The identity of the donor is not relevant to research purposes and is protected by privacy and confidentiality (Godard et al. 2003). Research using human specimens can bring new information about the donor, which is also relevant to his family. This option should play an important part in the ethical conduct; the acquired confidence of the donor may become irrelevant and the possibility of giving information about new findings could be taken into account.

Another important part of banking in which specific legal-ethical issues emerge as well as safety issues is the field of Human Genetic Research Databases (HGRD) and data protection and management. The creation and governance of HGRD has implications not only for the reliability of the bank

and the confidence donors have in it but also on the proper and accurate analysis of the data and interpretation of the results. To assure data protection well designed D-bases enable prompt access to the stored samples, proper matching and selection of specimen groups to meet the requirements of the scientific design and setup of experiments (Caulfield 2004; Sampogna 2006).

The issues at stake in data protection and privacy are correlated with the uniquely identifiable personal data collected and stored in BTB-banks, in digital form or otherwise. The currently used databases in BTB-banks contain mutation sequences, gene expression, protein structure, nucleotide sequences and pathological classification. Bar-coded databases and anonymized storage of data guarantee the privacy and confidentiality of the clinical, pathological and genetic information and donor anonymity at all times (Beaulieu 2004).

Information Technology (I.T.) plays an important role in BTB-banking, making sure the donors and researchers have faith in the operational setup of the bank, while at the same time the IT-tools should stay user-friendly and offer relatively simple sample queries for Bank-personnel and researchers. The good practice on the protection of privacy, identity and personal data should comply with local judicial regulations.

Financial gain

From a legal and ethical point of view, it is highly important to establish BTB-banks as non-profit making sources for human specimens for research. The human body and its parts shall not, as such, give rise to financial gain (Article 11 of the draft convention of the Council of Europe 2004). BTB-banks have to act as custodians of specimens which must not be commercially handled (Barnes and Hefferman 2004; Womack 2002). The costs of procurement, handling, storage and transport made by the bank should be covered by end-users; the professionals involved in the acquisition and diagnostics of the specimens have the right to be reimbursed for their services (L. Miranda (2007) The TTAB cost recovery model; lessons learned; the path to cost recovery and beyond. Also available at http://www.ESH.org/Biobanking2007, personal communication).

The missing link is structural funding of BTB-banks by the local government/health care authorities, as previously highlighted in this paper. Most active banks are coping with continuous funding problems; they are in general only partly government-funded and depend on non-profit organizations such as disease foundations, patient's associations and the bio-industry to support their needs (Gray et al. 1999; Womack and Gray 2000; Winickoff et al. 2003; Womack et al. 2001; Womack 2002).

Genetic testing

The recent developments in the human genome project and the quick progress in genetic research raise serious ethical problems and complexities; there is conflicting interest in the need for knowledge and information on the one hand and the use and implications of this information for the people involved (Cassel 1998; Dickens et al. 1996; Hakimian 2000). The issues of donor's privacy and the proper and ethical use of information in conducting genetic testing and biomedical research, play an important role in the decision and policy making of the guidelines and regulations for BTB-banks (Korn 1999, 2000; Page 2004; Van Swieten et al. 2007).

The link found between certain genes and neurological diseases creates a heavy burden on physicians, health care workers and brain banks who test for these genetic factors, as they are essential for the scientific interpretation of the research results on post-mortem human brain tissues. Most banks perform genotyping of specimens as this information is essential for research. This may pose difficult questions to individuals concerned or afflicted and their families (Hakimian 2000; Roses 1998; Nielsen et al. 2003).

Genetic testing has in some cases a very limited predictive value and brings us back to the ethical issue of confidentiality in BTB-banking. Who has the right to know? Should the bank include this information to the family members and inform them about the possible risks? Should the bank ask relatives to collaborate on genetic testing and seek genetic counselling once this information has been obtained?

Testing for the various diseases can be psychologically incapacitating, especially when at the moment there is no treatment or cure in most cases. One must conclude that at present, patient autonomy is the best way to deal with the ethical decision making when it comes to genetic testing and counselling. It is recommended that the disclosure of medical and genetic information to donors and family members should be mediated through a clinical geneticist and counseling unit.

Safety measures

Safety issues are of great concern for protection of BTB-bank employees and investigators using human specimens. Human fresh post-mortem tissues and fluids may contain highly infectious agents and have potential risks of diseases that are highly communicable to other humans. All specimens should be treated as a potential risk for such transmission and handled carefully as certain extremely hazardous infectious agents (viruses, prions) are very stable. The Creutzfeldt-Jakob (CJ) agent, for example, has been shown to be present in tissue, which has been fixed for over 30 years and could then still be transmissible. It is resistant to formalin and withstands the conventional autoclaving. Dissection of fresh tissue is performed under a biohazard hood and discarded according to the policy for handling contagious material (Bell and Ironside 1997; Ironside and Bell 1996; Salai et al. 1997). The risk of dealing with infectious material (e.g. with Hepatitis, retroviruses such as HIV and Prions) is not negligible, even in patients who are not supposed to be affected. Investigators should be clearly informed of the possible risk of infection and asked to apply all necessary measures (Padley et al. 2005). Autopsies of donors carrying a probable infectious diseases have to be performed under special strict protocol, after estimating the possible infectious risk of the specimens, taking all safety precautions to protect the laboratory/autopsy staff, disinfection of the autopsy rooms and tools, specific fixation protocols for the collected specimens and a proper decontamination of the autopsy room and tools and the disposal/incineration of solid and liquid wastes. Similarly all precautions should be taken to protect while transporting samples to another location and ensure all end-users are aware of the possible hazardous nature of the obtained specimens.

The shipment of biospecimens have to adhere by special requirements for safe, reliable and transparent shipment of temperature critical specimens and safe product packaging compliant to packaging instructions for biological and infectious substances and the combined IATA regulations. The handling of infectious material as well as dry ice and liquid nitrogen requires trained personnel. Dry ice is defined at present as Dangerous Goods and outer packaging has to be compliant with P1650/602 regulations and all other applicable local, state and federal laws governing packaging, marking and labelling. The optimal procedure for shipment involves networking of all parties involved and web-based booking, tracking and monitoring, interfacing of repository dbase systems and fully automated reporting system, open to all parties involved (D. Look, available at http://www.inform-ls.com/biobanking, personal communication). Safety and protection are clearly important issues for BTB-banks staff and researchers handling human samples (P. Di Blasio, available at http://www.esh.org/powerpoint/biobanking2007/7/index.htm, personal communication)

Discussion conclusions and recommendations

BTB-banks are an essential component of Healthcare Systems worldwide and are vital to the international scientific research community and the bio-industry. The specimens collected, stored and supplied for research are a major contributor to the ongoing effort to elucidate the molecular and genetic basis as well as the underlying mechanism of various diseases. The prognostic value of biomarkers is used by the bio-industry to support target development and the search for successful targets/therapeutic strategies.

Recommendations

(1) A combined international effort should seek to highlight the network of BTB-banks as an area worthy of bids for future funding. The international network of research BTB-banks should be funded in a formalized manner, which will facilitate sharing of samples.

The present paper pleads that the strongest priority at the moment lies at reaching an international consensus on the methodological, ethical, legal guidelines and a global consensus on structural funding for BTB-banks. To overcome these challenges and reach the goals, the public and private domains must join forces.

Various models have been proposed for uniting tissue banks into a network, such as the consortium of the European network for frozen tumour banks, TubaFrost (Lopez-Guerrero et al. 2006; Morente et al. 2004, 2006; Riegman et al. 2006) and the European Network of psychiatric brain banks (Schmitt et al. 2007).

(2) Standardization of the daily practice of BTB-banks and the SOPs is a prerequisite to an international consensus and exchange of data and specimens.

(3) Facilitation of the review system of ethical issues and code of conduct can be the best achieved by a new system of review by multicoated research ethics committees (Holm 2002, 2006; Tully et al. 2000) which will reduce the costs, speed up the reviewing process and harmonize the specific views and needs of the local ethics committees.

(4) International Code of Conduct and consensus on the ethical guidelines concerning the use of human specimens for research.

The lack of uniformity in the legal and ethical guidelines in BTB-banking is a major problem and has many drawbacks on the daily practice of BTB-banks (Maschke and Murray 2004; Furness 2001). Whether future global bioethics will stay a myth or become a reality remains to be seen (Baker 2005; Borry et al. 2006; Holm and Williams-Jones 2006; Novotny et al. 2006).

Bioethics in research in developing countries is still it its initial development steps (Kass et al. 2003; Molyneux 2005).

Various groups of BTB-banks are currently formulating the Code of Conduct and the SOPs. Adequate funding by the local governments in combination with central global funding will facilitate multi-centre concordance studies and all banks will be able to develop an active ongoing exchange system in which knowledge, expertise, specimens and data can efficiently serve public health and the international scientific community. Governments, legislators, health care professionals and funding authorities should be fully informed about the important contributions made by BTB-banks to improve/advance health care.

The present paper has outlined most of the pressing issues in the BTB-banking and suggests several possible future scenarios to ease up these problems. What needs to be done urgently is fill in the missing gaps and get passed the national, cross-cultural and social differences and obstacles; this process will require a long-term joint effort of all disciplines involved and a compilation of all active BTB-banks in the form of consortia, networks and concordance and multicentre research studies. This harmonized network approach will facilitate and ease the increased pressure on BTB-banks to supply suitable specimens for the international research community. Subsequently this approach will result in consensus statements, a generally accepted Auditing system for BTB-Banks and a united Code of Conduct (see Appendices 1, 2). Only when this goal has been reached we would rapidly be able to move on, make optimal use of the precious samples and meet the expectation of the donors, science, medicine and society by providing numerous high quality specimens and data for excellent research and public health.

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Appendix 1: Proposed model Code of conduct (‘*The Code*’) for Brain/Tissue banks (Referred to as ‘*The Bank*’)

Whenever ‘*The Bank*’ is engaged in the process of recruiting and disseminating human biological material for scientific research it abides by the local law for procuring and sharing human tissue for research and adheres to the following Code of Conduct. In order to provide safe specimens of reliable quality,

good practice standards must be applied; the proposed Code addresses these issues, bringing together the generally accepted methodological, legal and ethical guidelines. '*The Code*' does not limit newly developed technologies, e.g. tissue engineering and cell cultures; once tested, validated and accepted by international concensus, they can be added to the Code.

'*The Bank*' will make sure to promote transparancy and probity with all parties involved, as shown in Figs. 1 and 2 and will make all information available to the public and researchers concerning the organization, funding resources, SOPs and Code of Conduct. This can be done through information flyers, website, annual financial accountant report and scientific publications.

Consent/Authorization

1. The specimens collected by '*The Bank*' are obtained with *informed consent* of the donor or the next-of-kin (or a designated confidant in absence of family) for the following:

(a) Brain or whole body autopsy during which the brain, the spinal cord and dorsal root ganglia are removed.
(b) The subsequent use of the material for scientific research.
(c) Access to clinical/genetic data/donor's medical records.

2. In case a power of attorney has been given by a person, the holder of this power of attorney can give the *authorization* and sign the consent forms on behalf of the person who for reasons of mental of physical health is no longer capable to give the permission in person. This is also the case for surgical specimens or biological materials obtained from minors.
   The consent of the holder of the power of attorney also covers sub 1(a–c).
3. '*The Bank*' will provide the donors/next of kin/person/legal authority who give the authorization with all relevant information concerning the consent beforehand.
4. The potential donor or the person/legal authority who gave an authorization can always withdraw their/consent/authorization and the participation in a donor-program.

Handling of specimens

'*The Bank*' formulates the general scope, aims, regulations and SOPs, which will be used for collecting and handling the obtained specimens. The overall scope and regulations of the bank should be open to the public, transparent and well known to the donors and recipients of the specimens.

1. '*The Bank*' will anonymize the collected specimens during the handling, storage and sharing with researchers.
2. The obtained specimens should be registered, documented, handled and stored according to specific SOPs. Each specimen is registered by '*The Bank*' as a coded Bank-number which is linked to the autopsy number; '*The Bank*' is the only one who can break the code.
3. All specimens are prepared for pathological validation and the pathology report is stored in the D-base together with all the clinical/genetic data.
4. Quality control is performed on all collected specimens to guarantee their suitability for research. All samples which do not match the parameters for quality control will be either discarded or used for different purposes (e.g. teaching, internal use within '*The Bank*').

Safety

1. '*The Bank*' informs all tissue recipients on the possible hazardous nature of the specimens and asks the recipient to sign for handling all material with the necessary safety methods. '*The Bank*' will not be liable to any health risk/damage resulting from unsafe handling of the specimens.
2. All those potentially exposed to human specimens should be vaccinated against possible risks and regularly checked for the level of immunity.
3. Sharing data with applicants is performed under data protection.

4. All tissue recipients are responsible to return unused specimens to '*The Bank*' and dispose of rests according to local legal, ethical and safety rules for disposal of human remains.

Sharing of specimens

1. '*The Bank*' supplies specimens for peer-reviewed, ethically approved scientific projects. Applicants are subject to an accreditation process and have to fulfill a minimal set of criteria before their application is approved. These criteria are published by '*The Bank*' and know in advance to each applicant.
2. The internal review committee of '*The Bank*' will evaluate and approve the request based on availability of specimens, the feasibility and scientific merit of the proposed project.
3. Specimens are to be used solely for the requested/approved project and are not to be passed on to a third party without written permission from '*The Bank*'. The review committee communicates her decision to the applicant.
4. '*The Bank*' will act as a custodian of specimens (and their derivatives such as cells, RNA and DNA extracts) and there is no ownership.
5. '*The Bank*' will accompany the specimens with all available clinical/genetic/pathological data in an anonymized form.
6. '*The Bank*' formulates the terms and contractual obligations of sharing/transfer of specimens/data in a MTA and a Tissue recipient statement.

Financial gain

1. '*The Bank*' defines the terms for financial compensation and cost-recovery obtained from recipients for the requested specimens.
2. Donated specimens may not be sold by '*The Bank*' for commercial purposes to a for-profit organization. '*The Bank*' will not have 'financial gain'; it operates as a non-profit organization but has the right to recover any legitimate costs made for technical or scientific services used for collecting, handling, management, storage and transport of the specimens.
3. When supplying specimens for the Bio-industry, '*The Bank*' will sign a written agreement (MTA), which will define the terms of supplying the specimens and the future intellectual property, in case of registered patents, resulting from research performed on the specimens.

Publications

1. Each researcher/recipient of specimens will send an annual report to '*The Bank*' about the results obtained with the specimens, including a list of published data/filed patent applications/registered patents.
2. In publications, use shall be made exclusively of the specific Bank-coded numbers (not autopsy numbers), in order to fully protect the anonymity of the donors. This also makes it possible for different researchers who were using specimens from the same donors, to get a full picture of the studied cases.
3. '*The Bank*' will always be acknowledged in the scientific publications for supplying the specimens. Guidelines for authorship will be formulated in advance and make a clear distinction between the cases in which '*The Bank*' acts as supplier of specimens or the studied in which scientific staff of '*The Bank*' actively participates in the research project.

Appendix 2: Model standard evaluation protocol for Auditing BTB-banks (Referred to as '*The Bank*')

1. '*The Bank*' will undergo a review process biannually in the start-period and once in 5 years to come.
2. The evaluation will be conducted by an external review board, consisting of members who have a high scientific reputation in this field and have no direct contact or a conflict of interest with '*The Bank*', so the process will be as objective as possible. The impact measures are required to determine the performance of '*The Bank*' and state whether it is effectively meeting a critical scientific need. The impact of a bank is the most

difficult characteristic to measure, although it becomes easier with time as the bank has established its methodological and legal-ethical code of conduct; also, with time, more researchers have been using specimens from the bank and more papers with high impact have been published base on these results. The achievement aspects include the strategic value of the Bank, the performance of the management and all the aspects relevant to scientific standing.

3. '*The Bank*' will present the audit committee in advance with a report containing all relevant information.
4. '*The Bank*' will organize a site visit in which the facility will be examined and all topics discussed between the Audit committee and the team of '*The Bank*'.
5. The Audit-committee will evaluate/review various aspects of achievement by checking the following points:

- What is the overall effective performance of '*The Bank*'?
- Does '*The Bank*' operate through a donor program?
- How many enrolled donors are registered and is there an increase/decrease in donor registration?
- How many specimens have been provided by '*The Bank*' for research? (in the current year and an Audit of the past years from the establishment of '*The Bank*').
- How many complex projects involving unusual or large quantity requests did '*The Bank*' handle?
- Does '*The Bank*' apply a quality control of the specimens? Which method is used?
- How many research projects have obtained specimens from '*The Bank*'?
- What was the quality of the supplied specimens?
- How many publications resulted from the use of specimens (including bibliometric data analysis related to the number of publications and citation index)?
- Does '*The Bank*' circulate survey-questionnaires to request feedback from end-users on its general performance and the number, quality and timeliness of the supplied specimens?
- How are the technical transfer and the intellectual property issues regulated?
- Does '*The Bank*' collaborate or supply specimens to the pharmaceutical industry and under what financial terms?
- Does '*The Bank*' claim a compensation for cost recovery from the academic end-users? If yes, under which regulations?
- Does '*The Bank*' perform a regular Strength; Weekness; Opportunities; Threats (SWOT) analysis of its operation?
- Can the team of '*The Bank*' cope with all the activities?
- Is the facility appropriate/is there shortage of space/apparatuses?
- Does '*The Bank*' perform research on collected specimens? If yes, what are the national/international collaborations?
- Is '*The Bank*' still serving a critical need in the scientific community/bio-industry?
- What are the funding resources of '*The Bank*'?
- Is '*The Bank*' self sustainable and is it successful in attracting external funding/resources?
- How does the management of '*The Bank*' reach decisions concerning technical investments and personnel management?
- Is there enough transparency in the presentation of '*The Bank*' to the public?

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