Multi-Institutional Tumor Banking
Lessons Learned From a Pancreatic Cancer Biospecimen Repository

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Abstract: Clinically annotated pancreatic cancer samples are needed for progress to be made toward developing more effective treatments for this deadly cancer. As part of a National Cancer Institute–funded program project, we established a biospecimen core to support the research efforts. This article summarizes the key hurdles encountered and solutions we found in the process of developing a successful multi-institutional biospecimen repository.

Key Words: pancreas, cancer, multi-institutional tumor banking

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A denocarcinoma of the pancreas is the fourth most common cause of death from cancer each year in the United States, accounting for approximately 35,240 deaths in 2009.1 It is associated with the worst survival rate of any gastrointestinal cancer. The principal reasons for the poor survival rate include a paucity of symptoms until the tumor has progressed beyond a localized resectable stage and the propensity for early metastasis to regional nodes and the liver. The development of techniques for early diagnosis and new more effective systemic treatments are imperative.

The human genomics revolution offers the potential to change how physicians diagnose and treat cancer. For scientists to develop new treatment strategies and therapeutic agents, there must be access to tumor samples.2 In a 2001 Pancreas Cancer Think Tank, Dr Scott Kern stated, “Of the resources required, the most pressing was a need for comprehensive tissue banks.”3 Tumor banks are facilities that are established to collect, store, and distribute biologic specimens to support the translational investigative efforts of cancer researchers. Clinical data, with appropriate confidentiality safeguards, are annotated to the stored samples, allowing investigators to make conclusions regarding the prognostic significance or therapeutic response related to a tumor’s genetic characteristics. For a tumor bank to be useful, clinical information and samples must be collected and stored in a manner assuring quality and accessibility. Central tumor banks that acquire donations from several sites allow for the collection of large numbers of tumor samples when any individual contributing site may see relatively few cases of any particular tumor. Such central banks increase the likelihood of successful investigations and speed the development of new therapeutic agents.

As part of a National Cancer Institute (NCI)–funded program project grant (PPG) for pancreatic cancer, a multi-institutional biospecimen repository was created as a core facility to facilitate the acquisition of tissue and corresponding clinical and pathological data for the support of the proposed research carried on by the PPG investigators. The goal for the core was to enroll 50 patients yearly. During the first 2 years of PPG enrollment, we were unable to achieve that goal for several reasons, including longer than expected site initiation times, site-specific restrictions, and others that will be discussed in later sections. After recognizing the logistical issues responsible for lower than anticipated patient accrual, we developed new strategies in latter years, which resulted in a marked increase in accrual in years 3 and 4 (Fig. 1). We analyze here some of the hurdles faced and examine lessons learned in developing a robust donor base and resulting biorepository.

IDENTIFYING COLLABORATORS WHO WILL PARTICIPATE

To establish clinical collection sites with access to pancreatic cancer patients, we initially identified institutions with a previous record of collaboration with PPG investigators. A track record of successful collaboration in the past was a good starting point but did not guarantee success. Seven sites were identified and submitted as collaborative institutions as part of the initial PPG submission. Of these proposed sites, only 3 successfully opened the protocol and submitted samples to the biorepository within the first year. As a result, our group sought and was able to obtain collaboration from additional sites not originally proposed in the initial PPG application. The 4 initially proposed sites that failed to enroll cases did not do so for one or more of the following reasons: (a) in 2 cases, the principal investigators (PIs) at the sites were medical oncologists, and ultimately, they were unable to get the participation of surgeons and pathologists at their sites; (b) the PI and other investigators at the same institution had competing priorities for the same patient population specimen; (c) failure to gain institutional review board (IRB) approval at the site. One of the sites that initially participated and submitted samples (n = 11) withdrew participation during year 4 because the surgeon who was the site PI left the institution for another position. This site was replaced for year 5 with a new site that has so far submitted 2 sample sets. The relative contribution per site is depicted in Figure 2. Other concerns were more global and should be addressed proactively. These issues include such matters, which will be addressed later, such as the possible inclusion of specimen contributors as coauthors on articles, ownership of intellectual property, and the possible access of specimens from the biorepository for other studies.
Academic Versus Community Hospitals

Both academic and community medical centers are amenable to collaborations and are participants in our repository, but these sites may have different concerns. Collaborating investigators at academic medical centers seek, in exchange for their participation, the opportunity for meaningful collaboration in the biomedical research work done on the samples and authorship as recognition for their efforts. Many journals have published guidelines that say if one merely provides samples, this does not justify authorship on an article. Participants in our protocol, however, have worked to get IRB and contract approval at their institutions, a process that can be extremely time consuming, and to assure that collection of high-quality samples is done in a manner that is in accordance with the protocol. In recognition of these efforts, the PPG Executive Committee, composed of project and core leaders, made it clear that recognition including authorship is warranted for investigators who provide tissues if their roles also included the initiation and follow-up of processes necessary for IRB review, maintenance of interinstitutional agreements, and for oversight of the efforts of the site pathologists, research nurses, and other appropriate staff who assure the collection and shipping of annotated biospecimens for our program.

Participation in this program also has led to additional collaborations as a result of the communication between various investigators. Surgeons and pathologists at community hospitals who are not seeking advancement in their academic rank are less concerned with authorship but warrant, nonetheless, consideration based on their level of contribution. It is particularly noteworthy that surgeons and pathologists at community hospitals recognize the importance of biomedical research and actively support it by participation in these efforts. Our program project also has yearly retreats during which the projects and cores present updates on their progress. The contributing surgeons and pathologists are invited to attend and in this way are able to see the relevance of their contributions to the scientific work.

Surgeons or Pathologists?

It is essential that both the surgeons and the pathologists at the participating sites work together and are actively engaged in the patient accrual and biospecimen collection processes. In both the academic and community hospital settings, we have been most successful when the driver or initiator of the collaboration was the pancreatic surgeon who then enlisted his pathologist colleagues. For patients to be enrolled in the specimen donation study, they had to be approached preoperatively by their treating physician. Pathologists are a critical collaborator in that they must agree to assist in the processing of tissue specimens, however, they rarely are in a position to identify and enroll study subjects before their operations. In some cases where a pathologist is not a collaborator, pathology departments are reluctant...
to release archival specimens. These issues need to be addressed proactively and in a collegial manner. In the case of our core leadership, the director is a surgeon and the codirector is a pathologist.

**Site-Specific Limitations**

Not all the sites are able to participate fully in the collection of samples. One site was willing to participate, but its pathologists were concerned that submitting a portion of a regional lymph node to the repository would limit the accuracy of their tumor staging. Although the core leadership did not agree with this concern, we understood it and modified the collection protocol at their hospital accordingly. In this way, the hospital could participate, and we have been able to collect useful samples. Other sites are unable, because of their referral pattern, to collect blood samples from patients at 6-monthly intervals for 2 years as per our protocol. The follow-up clinical outcome data are important, and the site did agree to monitor patients by phone contact with its treating oncologists. We found that if necessary, flexibility on the part of the core in designing site-specific protocol variations has allowed increased participation and accrual of additional patient samples to the biospecimen core.

**SUPPORT FOR SCIENTIFIC INVESTIGATIONS BY THE INVESTIGATORS AND THE CORE**

The central hypothesis of the research in our PPG is that pancreatic cancers harbor genetic and epigenetic abnormalities that allow cell growth, survival, and drug resistance. These abnormalities that we refer to as contexts of vulnerability can be exploited for therapeutic purposes. There are 3 main projects including (a) treatment of hypoxia resistance in pancreatic cancer focusing on thioredoxin and HIF-1α inhibitors, (b) a method to eliminate pancreatic cells with specific patterns of mutations or deletions focusing on synthetic lethal combinations with DPC4/SMAD4 or p16 deletions, and (c) identification of novel sensitizing targets for improved gemcitabine therapy using a functional genomic high-throughput siRNA screen approach. Use of the samples from the core for these investigations and other projects is depicted in Table 1. Other investigators have petitioned the core for access to samples for other worthy studies. The mechanism for this process is detailed later. In all, more than 1000 samples of various types have been shared with investigators.

Although the investigators leading the core acknowledge that their central role is to provide a service, there are many opportunities to ask scientifically important questions and conduct additional relevant studies where funding is available. In the case of this core, 1 question that has been investigated relates to the rapidity with which RNA may degrade in a sample and whether RNA profiles could change over time because RNA species do not degrade equally. A set of murine xenograft experiments was designed to test this question. Another initiative by the core found that tumor samples stored in RNAlater were suitable for proteomic analysis, thereby saving the precious frozen samples for other uses. In another project, we are currently working with an investigator who is conducting a set of experiments comparing the proteomic analysis of serum and plasma samples from the same patients. These fundamental questions address the quality of the samples in our core and their suitability for use by investigators.

**OPERATIONAL AND REGULATORY ISSUES**

**Institutional Review Board**

Tissues are collected under an informed consent procedure that follows NCI guidelines and is approved by each IRB where required. Our governing protocol has been approved by the Western IRB (WIRB). This national IRB is recognized widely and in some cases accepted in lieu of a separate local IRB approval. In other cases, the local-site IRB has weighed in but with generally minor concerns such as to seek a change in the wording of the consent form to conform to local standards. In all cases, WIRB approval facilitated local implementation of the tissue procurement protocol. Current procedures require that tumor specimens be collected from unused portions of surgically resected specimens. In recognition that the full value of these tissues specimens will only be achieved with proper annotation of clinical data, each specimen has been linked to patient demographics, including environmental risk exposure, medical and

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**TABLE 1. Use of Samples From the Tissue Repository**

<table>
<thead>
<tr>
<th>Project/Investigator</th>
<th>Frozen Tumor</th>
<th>Frozen Normal</th>
<th>Frozen Benign</th>
<th>Paraffin Block Tumor</th>
<th>Paraffin Block Normal</th>
<th>Paraffin Block Benign</th>
<th>H&amp;E Slides Tumor</th>
<th>H&amp;E Slides Normal</th>
<th>H&amp;E Slides Benign</th>
<th>RNA Later Tumor</th>
<th>RNA Later Normal</th>
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</table>

*Projects 1, 2, and 3 are the projects of the program project grant. The repository has also provided samples to other collaborators after requests were reviewed and approved.*

H&E, hematoxylin and eosin.
family history, treatment, and outcome. All clinical information and specimen identity are anonymized and entered into a comprehensive database, where it is available to investigators. Privacy and confidentiality are protected by a procedure where each site obtains informed consent, enrolls patients into the study, and maintains the key to patient identity and samples. An enrollment form is provided to the biospecimen core by facsimile, and samples are identified thereafter by a code number and a bar code.

Access to Tissue Samples

Tissues in our repository are a precious resource, which we shepherd closely. To manage this resource, a utilization committee reviews requests for tissue samples. For distribution of specimens, project investigators or participants from consortium institutions fill out a Specimen Request Form that is then submitted to the Pancreatic Bioresource Utilization Committee. The core director chairs this committee, and its members include the PI of the program project grant and the leaders of one of the projects, the core codirector, the TGEN vice president for research administration, and the head of the bioinformatics core. The committee decides on allocation priorities with the understanding that specimens are a valuable resource, and that there may be competing requests for specimens. Decisions are based on the scientific merit, progress, and preliminary data indicating the importance of each request. Priority is given to investigators in the program project and to projects sponsored by members who participate in tissue collection. The committee meets semiannually to oversee and ensure that all NCI confidentiality requirements and IRB progress reports and IRB approvals are maintained and on an ad hoc basis to review requests for tissue.

The tissue core also works to match the type of tissue requested to the tissues available. The core recognizes that the most precious samples are those where there exist fully annotated matched sets of tumor and normal tissue from the same patient. Because the samples are a precious resource, the committee shepherds the samples closely. For pilot studies, nonannotated tissues are first provided. If the pilot experiments are successful and suggest that clinical annotation would add important insights toward the development of new biomarkers or treatments, then the clinically annotated samples are released to the investigators. Similarly, if paraffin-embedded tissues are requested, first, a screening survey can be done on constructed tissue microarrays. If additional study is warranted, the core can then provide entire blocks with clinical annotation.

Ultimately, although it is desirable to maintain a well-stocked repository, our purpose and goal is to support investigators so as to make progress against pancreatic cancer. Our philosophy is that samples are collected to be used for study, albeit wisely. The utilization committee evaluates the scientific merit of each request. A decision is made not only as to whether to provide the requesting investigator with samples but how much of each sample to provide. The repository has accomplished our goals in sharing more than 1000 samples with not only the 3 central projects in the P-01 but with many other investigators as depicted in Table 1. As a result, 135 enrolled patients with pancreatic adenocarcinoma, 26 frozen tumor samples, and 11 RNAlater-preserved tumor samples have been exhausted. Ongoing accrual of samples replaces exhausted samples and renewal of the P-01 funding, if our renewal application is successful, will assure continued collection and availability for future studies. In all, the repository has supported the work of a productive Program Project that has resulted in 43 articles published and 36 abstracts presented at national meetings. For the competitive renewal application of the P-01, it will be important to demonstrate how successful the interactions of the repository investigators are with the program project investigators. A track record of publications is a reliable indicator of such interactions.

Responding to the Needs of Investigators

As the research evolves, it is important for the core to be continually responsive to the needs of investigators. Changes in the samples required mean that the core may need to rewrite collection protocols. For example, one of our investigators approached our core with a request for fresh tissue to be used to generate murine xenografts. We elected to change our tissue collection protocol at the 2 local sites in Phoenix so that a portion of the tumor harvested would now be placed in RPMI medium and transported immediately to the laboratory for establishment of primary cultures. We reasoned that time constraints caused by shipping alone would not justify such a modification in the overall protocol for sites at some distance from Phoenix. An additional example of necessary interactivity between the biospecimen core and a research project involved an investigator who had been successful with a flow cytometry-based sorting of tumor nuclei for his experiments. He had recently seen a problem with his results in the last batch of samples analyzed. The core director and codirector met with this investigator to review on a step-by-step basis each of the processes in our protocol to assure the quality of the samples provided to him.

A potential addition to our program is the result of a new request for matched samples from primary tumors and multiple foci of metastases. This group of investigators in the program project has seen clonal evolution of cancers as they metastasize. Additional samples are needed to explore this hypothesis, but getting these samples is not practical from patients undergoing pancreaticoduodenectomy because if metastases are known, then the primary will not be resected. We have just added a rapid autopsy tissue donation program enrolling patients with known metastatic pancreatic cancer. For this project, we are fortunate to be able to enter a service contract with another group of researchers who have an established rapid autopsy program for patients with diseases of the central nervous system. In doing so, we are not required to begin de novo with infrastructure and assume the associated fixed costs, but rather are able to take advantage of excess capacity within this group’s program.

Ownership and Intellectual Property

In the report of a symposia held by the National Institutes of Health in October 2007 concerning custodianship and ownership issues in biospecimen research, concerns were raised that access to biospecimens has been impeded by a recent trend of

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**TABLE 2. Summary of Lessons Learned**

- The science is paramount, and the core needs to be supportive
- Collaboration is essential
- Recognize the efforts of those who work to contribute samples
- Hard work, flexibility, and diligent attentiveness to operations is key to ongoing success
- Willingness to recruit new sites to replace sites that do not contribute samples
- Both academic and community medical centers can make productive Program Project that has resulted in 43 articles published and 36 abstracts presented at national meetings.
researchers stockpiling rather than sharing tissue samples, as well as by more aggressive patenting and licensing strategies for discoveries made from biospecimens. We have held that intellectual property rights are owned by the investigators whose discoveries come from the use of the biospecimens.

We are concerned but less so about the contributors of specimens seeking financial reward for discoveries that may have resulted from research involving their donated tissues, as was the subject of a well-publicized court case. This is a legal question. Of course, we do concur with the National Institutes of Health panel that patients enrolled have a right to know whether there is the potential financial reward for their participation in any protocol. Furthermore, they should be made aware of the disclosure and patent policies of the institutions using the tissues. Accordingly, the prospective tissue donor can choose to only donate samples to investigators who freely disclose their findings to the scientific community so that discoveries can be used by other investigators. Once it has been donated, Federal Court ruling has held that the donated tissue is a gift. The US Court of Appeals has held that patients who donate their tissues do retain certain rights relative to their gifted tissues, namely, the right to discontinue participation in research. Specifically, they may (a) not answer further questions, (b) not donate further samples, and (c) disallow the use of the tissue in further research. It would seem that the key to preventing legal issues of this sort is adequate informed consent and respect for the rights of the patients. The issues may include personal, religious, and cultural concerns as well.

**Legacy Concerns in the Case of a Loss of Funding**

“Biospecimen resources should have legacy or contingency plans that address the transition following the loss of management or funding. These plans should involve an assessment of whether the stored biospecimens still have value for research. If a resource’s stored biospecimens do have research value, the resource should attempt to become financially self-sustaining or transfer its collection to similarly accredited research facilities. Biospecimen resources should use the same decision-making criteria for allowing transfer of biospecimens to other biospecimen resources as they do when allowing transfer of biospecimens to investigators.”—NCI Web site

**Quality Control of Sample Collection**

A process to assure that samples from different sites all meet a sufficient level of quality is imperative. Our sample tracking data include time from removal to freezing. Collection kits are provided to each site with detailed standard operating procedures. These kits include cryovials, colored cassettes, blood collection tubes, reagents, and bar code labels. Shipping containers and pre-addressed commercial shipping labels are also provided. At the initiation of each site participation, the P-01 tissue repository staff visited the site to meet with the surgeons, pathologists, study coordinators, and technicians to review the protocol procedures, answer questions, and conduct a mock collection. In collection procedures, uniformity is important. Flexibility where quality is not impaired is necessary. For example, the pathology department at 1 site would not paraffin embed the research samples. We worked out a solution where the research samples to be embedded were shipped to the repository in a sealed vial with formalin and the paraffin embedding is done by the repository pathology staff. The samples handled in this manner have proved acceptable for immunohistochemistry and tissue microarray construction. Before samples are accrued and shipped, each site sends an enrollment form by facsimile. In this way, the repository is alerted to expect a set of samples. When the samples arrive at the repository, they are logged in by bar code and an inventory was done to assess the amount and nature of the samples. The repository staff also assures that the clinical data submission is complete, and if not, the site is contacted. The repository director is a pathologist who independently reviews the hematoxylin and eosin–stained permanent sections from every patient enrolled to confirm the clinical diagnosis provided by the site’s pathologist. Before sharing samples from each set, the quality control evaluation by our pathologist estimates the proportion of tumor in each sample for the investigator.

**Clinical Annotation, Tracking of Sample Flow, and Process Review**

The repository staff team meets each week as part of a regularly scheduled laboratory meeting. The staff coordinates annotation of each sample with the P-01 bioinformatics core and uses this same database to track the requests for and flow of specimens. When our biospecimen core was first constructed, we worked with the P-01 bioinformatics core and other investigators at our home institution, TGEN, and the commercial vendor we use for storage to develop bar code–tracking mechanisms for samples and a database that included the fields for the clinically relevant information suggested by the surgeons, medical oncologists, and researchers involved in the program project grant application. There have been challenges, as detailed herein, but the repository staff has worked diligently to analyze problem areas and present workable solutions. When necessary, program project leadership is consulted in the interests of the project.

The core experienced a turnover in repository personnel during its third year of operation. The process of orienting new staff illustrated several weaknesses in internal processes and policies instituted during the start-up phase of the PPG and provided for an opportunity to review and evaluate all existing guidelines and standard operating procedures. A few procedures required simple revisions, but infrastructure changes and several protocol amendments underscored the need for more clearly stated procedures. We concluded that a diligent periodic review of written procedures and guidelines is necessary. The primary areas of concern discovered involved internal sample tracking mechanisms and the accessibility of stored annotated clinical data. Tracking sheets and data entry instructions, which were satisfactory when a relatively few number of samples were being submitted become inadequate. The annotated clinical information for each subject is submitted on paper forms completed at each site and faxed or included with sample shipments. This clinical information relative to each enrolled patient is manually entered into a database. As the number of samples has increased, this effort has required more time and taxed available resources. More requests from investigators for samples, which are stored off-site, put a strain on the capacity of the pathology staff performing quality control analysis of samples before they are released.

Partially as a result of difficulty in generating useful results from the existing database and partially caused by the increased amount of research data available to link to each sample, in year 4 of the funding period, the decision was made to migrate the repository data to a new database framework. It is intended that the new database will provide for integrated sample tracking and storage, along with annotation of samples with clinical and research data ensuring that the repository meets NCI’s Best Practices recommendations. During the course of the funding period, the NCI has rolled out the CaTissue and CaBig initiatives. We have worked toward full integration of our information into the framework provided by the NCI for tissue tracking, storage, and annotation with clinical and research data. It is our

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belief that compliance with all NCI best practices will be an important criterion in the future evaluation of all proposals for tumor repositories. A consequence of the myriad of ad hoc individual institutional tissue banks is that the clinical annotation of samples within each bank varies. Most banks contain the basic information related to demographics, risk factors, and stage of disease. Fewer samples are annotated with longitudinal outcome data and response to treatment. Going forward, we envision tumor bank databases that fully annotate the samples with not only the relevant clinical information, but with the results of molecular profiling of tumors including genomic analysis and expression array data. It is hoped that integration of research data will provide for maximal knowledge from each sample. Furthermore, it is predicted that such integrated information will be increasingly valuable to investigators working to develop novel targeted treatments.

**BUDGETARY ISSUES**

The cost of obtaining and storing biosamples is not trivial. For the participating sites, there are fixed costs and incremental variable costs. The sponsor, the NCI in our case, has an interest in paying for performance, or more accurately not paying for sites that do not accrue patients. We moved to a model that varied with the particular needs of each site but held to a general concept. Our core paid a relatively small annual amount intended to defray fixed costs and cover part of the salaries of the research support personnel. The core provided the collection kits, providing prepaid shipping labels and provided for reimbursement of costs based on completed sample set submission. In this way, funding provided to each institution was proportionate to its actual work and costs.

The program project leadership has decided to contract for service when local expertise exists, rather than recreate duplicate services. Our core contracts for tissue storage with a local commercial firm. They provide high-quality commercial tumor banking services with bar code tracking of specimens and many safeguards of the samples. Contracting for services eliminates concerns such as maintaining the inventory tracking system and freezers but has required that we audit the performance of the firm and the billing for accuracy.

**RECOMMENDATIONS IN SUMMARY**

The acquisition of human tissue samples and their subsequent cellular and molecular analysis are key to many of the translational studies of cancer. Clinically annotated human specimens have historically been one of the most valuable and unique resources available for translational research. The need for multiple participating institutions is emphasized by the limited number of specimens typically available for research purposes within any single institution. To support the work of a pancreatic cancer program project grant, we brought together a consortium of institutions to collaborate with us by providing for this tissue acquisition. It has been and remains a challenging yet rewarding endeavor. This article described the challenges and possible solutions learned (Table 2). It is important to emphasize the importance that a cohesive and flexible team plays in the success of this type of tissue banking effort. Continuing communication is essential in an environment of constant change. This allowed the core to successfully address logistic and operational challenges faced during this funding period. Most importantly, we support the scientific efforts of our investigators. Our patients deserve that we in the community work together to find new diagnostics and treatments for pancreatic cancer.

**REFERENCES**