BIOPRESERVATION AND BIOBANKING
Volume 12, Number 2, 2014

DOI: 10.1089/bio.2013.0091

National Cancer Institute Biospecimen Evidence-Based Practices: A Novel Approach to Pre-analytical Standardization

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Variable biospecimen collection, processing, and storage practices may introduce variability in biospecimen quality and analytical results. This risk can be minimized within a facility through the use of standardized procedures; however, analysis of biospecimens from different facilities may be confounded by differences in procedures and inferred biospecimen quality. Thus, a global approach to standardization of biospecimen handling procedures and their validation is needed. Here we present the first in a series of procedural guidelines that were developed and annotated with published findings in the field of human biospecimen science. The series of documents will be known as NCI Biospecimen Evidence-Based Practices, or BEBPs. Pertinent literature was identified via the National Cancer Institute (NCI) Biospecimen Research Database (brd.nci.nih.gov) and findings were organized by specific biospecimen pre-analytical factors and analytes of interest (DNA, RNA, protein, morphology). Meta-analysis results were presented as annotated summaries, which highlight concordant and discordant findings and the threshold and magnitude of effects when applicable. The detailed and adaptable format of the document is intended to support the development and execution of evidence-based standard operating procedures (SOPs) for human biospecimen collection, processing, and storage operations.

Introduction

Suboptimal biospecimen collection, processing, and storage practices have been shown to alter biospecimen quality, as evidenced by reported alterations in DNA, RNA, protein and morphology endpoints (reviewed in Refs. 1–3).[1–3] Effects attributable to pre-analytical factors can be severe, resulting in misdiagnosis[4] and false discovery of biomarkers of disease,[5,6] and also both extensive and elusive, as 48%–58% of biobanked tissue collected and stored using institution-approved SOPs was deemed unfit for RNA analysis.[7,8] Thus, the availability of human biospecimens of sufficiently high quality continues to be a pressing need of the medical research community. To address this need, many facilities have implemented standard operating procedures (SOPs) for biospecimen procurement, processing, preservation, and storage. However, in most instances, SOPs are institution-specific, which can confound analysis of biospecimens collected at different hospitals or those obtained from different biobanks or biorepositories. Use of institution-specific SOPs may also preclude external validation of research findings, as well as meta-analysis efforts employed by both regulatory organizations, such as the United States Food and Drug Administration (USFDA) and the European Medicines Agency (EMA), and scientific organizations that aim to identify pre-analytical factors and their effects[1–3] or potential markers of biospecimen quality.[9] While there is a real and present need for a more global method of standardization and validation, universal adoption of a single collection of SOPs is impractical due to the different logistical and financial constraints associated with individual facilities.

The foundation on which SOPs are developed is also crucial in minimizing not only pre-analytical variability but biospecimen degradation. However, the question of whether SOPs are developed upon the current state of the science or ritual alone often escapes discussion. Incorporation of empirical evidence during the development or revision of SOPs would be marred with difficulty, in part, due to the disjointed publication forums available for published findings in the field of human biospecimen science. To illustrate, our office has identified over 300 journals that have published one or more articles in this field over the past 60 years. An additional concern is the inadequate reporting of biospecimen

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methodology in scientific publications. This issue has recently been addressed by the ''Biospecimen reporting for improved study quality (BRISQ)'' guidelines, which outlines critical factors that should be reported when applicable, and was published simultaneously in three journals,[10] and is referenced on Nature's instructions to authors webpage.[11]

Approach

The Biorepositories and Biospecimen Research Branch (BBRB, formerly known as OBBR) at the National Cancer Institute has undertaken a unique approach to the standardization of pre-analytical procedures for human biospecimens. The document entitled ''NCI Biospecimen Evidence-Based Practices: Snap-freezing of post-surgical tissue biospecimens'' is the first in an anticipated series. (The document is available as supplementary data in the online article at www.liebertpub.com/bio.) BEBPs are intended to augment existing best practices[12,13] by adding a level of granularity to the fundamental principles they outline through the inclusion of literature evidence and procedural detail, and can be used in tandem with biobanking management software systems. The BEBP document contains step-by-step procedural guidelines with annotated summaries of the literature evidence on which they are based. The detailed, yet adaptable, format facilitates the modification of existing SOPs that are currently in-use to minimize biospecimen degradation, while the modularity permits periodic updating to reflect the current state of the science. Notably, the format presents an ''optimal'' procedure, but allows for differences from the optimal due to lack of availability of key reagents (e.g., liquid nitrogen) or other conditions that make it impossible to implement optimal procedures. The primary goal of the document is to provide developers of SOPs with an evidence base from which to draw when developing and reviewing SOPs for research biobanking and biospecimen procedures during clinical trials.

Specific steps within the procedural guidelines were originally derived from SOPs designed for the Genotype-Tissue Expression (GTEx) project[14,15] and modifications were made based upon meta-analysis of literature evidence. While biospecimens collected and preserved under the BEBP presented here will be suitable for nucleic acid, protein, and morphological analyses, future BEBPs will be assessed individually for suitable downstream applications. Literature addressing pertinent pre-analytical factors was located using the NCI Biospecimen Research Database (BRD) (http://brd.nci.nih.gov/),[16] a free online database populated with peer-reviewed original and review articles in the field of human biospecimen science. A total of 48 published articles were referenced in the final document. Draft documents were shared informally with experts in the fields of biobanking and tissue cryopreservation to determine both institutional applicability and the suitability of biospecimens for downstream nucleic acid, proteomic and morphological applications. The resulting feedback substantially improved the document presented here.

What was expected to be a straightforward topic that would facilitate the development of the BEBP template was complex enough that internal citation would not suffice. The breadth of data available on each pre-analytical factor associated with snap-freezing human tissue differed widely. Further, reported findings at times conflicted, and in some instances the literature evidence failed to identify a preferred method clearly. Due to the complexity of meta-analysis findings, results were organized by pre-analytical factor and presented as an annotated literature summary. For each literature summary, concordant findings were collated for each analyte (DNA, RNA, peptide/protein, morphology) and concordant findings were extrapolated when possible. In such cases, an effort was made to include the threshold and magnitude of reported effects. Details and circumstances surrounding any discordant findings were also noted. When the evidence allowed, alternatives to the optimal procedure were specified. Both past and current versions of individual BEBPs will be maintained on BBRB's website.[17] Literature summaries will be updated annually to accommodate new and emerging science, at which time changes to procedural guidelines will be implemented as required.

Conclusion

We have presented the first in a series of evidence-based procedural guidelines on biospecimen collection, handling, and storage practices. This document identifies pre-analytical parameters capable of eliciting analyte-specific effects during snap-freezing of human tissue biospecimens, and provides a sound foundation for the development of evidence-based SOPs by individual projects and/or institutions. Ultimately, the use of evidence-based biospecimen procedures should raise the quality of research biospecimens and in turn raise the quality and reproducibility of biospecimen-based research and clinical trials. This document can also be found on BBRB's website.[17]

Acknowledgments

We thank Allison Hubel, Ph.D. (University of Minnesota), The Breast Cancer Campaign Tissue Bank, E. David Litwack (FDA), and Joanne Peter Demchock (NCI) for their consultation and insightful suggestions during the development of this document.

Author Disclosure Statement

No competing financial interests exist.

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This article has been cited by:

1. Moore Helen M.. 2014. Moving Toward Biospecimen Harmonization with Evidence-Based Practices. *Biopreservation and Biobanking* **12**:2, 79-80. [Citation] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]