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International Approaches to Advancing Biospecimen Science

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Abstract

Biospecimen quality is affected by a number of preanalytical factors that may or may not be obvious to the investigator. These factors are introduced through multiple biospecimen collection, processing and storage procedures which can differ dramatically within and between medical institutions and biorepositories. Biospecimen Science is the emerging field of study that is attempting to quantify and control such variability. A variety of efforts are under way around the world to establish research programs, evidence-based biospecimen protocols, and standards to improve the overall quality of biospecimens for research.

Keywords

Biospecimen science; Biospecimen research; Biospecimen; Best practices

Introduction

There are few resources as valuable to cancer researchers as tissue samples - the biospecimens that patients donate to aid in the search for cancer-related biomarkers. Harvesting and storing human tissue for research purposes is not new. Human biospecimens have been collected and stored for 100 years, and today, in excess of 300 million biospecimens are warehoused in freezers or stored in other formats such as paraffin-embedded tissue blocks (1). However, over the past decade or so it has become clear that the great majority of biospecimens stored in the world's biorepositories may not be suited for the state-of-the-art genomics, proteomics, metabolomics, and other bioanalytical technologies used today to search for cancer-related biomarkers. The irreproducibility of many reported biomarkers is due at least in part to the fact that the biospecimens utilized are often procured using different collection, processing and storage techniques. Such variability can lead to significant differences in biospecimen molecular integrity. Most recently, the National Cancer Institute (NCI) discovered that only small percentage of the biospecimens submitted for analysis in the pilot phase of The Cancer Genome Atlas Project were of a quality high enough to meet the project's analytical demands (2).

Biospecimen Science is the study of how biospecimen preanalytical variability affects downstream analytic results, and has been until recently a relatively neglected field. This variability is introduced through multiple biospecimen collection, processing and storage procedures which can differ dramatically between different medical institutions and

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biorepositories and even within the same institution. Biospecimen preanalytical variability can contribute significantly to bias in biomarker research (3), and in extreme cases can result in artifacts being misinterpreted as biomarkers. This problem is particularly significant when considering the results of genomic and proteomic tests, for example which assess multiple biomarkers within a single analysis (2).

In this article we outline NCI's approach to developing this scientific discipline and report on related international efforts. We also describe how new data from biospecimen research projects will inform national and international efforts to develop evidence-based SOPs, biospecimen best practices, and approaches to documenting these efforts through a publicly available data base and new biospecimen quality reporting metrics. Strategic thinking, dedicated efforts, and sustained funding for biospecimen research over the next 5–10 years will help realize much-needed progress.

Biospecimen Science at the NCI

In 2007, the NCI began an on-going effort to better understand the variability in biospecimen quality and its root causes. Under the "Biospecimen Research for Molecular Medicine" initiative of the Office of Biorepositories and Biospecimen Research (OBBR) (4), the Biospecimen Research Network (BRN) (5, 6) is supporting a cadre of extramural researchers to develop innovative approaches to control, monitor, and assess biospecimen quality, and to systematically define the impact of key biospecimen pre-analytical variables on downstream molecular data. Studies include the effects of blood specimen handling procedures on protein integrity; credentialing plasma and serum biospecimen banks for proteomic analyses; the effects of biospecimen integrity, intratumoral heterogeneity, and analytical variance on microarray-based pharmacogenomics tests for breast cancer; and the development of rapid methods for assessment of tissue quality. The BRN is also supporting a multi-site program to study the effect of different cancer tissue collection, processing and storage practices on biospecimen molecular integrity.

At the 2010 BRN symposium, "Advancing Cancer Research through Biospecimen Science," (7) the latest findings from this program highlighted real progress in understanding the key factors responsible for the preanalytical variability that can confound "omics" research. Investigators showed that it is possible to significantly reduce preanalytical variability by developing quality assurance and quality control measures specific for each type of sample and each type of analyte, and to have an informatics infrastructure capable of collecting the myriad data needed to rigorously annotate biospecimen collection and storage processes. It was also reported that the quality of analytes such as RNA may not prove reliable with stored samples no matter how rigorously controlled the collection and storage procedures may be (8). Another study showed that differences in surgical procedures, such as the time it takes a surgeon to remove a biospecimen after main artery ligation, can have a significant impact on biospecimen quality (9). A BRN-sponsored study is now being conducted to identify surgery-dependent gene expression signatures and protein biomarkers. Researchers are also examining whether mass spectrometry-based proteomic analysis can identify products of *ex vivo* proteolytic degradation, and ELISA assays can quantify the levels of protein oxidation and nitration. Statistical analyses of these quality control measures will quantify the effect of procedural variables and describe a normative distribution for a given sample handling procedure. It may be possible to develop a "signature" combination of peptide qualities that indicates that proteolysis has occurred.

The BRN has also developed the Biospecimen Research Database (BRD) (10), an online compendium of published research about how different biospecimen collection, processing and storage techniques affect specific downstream molecular analyses. This publicly

available, searchable database currently contains summary information on approximately 600 published studies. One of the remarkable findings in collecting biospecimen research literature for the BRD is that the relevant articles are found in a very large number of diverse medical and scientific journals (including CEBP) – certainly too many for researchers utilizing human biospecimens to regularly scan. In the future, the BRD will continue to include both legacy data and emerging data from new biospecimen research, as well as incorporate well-annotated, evidence-based biospecimen Standard Operating Procedures (SOPs).

Biospecimen Science is an essential part of the NCI's current development of the cancer human biobank, or caHUB. The pilot phase of caHUB will be implemented as a distributed network that brings cancererous and normal tissues into a centralized biospecimen resource, and their associated data into a centralized data resource. Biospecimen research results will provide an ongoing source of new data for caHUB, to advise rigorous, evidence-based Standard Operating Procedures for the collection, processing, storage, and distribution of biospecimens.

International Efforts in Biospecimen Science

Important biospecimen research is also being conducted outside the U.S. In Europe, for example, the four year initiative known as SPIDIA (Standardisation and improvement of generic Pre-analytical tools and procedures for In-vitro DIAgnostics) (11) is conducting a pilot study in which a network of molecular diagnostics laboratories is isolating nucleic acids from standardized blood and plasma samples. The nucleic acids will be analyzed in centralized facilities and their quality assessed. Guidance on how to improve the reliability of their procedures will be provided to those laboratories with poor preanalytical performance, and they will be invited to participate in SPIDIA training courses. The SPIDIA consortium, coordinated by QIAGEN GmbH, includes commercial laboratories, biobanks, universities and medical research centers, training and management companies, small companies (e.g. *in vitro* pre-analytical diagnostic tool and assay developers), a standards organization (European Committee for Standardization; CEN), a scientific advisory board, and an ethics committee. Its scope ranges from patient samples to clinical or diagnostic results, taking advantage of available sample and assay technologies.

BRISQ (Biospecimen Reporting for Improved Study Quality) and SPREC (Standard Preanalytical Coding for Biospecimens) are new international efforts that focus on the reporting of important biospecimen preanalytical variability. BRISQ (12) will provide a standardized approach to reporting information on the characteristics and handling of biospecimens when publishing in peer-reviewed journals. SPREC (13) outlines a method for coding biospecimen characteristics according to a set of standardized preanalytical variables.

Biospecimen Best Practices

Ultimately, the results of biospecimen research must be incorporated into rigorous, evidence-based practices for optimal biospecimen collection, processing and storage. The NCI Best Practices for Biospecimen Resources (14), first published in 2007, have been updated recently to include a new management and operations section, as well as updates from NCI workshops that addressed ethical issues such as specimen collections custodianship and pediatric informed consent. These Best Practices will be updated on an ongoing basis to include evidence-based SOPs supported by new biospecimen research results Although many best practices are in effect across the world (15), a set of harmonized, international best practices for human biospecimens does not exist. Reaching consensus on biospecimen best practices can be difficult and time consuming. For example, the Organisation for Economic Co-operation and Development (OECD) originally planned to

develop standards for biobanking. However, the effort resulted in the modified goal of producing non-binding “best practice guidelines” which must be evidence-based (16). Even with this modified goal, achieving consensus in this manner could constitute the beginning of a global conversation and would be a major achievement. The OECD is open to feedback on how guidelines work in practice, which may lead to subsequent revisions. To initiate this process, a meeting of the Global Biological Resource Centre Network (17) was held in November 2010 to identify groups interested in testing the applicability of guidelines and reporting back to the OECD. It is anticipated that such efforts will lead to more international cooperation to achieve harmonized best practices for biological resource centers.

The European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) (18) aims to better coordinate biospecimen access and research activities across Europe. As a first step the BBMRI is coordinating a general assessment of biobanking operations. The program has recognized the need to coordinate biospecimen quality improvement as well as ethical and legal issues, information technologies and economic strategies. BBMRI is coordinating its plans and practices with those already in place within the Public Population Project in Genetics (P3G), OECD and the International Agency for Research on Cancer (IARC) (19). Notably, BBMRI did not develop its own standards and guidelines; it instead built on OECD guidelines as a common basis for evaluation.

Selecting from many standards, the Marble Arch Working Group has published a compilation of existing recommendations into an international testing-laboratory-accreditation standards format (20). This approach puts quality control testing of the biomolecular quality of samples in the focus of the accreditation scope and thus bridges the gap between best practices and biospecimen science.

The promise of using harmonized biospecimen best practices is exemplified by a study on the molecular profiling of breast cancer tissues sponsored by the NCI Office of Latin American Cancer Program Development (21). The program will create partners in Latin America who can conduct high-quality research and collaborate with investigators in the U.S. and elsewhere in an effort to better understand and treat disease in underserved Hispanic and Latino populations. In this project, 2000 patients from Mexico, Argentina, Brazil, Chile, and Uruguay will be enrolled and biospecimens collected using a series of standards related to pathology and tissue annotation, tissue characterization, and preservation of biological samples. The program will abide by best practices promulgated by the OBBR and College of American Pathologists, and promote adherence to high-quality biospecimen standards in Latin America.

Future Directions in Biospecimen Research

The days of thinking that proper biospecimen procurement is simply a matter of harvesting tissue and flash freezing it are long past. Today, the state of biospecimen science has progressed to the point where it is starting to change what are considered acceptable practices at established biorepositories, and prompting the development of new facilities designed to capitalize on the increased understanding of how to best procure, store, and annotate biospecimens destined for cancer research and other research initiatives. Investigators are striving not only to identify the many factors that impact a biospecimen’s viability and utility, but to put this new knowledge to work in order to generate biospecimens of the highest quality possible. And while there is still a great deal yet to understand, the field has progressed to the point where large-scale initiatives such as The Cancer Genome Atlas and the recently launched Human Proteome Project can now proceed with new information to advise the procurement of high-quality samples needed for their

projects. Continued efforts in biospecimen science will build a strong foundation for generations of ‘omics-based research and the advent of personalized cancer therapy.

References

1. Eiseman, E.; Haga, S. A Handbook of Human Tissue Sources: a National Resource of Human Tissue Samples. Santa Monica, CA: RAND Corporation; 2000.
2. Compton C. Getting to personalized cancer medicine. Cancer. 2007; 110:1641–3. [PubMed: 17763370]
3. Ransohoff DF, Gourlay ML. Sources of bias in specimens for research about molecular markers for cancer. J Clin Oncol. 2010; 28:698–704. [PubMed: 20038718]
4. NCI Office of Biorepositories and Biospecimen Research. Available from: http://biospecimens.cancer.gov/
5. OBBR Biospecimen Research Network. Available from: http://biospecimens.cancer.gov/researchnetwork/default.asp
6. Moore HM, Compton CC, Lim MD, et al. Biospecimen research network symposium: advancing cancer research through biospecimen science. Cancer Res. 2009; 69:6770–2. [PubMed: 19706749]
7. OBBR Biospecimen Research Network Annual Symposium; Available from: http://biospecimens.cancer.gov/meeting/brnsymposium/2010/
8. Brooks, A. Sample Quality Control: Qualifying Renewable Biological Resources. BRN Symposium presentation; 2010. Available from: http://biospecimens.cancer.gov/meeting/brnsymposium/2010/docs/Brooks%20OBBR%202010.pdf
9. Spruessel A, Steimann G, Jung M, Lee SA, Carr T, Fentz AK, Spangenberg J, Zornig C, Juhl HH, David KA. Tissue ischemia time affects gene and protein expression patterns within minutes following surgical tumor excision. BioTechniques. 2004; 36:1030–7. [PubMed: 15211754]
10. Biospecimen Research Database. Available from: https://brd.nci.nih.gov/BRN/brnHome.seam
11. Standardisation and improvement of generic Pre-analytical tools and procedures for In-vitro DIAgnostics. Available from: http://www.spidia.eu/
12. Jewell, SD.; Moore, HM.; McShane, LM., et al. Biospecimen Reporting for Improved Study Quality (BRISQ). Biopreservation & Biobanking; 2011. In Press
13. Betsou F, Lehmann S, Ashton G, et al. Standard Preanalytical Coding for Biospecimens: Defining the sample PREanalytical Code. Cancer Epidemiol Biomarkers Prev. 2010; 19:1004–15. [PubMed: 20332280]
14. NCI Best Practices for Biospecimen Resources. Available from: http://biospecimens.cancer.gov/bestpractices
15. Vaught J, Caboux E, Hainaut P. International efforts to develop biospecimen best practices. Cancer Epidemiol Biomarkers Prev. 2010; 19:912–15. [PubMed: 20233852]
16. Organisation for Economic Co-operation and Development Best Practices. Available from: http://www.oecd.org/dataoecd/7/13/38777417.pdf
17. Global Biological Resource Centre Network. Available from: http://www.gbrcn.org/
18. Biobanking and Biomolecular Resources Research Infrastructure. Available from: http://www.bbmri.eu/
19. Yuille M, van Ommen GJ, Brechot C, et al. Biobanking for Europe. Brief Bioinform. 2008; 9:14–24. [PubMed: 17959611]
20. Betsou F, Luzergues A, Carter A, et al. the Marble Arch Working Group on International Biobanking. Towards norms for accreditation of biobanks for human health and medical research: Compilation of existing guidelines into an ISO certification/accreditation norm-compatible format. Quality Assurance Journal. 2008; 11:221–94.
21. NCI Office of Latin American Cancer Program Development. Available from: http://www.cancer.gov/aboutnci/organization/olacpd/researchnetwork