Mini Review

Logistic steps of tissue sample processing in a clinical biobank - a short overview

Abstract

Human tissue samples, collected and stored based on standardized processes, enable high quality research in the field of biomedicine and life sciences. Most of the tissue biospecimens used in medical research are derived from patients and are collected, processed and stored by clinical biobanks. Clinical biobanks are usually situated in hospitals and operate directly at the interface between research and clinical care. This position requires specific steps adapted to the demands of both clinicians and researchers. This review aims to provide a short overview of the six most significant steps in sample handling and sample logistics in a clinical biobank. The described steps are crucial stages in the sample preservation process and have significant impact on quality of tissue biospecimens used in diagnostics and research. Biobank Graz, one of the largest clinical biobanks in Europe, collects, processes and stores tissue samples according to this workflow to provide high-quality samples and data for research and development.

Keywords: clinical biobank, tissue sample processing, sample logistics, preanalytical phase, sample quality, diagnostic process of tissue samples, pathologist

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Introduction

Biobanks are facilities that collect, process, store and distribute biospecimens and associated data for use in research. The samples banked in biorepositories are used by academic (e.g. university) and non-academic (e.g. pharmaceutical industry) scientists in the field of biomedical research. These research projects include the development of new therapeutics and the identification of biomarkers for progression and prognosis of various diseases. The term "biobank" can be further categorized by institution, type of biomaterials, collection purpose and collection strategy: Biobanks can be operated by academic or non-academic institutions (academic biobank vs. industrial / commercial biobank). Biorepositories collect and store various types of biomaterials (e.g. tissue biobank, blood biobank, cell biobank, etc.). Furthermore, biobanks may also be classified by purpose (research, diagnostic, or therapeutic biobank) or by collection strategy (disease-specific vs. population-based).[1,2] In a biobank associated with a hospital, research and clinical practice are closely intertwined.[3] In these clinical biobanks several steps and processes are involved in collection and processing of samples until their final storage in a biorepository. This review aims to provide a short overview of the six most significant steps in sample handling and sample logistics in a clinical biobank. Biobank Graz, one of the largest clinical biobanks in Europe, stores more than 7.5 million samples. Tissue samples (FFPE as well as fresh frozen) are mostly collected at the Institute of Pathology of the Medical University of Graz and enter Biobank Graz via routine diagnostic processes.[4] In this context, the most critical stage is the preanalytical phase. Preanalytical activities have a high impact on the quality of the collected samples and subsequently on the results of laboratory testing performed on these specimens.[5,6] Critical factors in the preanalytical phase are cold and warm ischemia time, time intervals between the different stages of sample processing or transport and storage conditions (temperature, duration, or the used protocols: e.g. amount of formaline).[7]

Stages of tissue sample processing

Here we present an overview of the six most significant steps in sample handling and sample logistics in a clinical biobank (Figure 1).

1st step: Sample collection

In a clinical biobank, the banked human tissue samples directly originate from patients in a hospital. The samples are typically collected during operations or other medical interventions including diagnostic and/or therapeutic interventions such as biopsies, needle punctures, etc. To be able to maintain sample quality, documentation of specific parameters and information is important (for details see 2nd step). Preanalytical variables, such as ischemia time, temperature during sample transport or the type of preservation method, have been shown to cause the greatest variability in quality of different biomolecules such as RNA, DNA or protein. As an example, tissue ischemia time significantly affects gene and protein expression patterns within minutes following surgical tumor excision.[8]

2nd step: Transport to the laboratory

After collection, the samples are transported from the operating room to the laboratory, where the diagnostic process as well as tissue preservation takes place. Ideally, a unique number is assigned to each sample. For this purpose, most hospitals use paper based histopathology request forms containing the following basic information:

I. Sender of samples (hospital, clinical department, MD's name, …)

II. Patient details (surname, forename, date of birth, case number, patient identification number, …)

III. Date and time specimen collected

IV. Information on nature and site of specimen (localization, tentative diagnosis, …)

3rd step: Intra-operative consultation

In some cases, the surgeon needs pathologic information while the patient is still under anesthesia on the operating table. The required information may include evaluation of adequacy of margins or identification of lymph node metastases.[9] For such an "intra-operative consultation", a frozen section is taken from the specimen using a cryostat. Next, the section is stained and examined by a pathologist under the microscope. As quick as possible, the examination report is transmitted to the operating surgeon via telephone. The pathological findings may importantly influence the surgeon's intra-operational decision.

4th step: Sample preservation

After histologic quality assurance of the tissue (performed by a pathologist), the tissue specimen is handed over to the lab personnel for long term preservation and storage. For different applications, specific preservation methods and protocols for treatment of tissue samples exist. The most common methods in biobanking and diagnostics are cryopreservation[10] and fixation in formaline[11] followed by paraffin embedment. For specific studies, fixation using the commercial available PAXgene® system,[12] treatment with stabilization solutions (e.g. RNAlater®) or dissociation of cells from the tissue for establishment of a cell line,[13] are used. As for the 2nd step, also at this time the assignment of a unique barcode to each sample is important to be able to track the storage location and history of each sample.[14]

5th step: Sample analysis and pathological diagnosis

In the next step, the samples are distributed over various specialized laboratories in the hospital depending on the type of sample and the specific tests that are required. Examples for specialized laboratories are: histopathology lab, molecular genetics/DNA diagnostics lab, hematology lab, cytology lab or microbiology lab. The data obtained from assessment of stained tissue sections by the pathologist and from the laboratory testing are important for the diagnostic process as well as for researchers using the biomaterials.

6th step: Final sample storage

Depending on the type of biospecimen, different environmental conditions are required for long term storage. Hubel et al.[15] summarize different studies that demonstrate the importance of storage temperature on the stability of critical biomarkers for fluid, cell, and tissue biospecimens.[15] Formalin-fixed paraffin embedded (FFPE) tissues are commonly stored at room temperature.[16] The recommendations for storage of frozen tissue sample range from freezers with -20 to -80°C to cryo tanks with ultra-low temperatures (liquid nitrogen; -130°C to -190°C).[15] Cell lines frozen in DMSO should also be stored in the vapor phase of liquid nitrogen.[13] Well preserved tissue biospecimens (frozen as well as formalin-fixed paraffin embedded) that are stored under optimal conditions can preserve DNA, RNA and protein for many years.[6] One of the major tasks in a biobank is sample management. This general term encloses the logistics and documentation during all steps and stages of tissue sample processing from sample collection until final storage. Janzen and Zaayenga sum up the main traits of modern sample management systems. These traits include sample tracking using barcodes, accurate quantity tracking of (mass and/or volume), automated storage and retrieval, quality/purity monitoring, etc.[14]

Figure 1 Stages of tissue sample processing.

Conclusion

Tissue banking in a clinical setting is crucial for research, since high-quality samples are necessary for identification and validation of potential biomarker and new targets for therapy. This review presents an overview of the six most important steps in sample handling and sample logistics in a clinical biobank. In that regard, the preanalytical phase is known to be the most error-prone part in the total process. To improve and standardize the preanalytical sample handling procedures, the biobanks within BBMRI-ERIC network are currently implementing the newly published CEN Technical Specifications (CEN/TS).[17] For bio banks access to long-term public funding is crucial to be able to build up and maintain an infrastructure that allows establishing preanalytical quality control.[18,19] For clinical bio banks in particular, a long-term funding and cost recovery strategy is necessary for sustainable utilization.[19] In terms of sample logistics, one of the biggest challenges for a clinical biobank is the melding of research with clinical care.[3] This is also reflected by the dual function of the pathologist in tissue banking: On the one hand, he is responsible for diagnostic decisions, on the other hand, he is involved in reviewing and selecting specimens prior to specimen processing and distribution to research laboratories.[20] So, for clinical biobanks the cooperation and collaboration between biobank staff and pathology staff is the key to optimal sample management to ensure high sample quality for both diagnostics and research. However, in the end researchers and clinicians have one common objective: The optimization of treatment by continuous improvement of diagnostics and treatment strategies.

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Conflict of interest

The author declares no conflict of interest.

References

1. Parodi B. Biobanks: A definition. In: Mascalzoni D editor. *Ethics, law and governance of biobanking*. 8th ed. Netherlands: Springer; 2015. 277 p.

2. De Souza YG, Greenspan JS. Biobanking past, present and future: responsibilities and benefits. *AIDS*. 2013;27(3):303–312.

3. Smith ME, Aufox S. Biobanking: The melding of research with clinical care. *Curr Genet Med Rep*. 2013;1(2):122–128.

4. Huppertz B, Bayer M, Macheiner T, Biobank graz: The hub for innovative biomedical research. Open journal of bioresources. *Open Journal of Bioresources*. 2016;3(1):e3

5. Hicks D. *Preanalytic variables, tissue quality and clinical samples from breast cancer patients: Implications for treatment planning, drug discovery and translational research*. In: Badve S, Gökmen-Polar Y editors. Molecular pathology of breast cancer: Springer International Publishing Switzerland; 2016. 19 p.

6. Shabihkhani M, Lucey GM, Wei B, et al. The procurement, storage, and quality assurance of frozen blood and tissue biospecimens in pathology, biorepository, and biobank settings. *Clin Biochem*. 2014;47(4-5):258–266.

7. Rao S, Masilamani S, Sundaram S, et al. Quality measures in pre-analytical phase of tissue processing: Understanding its value in histopathology. *J Clin Diagn Res*. 2016;10(1):EC07–C11.

8. Spruessel A, Steimann G, Jung M, et al. Tissue ischemia time affects gene and protein expression patterns within minutes following surgical tumor excision. *BioTechniques*. 2004;36(6):1030–1037.

9. Jaafar H. Intra-operative frozen section consultation: Concepts, applications and limitations. *Malays J Med Sci*. 2006;13(1):4–12.

10. Steu S, Baucamp M, Von Dach G, et al. A procedure for tissue freezing and processing applicable to both intra-operative frozen section diagnosis and tissue banking in surgical pathology. *Virchows Arch*. 2008;452(3):305–312.

11. Berg D, Malinowsky K, Reischauer B, et al. Use of formalin-fixed and paraffin-embedded tissues for diagnosis and therapy in routine clinical settings. *Methods Mol Biol*. 2011;785:109–122.

12. PAX gene tissue systems.

13. Freshney R. *Culture of animal cells: A manual of basic technique and specialized applications*. 7th ed. USA: Wiley-Blackwell; 2016, 728 p.

14. Janzen W, Zaayenga A. *Introduction to sample management*. In: Wigglesworth M, Wood T editors. Germany: Wiley-VCH Verlag GmbH & Co KGaA; 2012.

15. Hubel A, Spindler R, Skubitz AP. Storage of human biospecimens: Selection of the optimal storage temperature. *Biopreserv Biobank*. 2014;12(3):165–175.

16. Lou JJ, Mirsadraei L, Sanchez DE, et al. A review of room temperature storage of biospecimen tissue and nucleic acids for anatomic pathology laboratories and biorepositories. *Clin Biochem*. 2014;47(4-5):267–273.

17. Partner Charter. Common Minimum Technical Standards and Protocols for Biological Resource Centres dedicated to Cancer Researc.

18. Sargsyan K, Macheiner T, Story P, et al. Sustainability in biobanking: Model of biobank graz. *Biopreserv Biobank*. 2015;13(6):410–420.

19. Macheiner T, Huppertz B, Bayer M, et al. Challenges and driving forces for business plans in biobanking. *Biopreserv Biobank*. 2017;15(2):21–125.

20. Bevilacqua G, Bosman F, Dassesse T, et al. The role of the pathologist in tissue banking: European consensus expert group report. *Virchows Arch*. 2010;456(4):449–454.