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The Importance of Human Tissue Bioresources in Advancing Biomedical Research

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Medical research advances enabling the realization of precision medicine have relied heavily on the biospecimens provided by bioresources to identify the targets and biomarkers that are the focus of the new generation of more effective molecular-based therapies for specific subtypes of diseases. Through the biospecimens they have distributed, bioresources have permitted subtypes of cancers to be identified and molecular features of these subtypes to be effectively targeted. A prototype example is the human epidermal growth factor receptor type 2 (HER2), which currently is targeted in breast and gastric cancers. In the future, the use of biospecimens from bioresources will continue to increase the understanding of the molecular actions of drugs and how drugs may be more or less active in subpopulations of patients. Although the biospecimen inventories of the initial forms of bioresources may not have always been optimally planned and, therefore, utilized in supporting biomedical research, bioresources are evolving and overall, bioresource inventories and increasingly their prospective collection capabilities will continue to be a critical component of the research infrastructure.

Keywords: bioresource, biobank, biomedical research, medical care, precision medicine

Introduction

Use of human tissues has been critical in advancing biomedical research, science, and medical care, including the recent development of precision medicine. Although ideas for new approaches to therapies for cancer and other diseases have, in the past, often emerged from studies that began with animal models and immortalized cell lines, basic research initiated using human biospecimens and associated annotating data is increasingly the starting point for new discoveries. Ultimately, the results from all such studies must be confirmed and expanded using numerous human tissues.[1] However, several articles have recently discussed that effective utilization of bioresources is a problem.[2,3] This is partly intrinsic to some biobank operational designs, but it is evident that this is also due to lack of coordination across the research system, as well as lack of strategy and planning of individual biobanks.[4–9] Nevertheless, human biospecimens provided by biobanks/bioresources have supported many of the most important recent advances in medicine.[4–7]

In 2000, Korn specifically discussed the importance of archival pathology collections of formalin-fixed paraffin-embedded (FFPE) blocks in advancing biomedical knowledge and medical care.[10] Since that time, although there have continued to be huge advances in medical care, there have been few discussions as to the importance of bioresources in supporting key medical developments.

Human biospecimens are vital in advancing basic science efforts, such as the profiling of genetic and molecular elements associated with specific pathologies. The collection, storage, and distribution of biospecimens, including liquid biospecimens (urine, saliva, spinal fluid, bile, semen, and bronchial lavage fluid) have always been important to biomedical research. With the new era of molecular medicine/precision medicine driven by research and the increasing dependence of research on biospecimens, the range of utilization of biospecimens from multiple sources has increased the need for uniformity in standards. Similarly, quality control within bioresources is critical to ensure that what is provided to investigators, both biospecimens and associated annotating data, are of appropriate quality and fit for purpose.[11,12]

There are many examples of how bioresources have been very important in improving medical therapies as well as increasing the understanding of the biology of normal and diseased tissues. To illustrate the importance of bioresources, we describe, medical advances arising from the use

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of biospecimens in the cancer field, and studies delineating the increased dependence on biospecimens in research.

Examples to Illustrate Importance of Bioresources

The Cooperative Human Tissue Network (CHTN) represents an example of a bioresource of multiple cooperating entities that has significantly advanced science and biomedicine.[5,6] Of note, the CHTN operates as a prospective bioresource whose goal is not to bank biospecimens, but to collect and directly distribute them to investigators.[5,6] Each of the six divisions of the CHTN distributes biospecimens to investigators located in North American as well as to a limited number of international investigators. Since its inception (1987), the CHTN has distributed ~1.5 million human biospecimens to investigators and these biospecimens have supported >5000 publications. These publications have been important in describing normal biological functions such as nontranslatable RNAs (e.g., microRNAs) as well as disease processes such as the identification of a viral etiology of Merkel cell carcinomas.

As just one example of the activity of one bioresource that has also contributed to the CHTN, in 2017 and 2018, the Tissue Procurement Shared Facility of the University of Alabama at Birmingham (UAB) O'Neal Comprehensive Cancer Center supported 51 clinical trials that required the collection and distribution of ~1200 human biospecimens.

Multiple molecular alterations in diseases have been discovered and characterized through utilization of human bioresources, which have provided substantial numbers of high-quality human biospecimens to support a wide range of research. The clinical significance of specific molecular changes has been determined and includes biomarkers of risk, diagnosis, prediction of therapeutic response, and prognosis. Also, molecular targets for specific therapies have been identified in breast cancers that include estrogen and progesterone receptors and human epidermal growth factor receptor type 2 (HER2).

Similarly, mutations that develop in genes during the progressions of cancers such as in the tumor suppressor gene, p53, have been associated with more aggressive malignancies and provided prognostic information. The identification of significant and medically targetable molecular alterations in precision medicine has played a very important role in medical management and therapy of a wide range of cancers and other diseases.

HER2 is a transmembrane tyrosine kinase receptor, and is a member of human epidermal growth factor family of molecules. Using biospecimens provided by bioresources, researchers initially discovered that overexpression of HER2 (mostly attributable to gene amplification) plays a primary role in the development and progression of an aggressive subtype of breast cancer that has a poor prognosis, as defined by higher recurrence rates and increased mortality.[13,14] This stimulated development of Herceptin to target the HER2 receptor expressed by this tumor subset comprising 15%–20% of all breast carcinomas. Subsequently, the availability through various tissue banks of other types of malignant tumors from different sites has helped to demonstrate the overexpression of HER2 in different anatomic types of cancer. Specifically, HER2 is now a well-established therapeutic target for gastric cancers, and is recently proposed to be a potential biomarker guiding adjuvant chemotherapy in stage II colorectal cancers.[15–17]

Biospecimens provided by biorepositories have facilitated the development of novel approaches to immunotherapy, which are applicable to a broad range of malignancies, including melanomas, ovarian, gastric, and lung adenocarcinomas, and uterine serous endometrial carcinomas.[18–20] The checkpoint protein programmed death-ligand 1 (PD-L1 or B7-H1) has a major role in suppressing the immune system. The immune system is inhibited by the binding of PD-L1 to the program cell death protein 1 (PD-1) on cytotoxic $CD8^+$ T cells; this increases apoptosis and provides an inhibitory signal that decreases the proliferation of antigen-specific T cells. This interaction also reduces apoptosis in regulatory T cells (anti-inflammatory suppressive T cells).

Studies of biospecimens have found that some human cancer cells express high levels of PD-L1, which through interaction with PD-1 on T cells permits the PD-L1 expressing cancer cells to escape surveillance by the host immune system. For example, investigation of 196 fresh frozen renal cell carcinomas (RCC) concluded that an increased expression in tumor cells of PD-L1 was linked to increased aggressiveness of the RCC.[21] Therapeutic blockade of programmed death-ligand 1 or programmed cell death protein 1 with monoclonal antibodies leads to durable tumor control in a minority of patients across many cancer types.[22–24] Although this effect is only seen in a minority of patients, so-called immune check point blockade therapy represents a dramatic advance and has ushered in a new approach to cancer therapy.

The reasons why some families have inheritable tendencies to develop specific cancers also has been clarified by studies using human biospecimens. This includes the identification of inherited mutational patterns in tumor suppressor genes involved in DNA repair-breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2). These mutations occur in familial breast and ovarian cancers.[25] Similarly, mutations in members of a group of seven DNA mismatch repair genes also increase the tendency of specific cancers to develop such as colon cancers.[26]

Another example of the importance of human tissue biospecimens and bioresources is the characterization of a tumor protein, p53, also known as tumor suppressor p53, which acts to regulate the cell cycle. p53 is activated by various events such as DNA damage, heat shock, hypoxia, oncogene overexpression and therapeutic drugs. Thus, the main role for p53 is as a regulatory protein that acts as the ''guardian of the genome''; it is responsible for genetic constancy and stability by minimizing the impact of genome mutations.[27] Studies have shown that the p53 gene is mutated at an early stage of tumorigenesis in about half of all human cancers, indicating that the TP53 gene plays a crucial role in preventing cancer formation.[27] Certain pathogens also can affect the function of the p53 protein. These include human papillomavirus that encodes a protein, E6, which inactivates p53 protein by binding to it.[28] Although once considered to be ''undrugable,'' point mutations in p53 may now be targeted by agents that change the overall configuration of the molecule and hence, convert the mutated p53 into a functional protein.[29,30]

Further examples are provided by the spectrum of biomarker assays that have been and continue to be implemented as part of routine diagnostic tumor pathology that

provide prognostic and/or predictive information to guide therapies. To highlight such advances in a few other tumor systems, the approach to diagnosis and treatment of non-small cell lung cancer (NSCLC) has been transformed by the identification of multiple molecular subgroups of NSCLC; these are defined by specific targetable gene mutations and new assays to detect relevant altered gene expression in tumors to guide therapeutic decisions (e.g., epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], reactive oxygen species [ROS] assays).[31]

Similarly, the approach to diagnosis and prediction of response to treatment of other cancers such as glioblastoma multiforme has been advanced by the identification of gene mutations and other alterations and implementation of new clinical assays that provide prognostic information (e.g., isocitrate dehydrogenase (IDH), 0-6-Methylguanine-DNA Methyltransferase (MGMT) assays).[32] In all cases these advances have been dependent on bioresources that have enabled identification, development of antibodies, and validation and implementation of clinical immunohistochemistry assays.

Bioresources have been very important in most aspects of health care developments, including new therapeutic approaches and evaluation of medical devices. In the USA, the final stage of such developments involves a commercial (for-profit) company, which submits its supporting information, including tissue-based research to the U.S. Food and Drug Administration (FDA). Such research usually is supported by results on biospecimens obtained from an internal bioresource of the commercial company as well as from external bioresources. In addition, many bioresources will have provided hundreds to thousands of biospecimens to a wide range of investigators who generated much of the biospecimen research results that have led to the consideration by commercial companies of various therapeutic approaches.

These results ultimately may be incorporated in the relevant FDA applications. Although some bioresources may not incorporate the necessary information about providing specimens to commercial companies in their consent protocol or may be reluctant to provide biospecimens to commercial organizations, providing biospecimens to the for-profit entities is a critical activity that fulfills important bioresource goals; biomedical care would not adequately advance without such support.

Studies to Delineate Importance of Bioresources

In a series of studies on the use of human biospecimens in cancer research, we have documented the high prevalence of biospecimen use in contributing to the knowledge generated through cancer research, from the perspective of individual investigators, funded research, and publications in journals.[33–37] For example, Castillo-Pelayo et al.[37] studied the importance of biospecimens and bioresources across the sector of health research relevant to cancer. They selected a cohort of cancer researchers funded in 2010 by a national cancer research funder with a broad mandate and analyzed the publications generated for the following 5 year period. Although the cohort was small (35 investigators), they demonstrated that overall the scope of research conducted was reasonably representative of the scope across all cancer research supported in Canada.

The key finding was that biospecimens contributed to at least one data point in almost 40% of ~450 data articles relevant to cancer published by this group. Among several other indicators of research tools and infrastructures used, only cell lines were more important in supporting data generation. Approximately 50% of biospecimens were obtained from clinical pathology (encompassing both prospective and retrospective cohorts) and 30% were obtained from bioresources. The study also discussed the fact that agencies funding cancer research are looking for reassurance that funded studies are productive, reproducible, and will improve cancer care and outcomes.

In the short-term, this is measured by publications and citations, but behind these short-term measures of research productivity, the issue of reproducibility of research is very important for the eventual impact. They suggested that problems with research reproducibility may be related to the quality of biospecimens and/or the implementation of biobanking standards. Castillo-Pelayo et al. also identified some issues that may impede the operations of biorepositories, such as lack of sustainability of current operations and timeframes in use of biorepository inventories.[37]

Conclusion

In conclusion, the provision to investigators of high-quality human tissues by biobanks/bioresources has been critical to advancing biomedical research and science as well as improving medical care, especially of patients with cancer. Bioresources have been central to biomarker discovery and precision medicine, including diagnostics and targeted therapies. Investigators need access to bioresources that can provide high-quality and consistent biospecimens linked to reliable clinical and pathological information. Because research directions are constantly evolving, bioresources must adjust to provide biospecimens necessary to generate preliminary data for novel grants, as well as to establish reproducible results for key articles; also, the biomedical research data should lead to improvements in patient care. Thus, biorepositories are a critical component of the research infrastructure.

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