Making More Efficient Use of Biospecimens. ISBER Contributions and Initiatives

Members of the ISBER Education and Training Committee\textsuperscript{a,1}, Members of the ISBER Science Policy\textsuperscript{a,1}, Members of the ISBER Biospecimen Science Working Group\textsuperscript{a,1}, Review prepared and presented by Fay Betsou \textsuperscript{a,b,1,2}/

\textsuperscript{a}International Society for Biological and Environmental Biorepositories, \textsuperscript{b}Integrated Biobank of Luxembourg

Abstract. The International Society for Biological and Environmental Repositories (ISBER) is the leading global forum for promoting harmonized standards, ethical principles, and innovation in the science and management of biorepositories. Through development and publication of opinions and comments on ethical and legal issues underpinning the use of biospecimens in research, the ISBER Science Policy Committee supports biorepositories in all geographical regions, in order to ensure scientific use of biospecimens is possible, in accordance with applicable regulations and good ethical practice. In order for biospecimens to be fit-for-purpose, the ISBER Education and Training Committee and the Biospecimen Science Working Group have developed Best Practices, educational programs and tools in order to support quality assurance in the daily operations of the biorepositories and in the characterization of biospecimens.

Keywords. Biospecimen, ISBER, biorepository, biobank.

Introduction

ISBER is a global organization that creates opportunities for sharing ideas and innovations in biobanking and harmonizes approaches to evolving challenges for biological and environmental repositories. ISBER is a global scientific society, whose goal is to support biobanks worldwide.

The mission of a biobank is to support research. In order for biobanks to fulfill this mission, ethical / legal and technical / scientific issues have to be dealt with, in an efficient way, in compliance with applicable regulations while taking into account the most recent scientific results.

Efficient utilization of biospecimens requires that donors’ interests are respected, that biospecimens are not buried in biorepositories due to regulatory constraints, and that distribution takes place “in time” relative to their inherent stability. Efficiently utilized biospecimens are accurately identified and accompanied by relevant and verified data (taxonomical, clinical, pathological, epidemiological, pre-analytical). They have appropriate concentration, purity, integrity, and homogeneity for the end-uses and those that correspond to cases and controls are of comparable quality. Relevant ISBER Committees and Working Groups, composed of


\textsuperscript{2} Corresponding Author.
volunteer members from all over the world, have been actively developing documents and tools to ensure biospecimens can be used efficiently.

1. ISBER Science Policy Committee

The Science Policy Committee includes members from the USA, South Korea, Italy, Luxembourg, Australia and New Zealand. The main objectives of the Committee are to communicate regarding emerging science policy issues that may affect the biorepository community. In this role, the committee also responds to requests for public comment on draft regulatory and policy documents. Members of the Committee have contributed to the ISBER Best Practices section on “Legal and Ethical Issues for Biospecimens” (informed consent, protection from research risks, specimens from mentally impaired, specimens from autopsies, pediatric specimens, communities, animal and wildlife biospecimens, sharing and distribution of specimens and data) and the section on “Specimen Access, Utilization and Destruction” (access and utilization, data sharing, benefit sharing, Material Transfer Agreements, data transfer).

The ISBER Science Policy Committee has replied to the following requests for public comment:

► In 2011-2012, the Federal Government of the US Department of Health and Human Services proposed changes to the Common Rule. ISBER supported the use of left-over tissue without consent under appropriate circumstances with research oversight mechanisms and suggested that biospecimens should not be considered in and of themselves identifiable.

► ISBER fully endorsed the Australian Government National Health and Medical Research Council proposed revisions to Chapter 3.4: Human Tissue Samples and Chapter 3.6: Human Stem Cells of the National Statement on Ethical Conduct in Human Research.

► In 2013, in its Response to the European General Data Protection Regulation Proposal as provided by the European Parliament and the Council of the European Union, ISBER explained the possible impediment of some of the proposed provisions to the progress of global research, and supported the possibility of a waiver of consent under certain circumstances.

► In its response to the U.S. Presidential Commission for the Study of Bioethical Issues request for comments on issues related to incidental findings, ISBER suggested that instead of mandating return of incidental research findings to participants, that repositories should develop return of results policies that are reflected in the Informed Consent documents.

► In its response to the request for public comments on the Draft Genomic Data Sharing Policy, ISBER supported the need for data standards, the protection of indigenous populations, and the possibility of IRB approved waiver of consent under appropriate circumstances.

► In 2014, in its comments on the International Code of Conduct for genomic and health-related data sharing, ISBER suggested that the Code allow for waivers of informed consent for retrospective collections when approved by ethics review boards.
Finally, in its comments on the Working Document on Research on Biological Materials of Human Origin to the Committee on Bioethics of the Council of Europe, ISBER suggested a better definition of “identifiable” biospecimens, of “future research”, and supported the possibility of the use of broad consent, IRB/ethics committee board waiver of consent for persons not able to consent and storage of residual anonymized materials. ISBER supported the development of Biobank policies on individual feedback of results and raised the question of ownership of samples.

2. ISBER Education and Training Committee

The Education and Training Committee currently includes members from the US, Canada, Australia, Germany and South Africa. The main objective of the Committee is to identify ways to ensure that ISBER members have access to state-of-the-art information and tools to effectively establish and operate biorepositories, and preserve biospecimens for future research and analysis, following Best Practices.

The ISBER Education and Training Committee has developed the following educational and training documents and tools:

- The ISBER Best Practices. This document contains a description of effective practices for the management of specimen collections and repositories. Adherence to ISBER Best Practices is strictly on a voluntary basis. The ISBER Best Practices are periodically reviewed and revised to reflect advances in research and technology. The third edition of the Best Practices was published in 2012.
- The Self Assessment Tool. This is a survey allowing participants to assess their degree of compliance with the ISBER Best Practices. It provides a risk-balanced score, based on a proprietary algorithm (developed by the ET Committee), which can be used as a quantitative quality indicator by those biobanks who decide to implement a quality management system. It supports continuous improvement and facilitates accountability to stakeholders.
- The Committee is currently working on additional educational resources and a Repository Technician Certificate program.

3. ISBER Biospecimen Science Working Group

- The ISBER Biospecimen Science Working Group (BSWG) currently includes members from the US, UK, Luxembourg, Italy, Switzerland, Australia, Canada, Belgium, Germany and Sweden. Biospecimens stored in biorepositories are intended to be used for biomarker identification and validation, among other things. The performance of such a biomarker greatly depends upon the pre-analytical variations of the samples utilized for its initial identification. Quality Assurance therefore is of utmost importance, making it possible to establish the right correspondence between processing methods and end-use biomarkers. The objectives of the ISBER BSWG include:
  - selection of biospecimen quality assurance schemes
  - identification of biospecimen handling critical points
  - standardization of biospecimen research protocols
  - identification of Quality Control tools

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reviews on biospecimen science topics and validation of biospecimen processing and quality control methods.

The ISBER BSWG has developed the following educational and quality assurance documents and tools:

- The Sample PREanalytical Code (SPREC), initially developed in 2009, has been successfully implemented in several biobanks by different ISBER members in the US, Europe and Australia. Two informatics tools have been developed which facilitate its further implementation. The first, developed by IBBL, is an excel calculator which automatically calculates the SPREC time-associated elements for solid and fluid samples. The second tool, developed by San Raffaele University Hospital, supports coding and decoding of a sample’s SPREC, printing barcodes and storing the preanalytical data in a local database. The SPREC has spread beyond human biospecimens to the development of a SPREC paradigm for environmental biospecimens. SPREC version 2 was developed on the basis of feedback received from ISBER members who have implemented and utilized the SPREC since its first publication. The SPREC allows biorepositories to document the in vitro preanalytical history of biospecimens in a standardized way.

- Having established and updated a biospecimen science literature compilation, the BSWG “readers” did a critical review of more than 600 of these publications. The aim was to find biospecimen QC tools (markers or assays) that could be used to define sample quality. At present, there are few QC tools that are either predictive of downstream method feasibility and reliability, or diagnostic of upstream biospecimen processing steps. The most appropriate quality control tools, in terms of molecular diagnostic performance, and feasibility of application were selected by consensus. QC assays allow biorepositories to objectively assess the fitness for purpose of biospecimens.

- ISBER, together with the IBBL, has developed a biospecimen Proficiency Testing (PT) program for biorepositories, in compliance with ISO 17043. The PT program allows biobanks to assess the efficiency of their biospecimen processing methods, and the accuracy and precision of biospecimen QC methods. It supports biorepository accreditation initiatives, facilitates implementation of new QC tools and allows evaluation of their performance by comparing them to previously used QC methods. PT is another step towards standardized and accurately characterized biospecimens. The 2014 schemes include DNA extraction from whole blood, RNA extraction from whole blood, DNA extraction from FFPE cells, plasma metabolomics quality assessment, DNA quantification and purity, RNA integrity, cell viability and tissue histology.

- The BSWG also did some experimental work on RT RNA stability. Another experimental piece of work focused on the impact of shipping temperature and cryomedia on cell viability and functionality. The results were important for the RNA integrity and the cell viability PT schemes, mentioned above. Stability studies allow evidence-based biobanking.

- The Preanalytical External Quality Assurance (EQA) survey allows biorepositories to assess the quality assurance of their preanalytical phase (Fig. 1).

In conclusion, ISBER’s initiatives aim at facilitating research uses of biospecimens in ways that are legally possible and ethically sound, (Science Policy Committee), effectively orga-
nized (Education and Training Committee) and scientifically reliable (Biospecimen Science Working Group) (Fig. 2, Fig. 3). ISBER considers the above objectives as a manifestation of respect for both the environment and the human donors of specimens, by allowing researchers to make the best possible use of natural resources and clinical specimens.

**Figure 1. Example of Preanalytical EQA Survey Report.**

**QUESTION:**

7. What criteria do you have to define blood non-conformities?

- A. Hemolysis, above a certain threshold (8 out of 15)
- B. sCD40L, below a certain threshold (2 out of 15)
- C. DNA derivative, below a certain quantity/quality level (6 out of 15)
- D. RNA derivative, below a certain quantity/quality level (7 out of 15)
- E. Not applicable (4 out of 15)
- F. Other (3 out of 15)

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**QUESTION:**

8. What criteria do you have to define tissue non-conformities?

- A. Histology of bad quality (8 out of 15)
- B. IHC for specific markers (1 out of 15)
- C. DNA derivative, below a certain quantity/quality level (7 out of 15)
- D. RNA derivative, below a certain quantity/quality level (7 out of 15)
- E. Not applicable (5 out of 15)
- F. Other (1 out of 15)

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**QUESTION:**

9. What criteria do you have to define viable cell non-conformities?

- A. Viability, below a certain threshold (6 out of 15)
- B. Apoptosis, above a certain threshold (4 out of 15)
- C. Metabolic activity, below a certain threshold (0 out of 15)
- D. Totipotency (0 out of 15)
- E. Genetic/epigenetic stability (0 out of 15)
- F. Not applicable (8 out of 15)
- G. Other (1 out of 15)
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Figure 2. The continuum of ISBER’s contributions.

Figure 3. The continuum of Quality Assurance tools developed by ISBER.

Referenzen
