Stem Cell Biobanks for Research

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Biobancos de Células Madre para Investigación

ABSTRACT: The collection and storage of human tissue samples has been present in medicine for centuries, however, biobanking has recently become a dedicated activity. The technological developments that have allowed the isolation, storage and long term viability of human cells ex vivo, and to obtain relevant scientific information, including genetic information, open tremendous possibilities for advancing biomedical research. At the same time, these possibilities have raised complex ethical issues regarding tissue donors, researchers using samples and society awareness of biobanking as a whole.
This article aims to review the operation of stem cell biobanks, related ethical issues and the legal framework in Spain. Special consideration will be given to the new but revolutionary appearance of induced pluripotent stem cells. Most of the topics discussed here will be in the framework of banking adult derived stem cells, which do not entail in themselves any significant ethical dilemma.

KEYWORDS: stem cell, biobank, pluripotency, human sample, sample access

RESUMEN: La recogida y almacenamiento de muestras de tejido humano ha estado presente en la medicina desde hace siglos, no obstante, la actividad de biobanco sólo recientemente ha aparecido como tal. Los desarrollos tecnológicos que han permitido el aislamiento y almacenamiento viable a largo plazo de células humanas ex vivo, y la obtención de información científica relevante, incluyendo información genética, abre enormes posibilidades para el avance de la investigación biomédica. Al mismo tiempo, estas posibilidades han generado dilemas éticos complejos, que conciernen a los donantes, a los investigadores que utilizan las muestras y a la sociedad en su conjunto.
Este artículo pretende revisar las operaciones de los biobancos de células madre, los dilemas éticos relacionados y el marco legal existente en España. Se hará especial consideración al nuevo pero revolucionario campo de las células madre con pluripotencia inducida. Gran parte de los puntos discutidos aquí se aplican a la actividad de biobanco de células madre adultas, que en sí mismas no presentan dilemas éticos.

PALABRAS-CLAVE: célula madre, biobanco, pluripotencia, muestra humana, acceso a muestra

1. Introduction

Research in regenerative medicine has gained a strong impulse in the last few years, mainly through the explosion of stem cell research, materializing as a real therapeutical option for next generation medicine. Regenerative medicine is based on the self-renewing and multi- or pluripotency of the diverse kinds of stem cells identified throughout the body and pluripotent stem cells. For a detailed set of guidelines regarding the therapeutical application of stem cells, see the publication by the International Society for Stem Cell Research in 2008 (Hyun *et al.*, 2008). Indeed, several clinical trials are underway now in the

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United States using stem cell derived medicinal products as therapeutics (Goldring *et al.*, 2011). Nevertheless, the only real application of stem cell based therapies today is the grafting of hematopoietic progenitors from the bone marrow (in cancer treatment) or umbilical cord blood, though only indicated for small children, as the availability of hematopoietic progenitors in umbilical cord blood is limited. Indeed, allogeneic bone marrow transplantation is the only curative option in several types of leukemias. Therefore, the description and characterization of the biology of stem cells, both adult and pluripotent, is subject of intense research nowadays. It is imperative to count with reliable and high quality sources of human stem cells to push forward the necessary research that will eventually lead to novel cell-based therapies. Access to human adult stem cells requires the isolation of those cell types, most of them poorly identified yet, from tissue donations.

Population-based biobanks aim to recruit high quality samples from a large number of individuals, associated with detailed epidemiological, genealogical, lifestyle and clinical data. The goal is to carry on research projects studying the genetic/genomic factors underlying complex, multi-factorial human diseases and investigate how interaction between genes and environment affect our health. Harmonization of sample collection procedures, technical processing, quality standards and type of information recorded becomes a real issue, as international collaboration is required to allow studies with huge number of subjects, where generalizability of findings across populations can be investigated. For such studies, it is of vital importance to establish quality criteria concerning the nature of the sample, conditions of storage and adequacy of available information. Stem cell biobanks, on the contrary, do not aim to collect a large number of distinct individuals, but are focused on isolation of particular cell types based on strong scientific expertise. The goal is to ensure high quality cell type isolation and culture (when possible) so the researcher can ask the right questions on the right experimental system to understand the biology of stem cells, building blocks of future cell based therapies. Therefore, harmonization efforts in a stem cell biobank are directed towards exquisite cell isolation parameters and technique, precise culture conditions to preserve the phenotype and self-renewal of these populations, and long-term viability of the cells isolated. Precise definition of such parameters may vary according to the specific cell type and with the advancement of the state of the art, such as the stem cell field is changing rapidly.

Biobanks cannot reach their full potential in isolation. It is necessary that biobanks network in order to harmonize standard operating procedures and homogeneity in the services they provide, particularly on

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population-based biobanks, so samples retain high enough quality regardless of the location of the biobank. Networked biobanks do provide access to extensive collection of samples that allow wide scope research questions to be addressed. Networked biobanks facilitate access to the scientific community of biological samples of human origin and their associated data with the best quality standards and the assurance of donor rights provided in the actual legal framework. As an example, the Ministry of Science and Innovation in Spain, through the Instituto de Salud Carlos III, has launched 2 initiatives in this direction. One is the creation in 2005 of the National Stem Cell Bank (BNLC - http://www.isciii.es/htdocs/terapia/terapia_bancocelular.jsp -) as the sole repository of stem cell lines, both pluripotent (embryonic and iPSCs) and adult. The BNLC counts with 4 nodes dedicated to cell production and storage. Our biobank (Inbiobank, Fundacion Inbiomed) is the only node dedicated to adult stem cell banking. The other is the constitution in 2010 of the Biobank Network (http://www.redbiobancos.es), that agglutinates all kinds of biobanks organized in Spain, mainly at public hospitals. Similar initiatives are being created in other European countries, as well as a European-wide platform for biobanking, though attempts for legal harmonization of these biobanks is difficult due to incompatible legislation among different European countries.

Biobanks, whether dedicated stem cell biobanks or prospective population-based biobanks, need to build on public trust, ensuring high ethical awareness with sound ethical principles permeating all use of biobanked material to protect safety, integrity and autonomy of donors (for an excellent review of ethics applied to biobanking and guidelines see (Abascal Alonso *et al.*, 2007)). Biobanks must ensure that society recognizes the forthrightness and solidary end purpose of the research. It is desirable to raise public awareness so the public understands and values the donation of samples for the advancement of medicine and health care, encouraging responsible tissue donations, even if the sample will not probably help the donor but the next generation.

2. Why banking stem cells

Stem cell research is surrounded with great expectations, regardless of the source of stem cells (embryonic, adult stem cells, autologous or allogeneic). However, our knowledge about the behavior of these cells as medicinal products and the safety of these treatments needs to be investigated. Stem cells may be classified broadly into pluripotent or multipotent. Pluripotent stem cells are those capable of differentiating into all tissues of the body and present unlimited potential for renewal

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(in fact, tumorigenic potential is a major drawback for their use in therapy). Naturally occuring pluripotent stem cells are derived from the inner cell mass of an embryo in the blastocyst stage and termed embryonic stem cells. As the derivation of these cells requires necessarily the destruction of a human embryo, they are the center of intense ethical debate. For the purposes of this article we will not discuss embryonic stem cells and we will focus our biobanking topic to other types of pluripotent stem cells and adult stem cells. Regular, terminally differentiated somatic stem cells (such as skin fibroblasts) can be induced to convert to a pluripotent state simply by the forced expression of a few transcription factors (Oct4, Sox2, Klf4 and c-Myc were the first defined, though there are a number of combinations and methods available today) to generate the so called induced Pluripotent Stem Cells (iPSCs). iPSCs present the same characteristics of embryonic stem cells, without the ethical concerns raised by their derivation; furthermore, they may be obtained from the same individual subject for therapy, preventing immunological rejection. Extended discussion of biobanking issues associated with the generation of iPSCs and biobanking will be provided later on.

Adult stem cells, on the contrary, are stem cells that reside in developed tissues and are responsible for maintaining the cellular homeostasis of that tissue or organ. Examples of these are hematopoietic stem cells (generate blood cells), mesenchymal stem cells (make connective tissues), mammary stem cells (responsible for the changes observed in the breast tissue), neural stem cells, etc. In most cases, adult stem cells are retrieved from what is considered "surgical waste", such as discarded skin from plastic surgery, decidual teeth, umbilical cord vein or blood, fat aspirates from liposuction procedures, etc. Therefore, the donor is not intervened solely for the purpose of retrieving a tissue sample but the donation would come along another procedure the donor is undertaking, usually for medical reasons. Adult stem cells often display a limited differentiation potential, as they are capable of producing cells of a particular tissue, and cannot be cultured indefinetly, limiting their applications. However, they can be derived in an autologous manner, thus preventing immune rejection, and do not form tumors when transplanted (one of the major hurdles today for using pluripotent stem cells in the clinic). Nevertheless, for most tissues, the precise phenotypic definition of these cells is unknown, and they have not been successfully cultured *ex vivo* to grant systematic production in a biobank. Particularly interesting are mesenchymal stem cells (MSCs, also named mesenchymal stromal cells or adult-derived stromal cells), they have been shown to differentiate into cell lines displaying osteogenic, chondrogenic and adipogenic lineage traits (Prockop, 1997)

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and show an immunomodulatory effect on their microenvironment that may prove very useful for therapeutical applications (Aggarwal and Pittenger, 2005), particularly for allogeneic use. These cells may be easily obtained from bone marrow, fat tissue, umbilical cord vein wall, dental pulp, etc. Due to their availability and potentially beneficial properties, they have been the first adult stem cells to be explored for therapeutical applications, with 168 studies registered at the NIH Clinical Trials registry and 12 studies registered in the EU Clinical trials registry. Of notice, our biobank (Inbiobank, Fundacion Inbiomed, San Sebastian, Spain) is dedicated to the biobanking of MSCs since 2004, the first and only biobank in Spain authorized for such indication.

The characteristics of stem cells mentioned above are exploited for their use in drug discovery, disease modeling (particularly iPSCs) and regenerative medicine. It is clear that extensive research must be carried on in order to translate the potential of stem cells to real therapies. Understanding human stem cell biology is a must in this process and today it is fair to say that the field is in its infancy. Access to high quality, regulated human samples is instrumental in advancing the knowledge on these diseases. Due to the limited availability of human samples, the lenghty bureaucracy associated, and the necessary technical expertise required for their isolation, the existence of stem cell biobanks is justified.

3. Applicable law

In this article, we are describing the biobanking of stem cells in the context of Spain, thus, unless otherwise stated, all legal references apply only to the Spanish legal framework (see table 1 for a complete list of applicable laws related to stem cell biobanks). Policy in different countries may vary according to the different political environment and in some cases even found to be incompatible. The Spanish Law for Biomedical Research (Law 14/2007, released on July 3rd, 2007) is considered one of the most advanced and permissive in terms on what kind of research can be undertaken with stem cells. This law even allows for the creation of stem cell lines through somatic cell nuclear transfer in human cells.

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Table 1: Applicable laws related to stem cell biobanking

Law	*Application*	*Description*
L 14/2007	Spain	New law for biomedical research. Includes for the first time the definition of biobanks.
SCO/393/2006	Spain	Creation and operation of the National Stem Cell Bank
RD 1301/2006	Spain	Regulates safety and quality of human sample donations
RD 65/2006	Spain	Regulates import and export of human samples
RD 2132/2004	Spain	Regulates the use of human embryos and embryonic cells in research
RD 176/2004	Spain	Regulates the operation of the National Transplant Organization
Directive 2004/23/CE	EU	Guidelines for human tissue donations
L 45/2003	Spain	Modification of L 42/1988 ("New" assisted reproduction law)
L 41/2002	Spain	Law for the rights and responsibilities of the patients
RD 994/1999	Spain	Regulates security procedures for personal data protection
LO 15/1999	Spain	Personal data protection act
Directive 95/46/EU	EU	Guidelines for personal data protection
42/1988	Spain	Use of human embryos and fetuses and cells and tissue derived from them
35/1988	Spain	Assisted reproduction law

L=Ley (Law); SCO=Orden del Ministerio de Sanidad y Consumo (Order from the Ministry of Health); RD=Real Decreto (Royal Decree); LO=Ley Orgánica (Organic Law)

Law 14/2007 for biomedical research is the first law that specifically mentions the creation and operation of biobanks. Here, a biobank is described as a technological platform (that is, a defined facility) operating under quality certification norms (such as ISO9001) with clear objectives towards the collection, storage and distribution of human biological samples. This law establishes four key figures in the organization of a biobank:

1. Director: responsible for supervising the operation of the biobank within the legal framework.

2. Data manager: responsible for the custody of the biobank data files, including personal information from donations. This person is responsible for granting biobank data accession from interested requests (regulatory authorities, health authorities, researchers, donors, etc.). This position is usually assigned to a LIMS (laboratory information management system) master as this information is usually managed through it. The law mandates that the biobank file must be registered with the Spanish Agency for Data Protection (AEPD), therefore ensuring proper treatment of the information.

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3. External ethics committee, to advise the biobank director. This committee will protect the rights, dignity, safety, and well-being of the donors related to the operations of the biobank. Aspects such as informed consent, personal information confidentiality and risk-benefit balance in the use of samples fall under the scope of this committee.

4. External scientific committee, to advise the director. Aspects related to scientific objectives of the biobank, research carried on at the biobank and operation procedures fall under the scope of this committee.

The law mandates that samples from the biobanks are used in scientifically and ethically approved research projects to ensure that such projects receive just the appropriate samples and no samples are wasted. Sample donation in Spain is altruistic, that is, any interested researcher that requires a sample may use it, providing that the project is approved according to scientific and ethical standards. In practice, both external committees hold the decision power towards the allocation and destination of the samples, as the law mandates that all sample acquisition projects and every sample request must be informed favourably by these committees. Therefore, those external committees decide whether a sample request may be honoured or not. The biobank personnel have no decision power. This has raised some concerns among the clinical research community, since most human samples present now in biobanks were part of particular research collections, managed by clinical researchers that obtained the sample in the first place. Now, when included in a biobank, the samples must be made available to externally approved requests, therefore preventing the clinical researcher to deny access to other researchers that may compete for the same research. The donor, and not the researcher, holds the property of the sample, the biobank just manages access to it through the external committees. This situation has created also a logistic issue, as decisions from the external committees may not come in a timely fashion (some may meet monthly, 4 times a year or upon request), delaying the access to samples. Procedures must be placed to ensure the timely response from the committees so there is no unnecessary delay in the access to samples.

In Spain, health authority is distributed among the different regions, each one establishing their own regulations within the Spanish legal framework. Biobanking is one of those activities. However, only one region (Comunidad Valenciana) has issued a specific act for biobanking. Other regions, such as the Basque Country or Cataluña, have started implementing the authorization of biobanks. However, the normative

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development (Real Decreto) specific for biobanks, that is, the development of the concerned chapter in Law 14/2007, has not been released yet. This situation has created different standards for different regions, due to flexible interpretation of the terms of the law by different regional authorities. In fact, our biobank was authorized as such in 2009 by the Health Department of the Basque Country Government.

3.1. Informed Consent (IC)

The law establishes that every tissue donor must give his/her expressed informed consent for the collection, use and destination of the samples. The use for the sample in a biobank, the identity, responsible parties, location and definition of the biobank must be clearly stated. The possibility of revoquing the IC also has to be clearly defined, as well as the mechanisms to do so. This is easily accomplished when the sample is collected specifically for a research project in place or in preparation. However, samples to be stored in a stem cell biobank are prospective in nature, that is, do not anticipate in which project will the samples be used. This issue is particularly relevant for the stem cell/regenerative medicine field, as advancement of scientific knowledge, particularly new genetic advances and novel use of stem cells, will not be envisioned in the initial donation. Several avenues may be explored to overcome this apparent contradiction:

- Use a "biomedical research" wide consent for the use of the sample. In this case, it is in the criteria of the external committees to evaluate whether the sample may be used for a particular project. Of course, the donor may specify a particular use for their sample or a negative clause where a specific use is not consented, if so desired. Informed consent must provide a way to express whether the donor wishes to receive information from the results of the research, even genetic information that may have an impact in his/her health (right to know and right not to know).

- Use a specific consent to store the material in the biobank, but request specific consent for every project as necessary. While this is a strict interpretation of the law, it may become not feasible for long-term use of the materials.

In practice, most biobanks operate using a "biomedical research" consent so the sample in principle may be used in unforeseen projects. The law, however, establishes a procedure in these circumstances. This is the anonymization (also named as complete or irreversible anonymization) of the samples, where any trace to the original donor is removed and the sample cannot possibly be linked to the donor anymore. Then, the sample becomes the property of the biobank and it is

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only the scientific and ethical criteria (exerted through the external committees) that decide the destination of the sample. Of course, if some information, such as a genetic feature, needs to be traced back to the donor (for the purposes of the research or for medical reasons relevant for the donnor) it will not be possible. It is important to distinguish between true anonymization (also named complete or irreversible) and pseudo-anonymization (from now on named *dissociation* in the text). In this later scenario, the information from the donor is coded so may not be immediately accessible, although it is possible to trace back to the donnor. For clarity, we propose to use the term "anonymization" for complete/irreversible anonymization and "dissociation" for pseudo- or coded anonymization.

3.2. Material Transfer Agreement (MTA)

The researcher that desires to use a sample handled by a research oriented biobank must agree on the following terms, in order to guarantee that the sample complies with the intended use of "biomedical research" established in the informed consent. Points to be specifically agreed on are:

- Cells will not be used in human subjects.
- Commercial uses are not allowed.
- The recipient researcher will take all necessary steps to ensure the safe keeping of the cells and the information associated to the sample.
- The cells will not be distributed to third parties (collaborators involved in the project are not considered third party if the cells are used for the project) unless with expressed permission from the biobank (which would seek a new approval for the use of the sample).

Figure 1 and 2 describes the flow chart of how a biobank access a sample (fig. 1) and how a researcher may access a sample from a biobank (fig. 2). A specific channel through the BNLC is presented for stem cell samples, as it regulates, evaluates and grants access to them.

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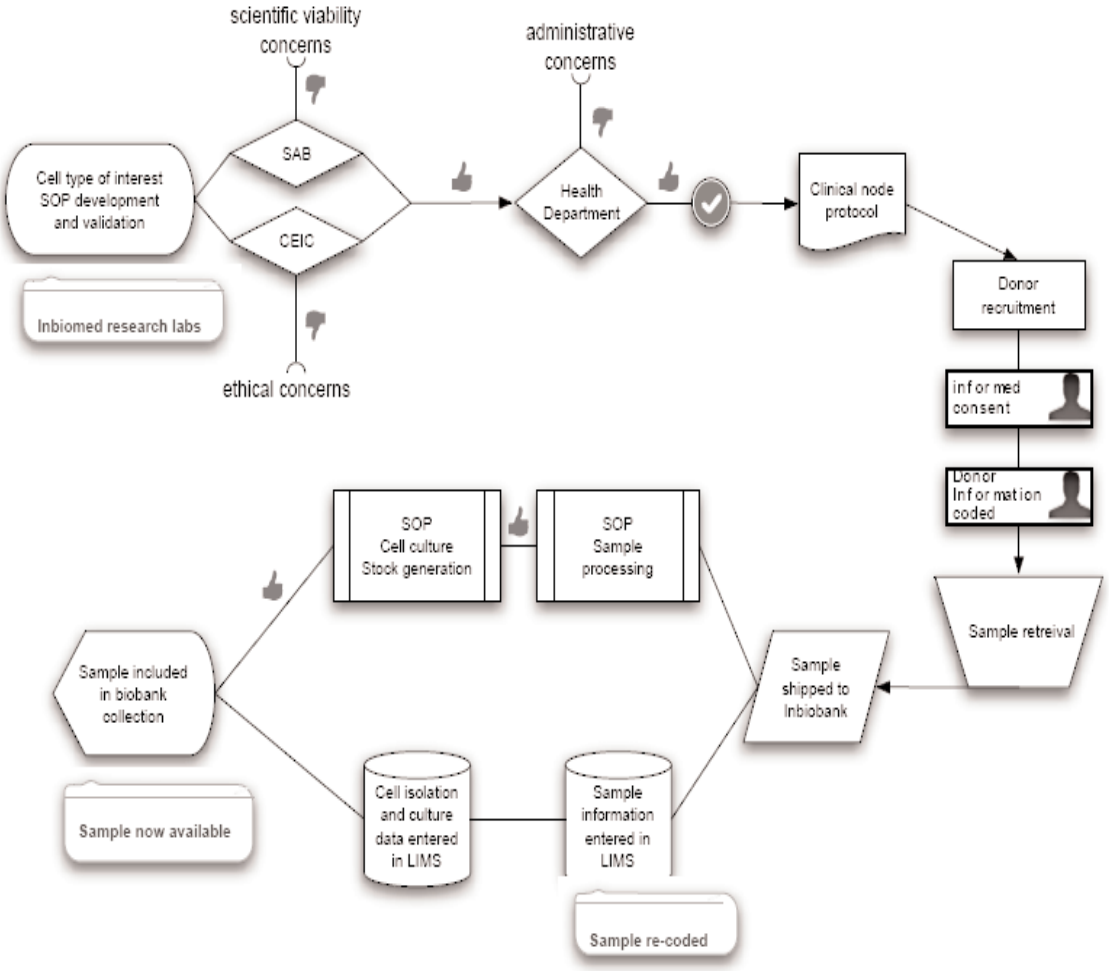

Figure 1: sample acquisition flow chart for a cell biobank. After a cell type of interest is identified and Standard Operation Procedures (SOPs) developed and validated for its isolation and culture, a request to add this cell type to the biobank collection is submitted to the scientific and ethical committees (SAB and CIEC). When informed favourably, the local Health Department (this is a requirement specific in the Basque Country, other regions differ) must approve the collection of new sample types. When all approvals are in place, then donnor recruitment starts in the clinical service, for which SOPs have been already agreed and established. The clinical service collects IC and sample, which is then shipped to the tissue culture facility at the biobank. Next, the cell type of interest is isolated and cultured, information recorded and quality controls implemented, to ensure the cells maintain the quality specification defined. These may include absence of microbiological contamination, cell surface marker phenotype and differentiation potential. Then the cells are frozen and stored ready for use.

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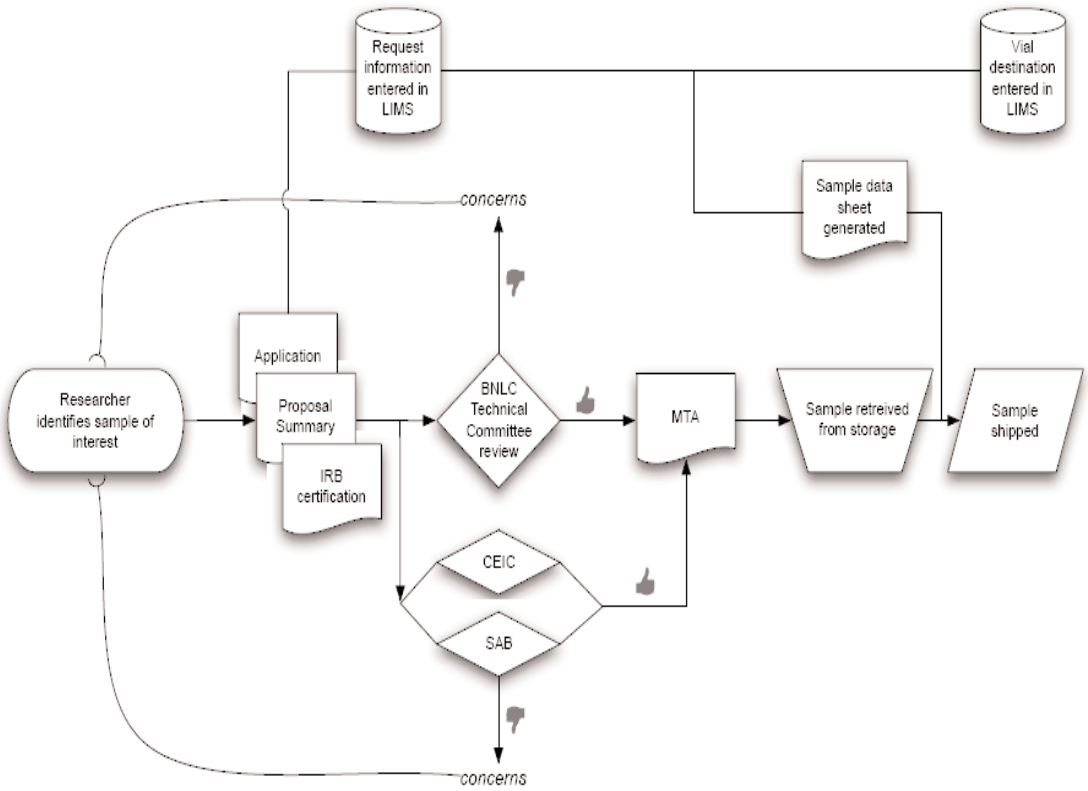

Figure 2: sample request flow chart from a cell biobank. After a researcher identifies a cell type of interest, an application is sent to the biobank stating the cell type, a research project summary, the Principal Investigator (IP) and receiving institution. This application must be accompanied by the IRB certification of the project. The application is recorded in the biobank information system and then evaluated by the CEIC and SAB (or by the executive committee of the BNLC in our case). If any concern is raised, the PI is contacted and offered to address those concerns. When informed favourably, the biobank starts processing the request and the MTA form is sent to the PI for signature. Once in place, the sample/s requested are shipped.

4. Operation of biobanks

Massive storage of stem cells presents several technical caveats that need to be considered:

- Operation within the legal framework specific in every country for collection of tissue donations. We have already pointed out the framework in Spain.
- Transportation of the donated tissue from the operating room to the biobank cell isolation facility. This is greatly aided if the biobank is located within a clinical service. Otherwise, resources need to be allocated for transportation. The responsibilities of the

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surgeon, nurse and other operating room staff members regarding handling of the tissue specimen, need to be previously agreed upon and documented. Standard Operating Procedures (SOPs) are preferred.

- Coding of the tissue donation according to data protection policies to ensure trazeability of the samples. In most cases samples are double coded, the first code to separate personal information (name, SSN, ID) from the sample, and a second code to separate the sample at the destination (the biobank gives the sample a second code for release). It is recommended the implementation of a validated LIMS (laboratory information management system) for the storage and access of all the data generated in the biobank, from information about the donation, to cell production and sample releases.

- The existence of standard operating procedures (SOPs) for every step of sample processing: the initial reception of the sample, the isolation of the specific cell type from a particular tissue and the storage and access to the sample. It is recommended that institutions supporting stem cell biobanks have long experience and strong expertise in stem cell research, as stem cell isolation is technically challenging, so training and expertise of the biobank operators is key.

- Redundant quality controls for cell culture, phenotype and potentiallity.

- Long-term cryopreservation of the materials.

It is preferred that stem cell biobanks operate in dedicated tissue culture facilities, designed as 'clean rooms'. If the biobank is aimed to produce stem cells just for research, compliance with good manufacturing conditions (GMP) is not required, and clean room operation is viewed as a quality value for the cells produced. Cell-based therapeuticals are considered in most countries as medicines, therefore, must undergo the same regulatory approval than drug-based medicines. This includes cell production in a cGMP dedicated facility. Thus, if banked cells are aimed for therapeutical use at any time in the future, it is advisable to start implementing cGMP conditions from the beggining. Otherwise, new lines will need to be developed under cGMP for therapeutical use. Although technically challenging, decision about clean room and/or cGMP operation also involve high economic cost of operation.

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5. Issues related to pluripotent stem cells

As discussed previously, pluripotent stem cells are undifferentiated cells with the ability to self-renew, that is, undergo numerous cell divisions resulting in identical undifferenciated daughter cells. These daughter cells may, in turn, differentiate into every cell type in the body with the exception of extra-embryonic tissues (Banito and Gil, 2010).

Based on this very same differentiation potential, pluripotent stem cells have raised great expectation regarding their applications in regenerative medicine. With this purpose, the idea of reverting cell fate as an unlimited and autologous source of pluripotent stem cells has been long explored by somatic cell nuclear transfer and cell fusion studies (Yamanaka and Blau, 2010). As shown in the groundbreaking work by Takahashi and Yamanaka (2006), iPSC can be readily induced from terminally differentiated somatic cells by the expression of four defined transcription factors related to pluripotency, from mouse and human cells (Takahashi *et al.*, 2007). Moreover, since iPSCs are generated from adult tissues, they overcome many of the ethical and legal concerns raised by the destruction of embryos to derive human embryonic stem cells (hESCs).

Interestingly, the Spanish law 14/2007 allows the use of ANY *any* technique, including somatic cell nuclear transfer, for obtaining human stem cells for therapeutic or research purposes, without resulting in the creation of an embryo. However, this does not consider the specific case of cellular reprogramming by defined factors. This is a clear example of how advancement of science precedes the establishment of a specific legal framework.

In Spain, iPSC biobanking falls within the same legal framework regulating embryonic stem cell biobanking (table 1). Any research project that aims to generate iPSCs must be informed favourably by the Commision of Guarantees for the Donation and Use of Human Cells and Tissues ("Commision of Guarantees", for short) from the Instituto de Salud Carlos III, which is the instrument used by the health authority to ensure the scientific, ethical and legal compliance of any and every research project carried on in Spain dealing with pluripotent stem cells (both hESCs and iPSCs). In fact, this evaluation must be in place before the project is started. In order to obtain a favourable report, the project must address the following points:

- Scientific relevance and suitability of the research team.
- Ethical compliance, including informed consent. An evaluation from an external ethics committee is preferred.

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- Authorization from the institute directive to carry on the project.
- Absence of conflict of interest between the research team and the donors.
- Mechanisms to ensure traceability of the donations, or the intention to anonymize the samples (when possible).
- Commitment to deposit in the BNLC the pluripotent cell lines generated.

The Commision of Guarantees is composed of 12 non-institutional members (recognized researchers, experts in bioethics, lawyers) and 12 institutional members (2 from the Ministry of Science, 2 from the Ministry of Health, 2 from the Minisry of Justice and 6 from the National Health Service).

The National Stem Cell Bank has set specific guidelines for the biobanking of iPSC that must be taken into account when obtaining the biological samples and the IC. According to the document CEI/HIP/CI-iPS (available online at http://www.isciii.es/htdocs/terapia/pdf_comite/CEI_HIP_CI_iPS_abril_2010.doc), one critical issue is the time frame for the preservation and use of the human samples and iPSC cells derived from them, that is, whether the pluripotent cell line established from one donor is going to be used for a specific research project and then destroyed, or kept indefinitely. In this regard, samples to be stored in a stem cell biobank are prospective in nature. In addition, the high costs of production, characterization and mainteinance of human iPSC make necessary exploring other options, such as the broad biomedical IC proposed above.

In the event that the iPSCs are to be stored indefinitely, it should be guaranteed that the biological sample will not be used in research that is not in compliance with the Spanish law (for instance, in the generation of viable embryos). In addition, for the long-term storage of an iPSC line, the BNLC will seek sample anonymization, and the donor will be informed about how difficult it would be to guarantee his/her rights if their samples are not anonymized. Such difficulties include:

- Keeping track of the donor indefinitely while preserving an immortalized cell line that will contain genetic information that might be of interest for the donor, his/her close relatives and their descendants.
- Revoking the consent once the iPSC lines are already established.

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This issue presents a contradiction regarding anonymization of the samples. For the correct characterizacion of the iPSC, it is required to study their HLA haplotype to prove it matches that of the cells of origin. This is biological information unique to the donnor (such as a biological ID). Therefore, a link is established between the iPSC cell line and the donnor or its biological sample of origin. As such, it may never achive complete anonymization. The BNLC solves this issue by limiting access to the HLA information to the act of the deposit of the cell line in the BNLC, as a quality control to ensure that the clones generated come from the original donnor. Once a cell line is deposited, this information is destroyed. Thus, an iPSC cell line is dissociated up until, as mandated by law, the cell line is deposited in the BNLC, when it becomes anonymized and available to the scientific community.

Another interesting avenue to explore pointing towards the development of cell-based therapies is the banking of iPSC with close immunological matches to a population. Previous studies have stimated that only 150 cell lines would suffice to provide close immunological matches for the UK population, and 50 cell lines would represent up to 90% of the Japanese population (reviewed in(Prescott, 2011)). As the efficiency and safety in the generation of iPSC improves, the number of patients treated with a single iPSC cell line would increase. Considering that the commercial use of the stem cells in biobanks is forbidden by the Spanish law, banking a limited number of iPSC lines with close immunological matches to the population offers a more affordable possibility than personalized medicine.

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