Clinical Biochemistry 47 (2014) 293–299

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

Developing an institutional cancer biorepository for personalized medicine

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ARTICLE INFO

Article history:
Received 23 September 2013
Received in revised form 6 December 2013
Accepted 13 December 2013
Available online 27 December 2013

Keywords:
Biorepository
Biospecimen
Cancer tissue
Pathology
Personalized medicine

ABSTRACT

High quality human biospecimens, such as tissue, blood, cell derivatives, and associated patient clinical information, are key elements of a scientific infrastructure that supports discovery and identification of molecular biomarkers and diagnostic agents. The goal of most biorepositories is to collect, process, store, and distribute human biospecimen for use in basic, translational and clinical research. A biorepository serving as the central hub provides investigators with an invaluable resource with appropriately examined and characterized biospecimens with associated patient clinical information. Expertise in standardization, quality control, and information technology, and awareness of cutting edge research developments are generally required for biorepository development and management. The availability of low cost whole genome profiles of individual tumors has opened up new possibilities for personalized medicine to deliver the most appropriate treatments to individual patients with minimal toxicity. A biorepository in support of personalized medicine thus requires the highest standards of operation and adequate funding, training and certification. This review provides an overview of the development of an institutional cancer biorepository for clinical research and personalized medicine advancement.

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Introduction

Modern research in cancer biology and the development of personalized medicine depend on readily available high-quality and well annotated human biospecimens. A biorepository is required to identify useful biomarkers and serves as the central hub to provide investigators with an invaluable resource with appropriately examined and characterized biospecimens with associated patient information. The identification and validation of biomarkers can facilitate the development of novel targeted therapies to advance personalized medicine. Combined with whole genome or whole exome sequencing using next generation sequencing technologies, the possibility of personalized medicine to deliver the most appropriate treatment to individual patients with minimal toxicity is approaching. Although this technology is extremely promising, in order to identify which mutations may be important in a given patient's tumor, it is critical to have a large collection of patient samples with well annotated clinical, pathologic and

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0009-9120/$ – see front matter
http://dx.doi.org/10.1016/j.clinbiochem.2013.12.015

outcome data [1,2]. Large scale efforts, such as that of The Cancer Genome Atlas (TCGA), are underway to help catalog the spectrum of mutations present in different tumor types and this information will be invaluable for the field to move forward (http://cancergenome.nih.gov/) [3]. However, it is likely that, given the scope of the problem, such large scale efforts on their own will not be able to determine in many cases which mutations may be of clinical relevance. This will require many more samples to be run and to have these samples tied to long term outcome data. Biorepositories provide high quality patient specimens for the assessment of biomarkers, with implications for personalized therapy, yet they can also provide a repository of mutational data associated with clinical outcomes that can ultimately help determine which mutations are clinically relevant. In addition, by banking the samples it is possible that as new technologies are implemented new assays performed on the banked samples will provide additional new insights in the future, especially when one can compare the new data with the existing sequencing data.

Biorepositories that support clinical research are highly complex in their operation including many technical, legal, ethical, and other issues [4,5]. Proper collection, processing, storage, and tracking of biospecimens are critical components for biorepository operation. Over recent years a number of "best practices" guidelines have been developed, that are mainly based on empirical observations, which are providing valuable information on standardized biorepository operation [6,7]. The emerging field of biorepository and biospecimen science has begun to deploy evidence-based practices in both research and clinical settings and to produce evidence-based standards [8,9].

The goal of most biorepositories is to collect, process, store, and distribute human biospecimens to support basic, translational, and clinical research. Within an institution, biospecimen repositories may include institution-wide large centralized biorepository and legacy or investigator driven satellite biorepositories. These investigator driven satellite biorepositories tend to offer control of tissue inventory and usage with customized databases and forms for clinical information entry and viewing. However the quality of tissue specimens in the satellite biorepositories may vary. Lack of a shared centralized informatics system often limits opportunities to coordinate collection and facilitate sharing of biospecimens and/or clinical information. Therefore, development of a centralized, coordinated, quality controlled and quality assured institutional cancer biorepository is widely viewed as an efficient way to promote research collaboration and better patient care. The ability to sequence the whole genome in an efficient and inexpensive way is the most powerful tool for personalized medicine currently. Personalized therapies are selected for the individual patient based on the genetic alterations in cancer cells. In non-small cell lung cancer, for example, patients with an ALK mutation are treated with the drug Xalkori, which is specific for this type of mutation, whereas patients with an EGFR mutation would receive treatment with EGFR tyrosine kinase inhibitors such as gefitinib and erlotinib [10–12]. The availability of high-quality and well annotated biospecimens therefore is a key requirement for biomarker identification and validation, and thus necessary to enhance personalized medicine. A biorepository that directly supports personalized medicine involves patient care and therefore should be categorized as a clinical biorepository. Such a clinical biorepository would require the highest standards for operations, rigorous quality assurance and quality control, adequate funding, training, and certification such as the College of American Pathologists (CAP) accreditation. Most traditional research-oriented biorepository models, while extremely valuable for discovery efforts, are not set up with such rigorous measures in place.

Informed consent

With respect to patient confidentiality and privacy, biospecimens that facilitate examination of the molecular basis of disease are generally collected from patients with informed consent. The essentials of informed consent are a description of the research, the participant's role that includes an explanation of all procedures, description of benefits and reasonably foreseeable risks, and an explanation that participation is voluntary [13]. By signing the consent, patients confirm that they are aware of the purpose of the research for which their samples are donated and understand the risks and benefits [14]. Addressing the need to obtain patient informed consent is a major consideration when developing a biorepository. Federal policy such as Common Rule and Health Insurance Portability and Accountability Act (HIPAA) mandate that consent forms be written in plain language that the subject can understand [15,16]. There are many options in this area. A broad consent with appropriate institutional review board (IRB) regulations allows the use of patient biospecimens and medical information for future research under an appropriate IRB approved study protocol, which generally requires two IRB approved protocols: a biospecimen collection protocol and a biospecimen study protocol. Broad consent allows biospecimens to be banked in a biorepository for unspecified future usage, thus is more of a general consent procedure and benefit to the biorepository's long term goals [17]. Broad consent and study-specified informed consent are opt-in methods in which participants take a more active role in the research. These opt-in methods generally receive more public acceptance with increase information and education [14,17]. Although written informed consent is considered the gold standard for ensuring that participants are fully intentional and voluntary, there is a general agreement that the consenting process is time-consuming and expensive and therefore remains a challenge [18,19]. Another type of consenting process, opt-out consenting, provides a rapid, cost-efficient collection of biospecimens from patients. The opt-out approach allows biospecimens obtained during routine clinical procedures to be "automatically" banked in a biorepository unless the patient proactively opts out [20,21]. This opt-out approach, however, provides little information to participants regarding the research program. Institutions have many options and may create customized procedures to meet their daily practice. Complex issues such as the return of incident research finding or individual research results generated by genetic research to consented patients should be considered and included in the consent procedure [22–24]. Although there are debates about whether or not the biorepository or molecular lab should be responsible for reporting incidental findings, as new high throughput technology is emerging, such as next generation sequencing, the development of patient consents should be done with specific consideration with incidental findings in mind. Although the biospecimen collection, storage and distribution for research use are typically thought to involve minimal risk [25], it is important to carefully examine whether or not the consenting procedure for the biorepository is ethical and satisfies the national and institutional guidelines.

Cancer tissue pathology

Cancer tissues obtained from either surgery or biopsy are required to be examined by pathologists. Redundant tissue can be collected for biobanking purposes without compromising diagnosis. Subsequent morphological analysis is generally required for clinical and research purposes; this includes tissue heterogeneity, tissue scoring, present or absent tumor cells, inflammatory and necrotic areas, etc. When discrepancy between the original pathological diagnosis and the tissue section generated from banked tissue occurs, the banked frozen tissue may be released for subsequent diagnostic analysis. Non-redundant tissue such as venipunctures or biopsies may be collected explicitly for biobanking purposes. In these cases, an additional biopsy or pap cytology is high recommended for pathological diagnosis, and an IRB approved consented protocol is generally required.

There is high demand for high quality and well annotated cancer tissues for non-morphological analyses in new high throughput technologies such as tissue microarray and proteomics, which requires minimized tissue ischemia time. Availability of cutting edge technologies