Biobanking in the Year 2007

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Key Words

Biobank · Biological material · Genetics ·
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Summary

Biobanking is an emerging specialty in which competencies in cellular and molecular biology, medicine, genetics, cryobiology, bioengineering, information technology and ethics merge into a service aimed at the regular collection, characterization, long-term storage and distribution – mostly at subzero temperatures – of a large set of biological materials. Among the possible different modalities to organize biobanking activities, the operational setting and typical infrastructures of blood centers and clinical pathology laboratories seem to offer significant advantages as compared to other frameworks, with regard to sample traceability, staff qualification, large-volume operation, networking capability. In view of a broader use of biological materials and the expansion of biobanking research, efforts should be developed to harmonize local, regional, national and international regulations, guidelines, norms and laws on biobanking, and to increase the population awareness of the importance of participating in biobanking programs. We propose that the model of the ‘Biological Resource Centre’ described by the Organization for the Economic Cooperation and Development (OECD) is used as a structural and operational reference for the consolidation of multispecialty biobanking programs.

Schlüsselwörter

Biobank · Biologisches Material · Genetik ·
Klinische Pathologie · Ethik

Zusammenfassung

Biobanken sind eine aufwärtsstrebende Spezialität, in die Kompetenzen in Zell- und Molekularbiologie, Medizin, Genetik, Kryobiologie, Bioengineering, Informationstechnologie und Ethik einfließen müssen. Nur so kann eine regelhafte Gewinnung, Charakterisierung, Langzeitlagerung und Verteilung – zum großen Teil bei Temperaturen unterhalb des Gefrierpunktes – einer großen Vielfalt biologischer Materialien sichergestellt werden. Unter den verschiedenen Modalitäten, mit denen man Biobank-Aktivitäten organisieren kann, eignen sich aufgrund ihrer typischen Infrastrukturen Blutbanken und klinisch-pathologische Laboratorien besonders. Sie haben Erfahrungen im Umgang mit Fragen wie (Rück-)Verfolgbarkeit, personeller Eignung, dem Arbeiten mit großen Volumina und der Zusammenarbeit in Netzwerken. Unter dem Aspekt der Zunahme des Gebrauchs von biologischen Materialien und der Ausdehnung der Forschung an Biobanken sollte versucht werden, örtliche, regionale, nationale und internationale Richtlinien, Leitlinien, Normen und Gesetze zu harmonisieren und die öffentliche Wahrnehmung der Notwendigkeit zur Teilnahme an Biobank-Programmen zu steigern. Wir schlagen vor, das Modell des «Biological Resource Centers», wie von der Organization for the Economic Cooperation and Development (OECD) beschrieben, als strukturelles und operationelles Vorbild für die Konsolidierung multispezialisierter Biobank-Programme heranzuziehen.

Introduction

A search in the Pubmed database performed on March 7, 2007 with the terms 'bank', 'blood bank', 'banking', 'biobank or biorepository' and 'biobanking' identified 18,736, 6,076, 2,069, 118, and 16 publications, respectively. Not surprisingly, a progressively decreasing number of publications parallels the evolution from a broad and consolidated term like 'bank', traditionally used and widely applicable to numerous elements of biological processes and medical procedures, to a more recent word like 'biobanking', which combines into one single term multiple specialist activities concerning the collection, characterization, storage, and distribution of a large set of biological materials.

The small number of articles associated with the term 'biobanking' suggests that research in this field is still in its infancy. Nonetheless, although numerically limited, the set of articles selected with this basic search describe a vast area of diverse competencies and interests, spanning from biobank management models applicable to biomedical research [1], to epidemiology of Kaposi's sarcoma [2], to RNA stability in frozen surgical tissue samples [3], to ethical issues [4, 5], technology transfer [6], accountability [7].

In this article, we review the perspectives of biobanking in 2007, with particular attention to public biobanking programs involved in biomedical research and cellular therapy. Our reference organizational model for the harmonic combination of these activities is that of the Biological Resource Centers proposed by the Organization for the Economic Cooperation and Development (OECD) in 1999 [8, 9].

Definitions

Biological resources have been defined by the OECD as the composition of living organisms, cells, genes, and the related information [8]. The same organization also provides a definition of Biological Resource Centers (BRC). According to this definition, BRC are 'an essential part of the infrastructure underpinning biotechnology. They consist of service providers and repositories of the living cells, genomes of organisms, and information relating to heredity and the functions of biological systems. BRCs contain collections of culturable organisms (e.g. micro-organisms, plant, animal, and human cells), replicable parts of these (e.g. genomes, plasmids, viruses, cDNAs), viable but not yet culturable organisms, cells and tissues, as well as databases containing molecular, physiological, and structural information relevant to these collections and related bioinformatics. BRC must meet the high standard of quality and expertise demanded by the international community of scientists and industry for the delivery of biological information and materials. They must provide access to biological resources on which R and D in the life sciences and the advancement of biotechnology depends.' [9].

From the wording of this definition, it is clearly evident that the BRC model is the historical evolution of the classical repository of biological materials, traditionally termed 'biobank'. It should be noted, however, that the current BRC definition puts a particular emphasis not only on the internal activities of the BRC, but also on the need of and opportunity for national and international, actual or virtual networking of biobanking activities through this type of organization.

Different Types of Biobanks

There are different types of biobanks, depending on the biobank mission and objectives (table 1). For example, there are biobanks entirely devoted to the prospective banking of leftover normal and pathological tissues collected during routine clinical pathology diagnostic procedures ('leftover tissue biobank') [10]. In view of developing a national network, an extensive survey of activities at 12 cancer biorepositories in the USA, aimed at identifying 'best practices' at these institutions, was carried out by RAND Science and Technology, a unit of the RAND corporation. A freely downloadable report of this detailed survey is available at www.rand.org/pubs/monographs/2004/RAND_MG120.pdf. This report contains valuable information on biobanking costs, and provides an effective methodological approach to the identification of 'best practices' that could be profitably exploited in other settings and other countries.

Other biobanks, collectively termed 'genetic biobanks' [11–13] collect biological samples from the general population ('population biobanks') [14–21] or from particular subsets of individuals ('twin biobanks') [22, 23]. Other programs specifically aim at developing collections of biological samples from patients suffering from selected conditions ('disease biobank') [24–29] or from a specific organ ('organ biobank'). Another distinction regards the human versus non-human biological materials (e.g. 'primate biobanks'), or the purpose of expanding the storage services beyond the animal world into the plant domain or into programs related to environment protection ('biodiversity biobank' [30], 'biomonitoring biobank').

Far from being comprehensive, the previous paragraphs report just a few examples of the numerous types and terms which characterize biobanks. The international experience so far developed supports the choice of networking biobanking activities, with the main purposes of increasing the critical mass and the bio-diversity of stored samples, of standardizing collection, characterization, storage and distribution procedures, of facilitating sample access to investigators, of sharing with the population the results of studies performed with the collected samples, and to optimize the use of the financial, professional and technological resources (table 2). Several examples of international networks of biobanks can be easily identified by searching through the internet. A notable ex-

Table 1. A selective list of different types of biobank

Type	Examples	Website
Leftover Tissue Biobank	See RAND report	www.rand.org/pubs/monographs/MG120/
Population Biobank	UK Biobank Iceland Genomic Corporation Estonian Genome Project EPIC	www.ukbiobank.ac.uk www.uvs.is/eng/scitech/icp.html www.geenivaramu.ee www.iarc.fr/epic
Twin Biobank	Swedish Twin Registry Danish Twin Registry Australian Twin Registry Italian Twin Registry	www.biobanks.se www.dtr.sdu.dk www.twins.org.au www.gemelli.iss.it
Disease Biobank	International Bladder Cancer Bank	http://clincancerres.aacrjournals.org/cgi/content/full/11/2/413
Organ Biobank	The Netherlands Brain Bank	www.brainbank.nl
Non Human Biobank	Primate Brain Bank	http://131.211.49.144/~webmanager/PBB/PBB-Start.html

Table 2. Advantages of large international biobanking networks

Large critical mass
Bio-diversity
Standardization
Easy access
Transparency
Resource optimization
Financial
Professional
Technological

ample is the P³G Consortium (www.p3gconsortium.org) which provides in its website the following definition: ‘The Public Population Project in Genomics (P³G) is an international consortium for the development and management of a multidisciplinary infrastructure for comparing and merging results from population genomic studies. P³G will enable the international research community to deliver more effective health care strategies aimed at disease prevention, and at tailoring medicines and other treatment regimens to individuals, families and communities’. An example of a local multinational program, which is part of the P³G, is the Danubian Biobank Foundation which involves 6 countries in central Europe.

Besides the biobanking initiatives directed at the general population, an interesting biobanking opportunity is offered by settings where selected population groups regularly undergo blood collection for different purposes. Notable examples are blood donation for transfusion purposes (healthy subjects, on average between 2 and 5% of the population), and blood collection for clinical pathology laboratory testing (diseased subjects). Such settings offer the advantage that a ‘left-over research blood sample’ can be easily and routinely obtained as a by-product of the main procedures for which blood is collected, i.e. avoiding additional recruitment costs. Of course, such

biobanking programs require specific informed consent and adequate information technology. Moreover, they need to take into account that blood donors and diseased subjects are selected cohorts, this feature being a specific characteristic rather than a limitation. A recent example of a regular biobanking program involving blood donors which was developed not just for legal matters related to liability of the blood center in case of post-transfusion complications is the ‘Biobank der Blutspender’ (Blood Donor Biobank) of the Bavarian Red Cross Blood Bank. The purpose of this program is to offer unique resources for biomarker research, i.e. to investigate the prognostic value of known biomarkers or to identify new biomarkers by using blood samples collected before the onset of a certain disease [31].

A technological unifier of all biobanking programs is the cryogenic area which requires a sophisticated integration of liquid nitrogen pipelines, reservoirs and storage tanks, mechanical freezers, information technology [32, 33], cryobiology skills [34, 35] and safety features suitable to protect operators and preserve the quality of the stored samples [36–39]. A list of reference norms, laws and regulations that were taken into consideration during the construction of our cryobiology area and which are currently used for maintenance and repair purposes, is shown in table 3. Similar sets of documents and local laws, mostly related to safety assurance for the staff, are used by biobanks which operate in different countries.

Because of the need for all biobanks to use high and expensive technology in the cryogenic area and to follow stringent regulations to assure operations safety, it is evident that models integrating different types of biobanks into a unique facility of appropriate size may offer economic and operational advantages [8]. Moreover, the relatively limited availability of specifically trained staff may favor integrated models (‘multi-specialty biobanks’) as opposed to programs limited to one specialist interest.

Table 3. Norms and regulations considered in the construction of the cryogenic area in our facility

Laws/Norms/Standards	Description
Italian D.P.R. n. 547, 27 April 1955	norms on safety at the work place
Italian D.P.R. n. 303, 19 March 1956	norms on hygiene at the work place
Italian D.L. 475/1992	individual protection devices
Italian D.L. 626/1994	safety on the job
Italian D.L. 493, 14 August 1996	safety signals
Journal Officiel de la République Française, 8 January 1999	good tissue practices for therapeutic use
Journal Officiel de la République Française, 30 January 1999	good practices for human hemopoietic cells for therapeutic use
NetCord-FACT Standards	International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection and Release. 3rd Edition, 2007

Ethical and Biojuridical Issues

Besides the fundamental biological, medical, technological, and administrative skills necessary for an efficient biobank management, issues regarding the compliance of all biobanking procedures with ethical and biojuridical requirements are of utmost importance [16, 40–45]. In fact, the growing development of biobanking research raises a number of ethical and legal issues related to the involvement of human subjects into the process of biological material donation.

As reported in the international literature, the principal issues concern the informed consent of participants in biobanking research, ownership of donated samples, data protection, intellectual property rights. In particular, the definition of an appropriate informed consent model for the storage of human biological materials (such as blood, serum, tissue, DNA, RNA) in view of future research raised a widespread debate at the international, national, and regional levels [46]. What is prevalently debated is the type of information to be given to a potential donor and the type of consent a research subject should be asked for [47–55].

Currently, there is no common view on ethical and legal requirements for biobanking research [45, 56]. Accordingly, there are a large number of differences among regulations, laws, recommendations, and policies at the international and national levels. There are also different standards of informed consent for biobanking research. This fragmentation generates confusion in operators involved in technical procedures and uncertainty in the general population [57–64]. At our institution, we had the chance to deal with these issues and to propose a practical solution to the controversial problem of the informed consent model for biobanking research. In this regard, we developed a method, based on a multidisciplinary work group including several scientists and a jurist, to design a standard informed consent model for the collection, the storage, and the use of human biological materials for known and unplanned research purposes. This model, which was derived from the analysis of 51 medical and surgical procedures performed in our hospital which could yield biological materials, was approved by the competent body of our hospital and has

become a formal procedure to store and use human biological materials for research studies. Cornerstones of this recent, as yet unpublished experience, were i) the review of different types of informed consent models published in the literature; ii) the development of an adequate communication model with research subjects; iii) the development of a particular educational program for health operators about information, communication, and consent to store biological materials of human origin for planned and unplanned studies.

The Biological Resource Center of the Foundation ‘Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena’

The purpose of this paragraph is to describe our interpretation of the model of the BRC proposed by the OECD, as applied to the local setting of a large university hospital interested in biobanking research. To this aim, we report our mission and briefly describe our main functions.

The mission of the BRC of our hospital is to collect, characterize, process, store, and release human and non-human biological materials and their associated data according to national and international standards of excellence. The BRC was formally founded in 2006 through the association of 4 small units of the Department of Regenerative Medicine into a larger unit, named ‘Center of Transfusion Medicine, Cellular Therapy, and Cryobiology – Centro di Medicina Trasfusionale, Terapia Cellulare e Criobiologia’ (CMTC). Currently, the CMTC staff includes 2 physicians, 4 biotechnologists, 14 biologists, 2 laboratory technicians, 1 bio-jurist, 1 administrator, 1 student, and 1 part-time secretary. 7 operators have a permanent position, whereas the remaining 19 are paid by 1–3 year contracts derived from both public and private research grants. The activities of the 4 sections, presented in the chronological order of implementation, are summarized below.

The Milano Cord Blood Bank (MICB) started its activities in 1993. The initial objective was to develop a cryopreserved inventory of 5,000 cord blood units for related and unrelated al-

Table 4. Current inventory of the Italian Biobank^a

Type of sample (sample tutor/responsible person or reference organization)	Number of vials
Maternal and newborn's cord blood (Lucilla Lecchi, DSc)	48,894
Red blood cells from rare blood donors (Fernanda Morelati, DSc)	4,698
Cell lines from cord blood, umbilical cord, adipocytes, bone marrow (Lorenza Lazzari, DSc and Rosaria Giordano, MD)	1,511
Cells from human and animal livers (Laura Porretti, DSc and Roberto Gramignoli, DSc)	370
Sera, membranes, RNA, blood from hematology patients (Alberto Zanella, MD)	3,446
Sera from cancer patients (Francesca Poli, DSc, Alleanza Contro il Cancro)	6,180
Amniocyte and chorial villi cultures (Faustina Lalatta, MD)	120
Sera from patients with celiac disease and their relatives (Maria Teresa Bardella, MD)	810
Lung cancer (Luigi Santambrogio, MD, Guido Coggi, MD)	76
Lymphocytes (Francesca Poli, DSc)	253

^aThe biological samples were collected by investigators reported in parentheses. Samples are managed under their direct tutorship and allocation responsibility. The biobank staff operates in full compliance with a detailed agreement signed by the director of the biobank, and by the director of the unit requesting sample storage.

logeneic transplantation. This target was achieved in 2004. In December 2004, the MICB was accredited by the Foundation for the Accreditation of Cellular Therapy (FACT). Afterwards, a second phase was started, with the aim to increase the inventory to 10,000 units. During 1993–2006, the MICB released 296 unrelated and 14 related cord blood units for allogeneic transplantation to transplant centers in 21 countries. The current inventory of the MICB totals 6,529 units.

In 1995, the MICB promoted the formation of the Italian network of cord blood banks named GRACE (acronym of the Italian translation of Group for the collection and expansion of hematopoietic cells), which included the cord blood banks located in Milan, Pavia, Turin, Florence, Rome, and Padua. The GRACE network achieved an ISO 9000 certification in 1997. During 2001–2006, the MICB managed 5,532 cord blood searches on behalf of the GRACE banks. The searches were received from 92 Italian and 178 foreign transplant centers. Since February 2007, the search function has been transferred to the Italian Bone Marrow Donor Registry in Genoa, within a broad national effort to simplify administrative procedures, to implement an institutional network including all Italian cord blood banks, and to manage a single search office for bone marrow, peripheral blood, and cord blood hematopoietic progenitors.

In 1997, following the positive experience at the national level, the MICB and the cord blood banks in Düsseldorf and Barcelona promoted the formation of the international network of cord blood banks named 'NetCord', which currently includes 22 not-profit cord blood banks with a global inventory of 137,820 allogeneic cord blood units. The NetCord banks distributed so far 5,452 units for transplantation – 2,940 and 2,477 in children and adults, respectively (www.netcord.org).

During the late 1990s, supported by the promising discoveries on stem cells, a program was started to implement a clinical grade cell processing unit focussed on human adult stem cell isolation, characterization, and culture for therapeutic purposes. This unit, named the 'Franco Calori' Cell Factory after the

generous founder of the charity which provided the funds for its construction, operates in compliance with the requirements of good manufacturing practice (GMP).

The 3rd unit that was developed in chronological order was the Italian Biobank, formally constituted in 2004. Its initial task was to develop a cryogenic area for permanent storage of cryopreserved supernumerary embryos generated in medically assisted fertility procedures. Soon after the completion of this construction, the Italian Biobank, which shares the cryogenic area with the MICB, started developing additional biobanking programs in cooperation with all departments of our hospital willing to store their precious biological samples under improved cryogenic conditions and full compliance with the most advanced standards, norms, laws, and regulations on biobanking. The current inventory of the Italian Biobank is shown in table 4.

The 4th and most recently added unit is the 'Flow Cytometry and Experimental Hepatology Laboratory' which provides cytometry services to the other departments of our hospital, and performs research programs on liver cell regeneration and liver cell cancer transformation. The CMTC operates synergically with other units of the Department of Regenerative Medicine, in particular with the Immunogenetics Laboratory, with the Center of Blood Transfusion and Immunohematology, and with the National Institute of Molecular Genetics.

Conclusions

Hitting Google with the term 'biobanking' on March 7, 2007 yielded 61,300 connections. Although a significant discrepancy between the aforementioned small number of peer-reviewed publications found with Pubmed and the large number of connections selected by Google with this searching term can be justified based on the different search algorithm and searched database, it is interesting to note that 'biobanking' seems to be a very popular term in the grey literature. It is therefore appro-

appropriate to plan harmonic local, regional, national, and international programs to integrate and further develop current procedures to collect, characterize, store, and distribute top quality biological materials through a worldwide network of Biological Resource Centers. Needless to say, the ability to involve the community with effective consulting strategies will be of crucial importance to ensure the success of these programs [65].

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