Establishing and Maintaining an Academic Biorepository

Sonia Ashley, MAS
UC San Diego Moores Cancer Center

Ira Goodman, CRA
UC San Diego Moores Cancer Center

Abstract: *The significance of biorepositories has been known for many years but the latest advances in clinical and translational research and increased collaborations among investigators have made biorepositories even more prominent. Biorepositories collect and store human tissue and serum samples used in both the research and treatment of disease. In cancer, researchers are now able to take a tissue sample of a human tumor and implant it into a mouse to duplicate the human disease progression and response to treatment. Thus, new drugs are tested in animal model systems with human tumors before they reach the stage of human clinical trials. The deciphering of the human genome has also led to greater use of and dependence on biorepositories. Tumor tissue can now be analyzed to determine the genetic alterations that appear consistently in tumors. These aberrant and tumor related genes then become biomarkers for drugs; thus, the genetic profile of a tumor becomes a target for drug treatment unique to that patient. The implementation and administration of a biorepository core facility is very challenging and requires organized infrastructure that involves strong institutional support and commitment. More than ever, institutions face ethical and regulatory issues with regard to tissue procurement and research, confidentiality, consent procedures and the handling of research results. In addition, securing steady financial support could pose one of the biggest challenges during these economic times when funding is limited. Overcoming these challenges is essential to ensure the long-term sustainability of the core facility. The research administrator can provide valuable insights into the many aspects of running an effective biorepository by focusing on both the financial and the administrative aspects of a biorepository core facility, including establishment of a recharge account so that services can be billed, user fee rates that can sustain business fluctuations, financial monitoring so that the business does not go into deficit, business plans and performance review to ensure that the business stays viable.*

Introduction

Biorepositories are essential to research in order to advance the treatment of many diseases. Their products can assist researchers in the areas of prevention and control and in providing personalized medicine to patients. Establishing the infrastructure for a biorepository requires significant efforts in strategic planning to effectively identify and request consent from participants as well as prepare for the proper collection, processing and storage of specimens while maintaining participant privacy rights (Ambrosone, Nesline, & Davis, 2006).

There are many aspects to a biorepository system. The operational aspects include the collection, processing, storage, retrieval and distribution of biospecimens; collection and management of clinical data; quality assurance and control; and biosafety and bioinformatics system. The legal and ethical aspects include custodianship; informed consent from human subjects; privacy protections for individuals who donate biospecimens; researcher's access to biospecimens and intellectual property and resource sharing (National Cancer Institute, 2011). The business aspects involve the development of a business model that adequately incorporates building a recharge facility with proper rate user fee structure, procedures and tools to appropriately monitor funding, business plans and performance review to ensure effective management of the core facility. This article will highlight the role of biorepositories in cancer research and the practical steps taken at the Moores Cancer Center to administer and enhance the procurement, storage and distribution of human tissue samples as well as the business aspects including the rate setting, billing, financial monitoring, annual business plans and performance reviews.

Use of the Biorepository

It is now well known that biorepositories are a key resource for cancer research. It is therefore vital to have biorepositories in the Cancer Center as new therapies are developed and made available to patients to save and prolong lives. Their products can assist researchers in the areas of prevention and control and in providing personalized medicine to patients.

Scientists have developed many ways to identify genes and their functions and have learned a great deal about the role they play in the origin and progression of diseases. With the help of biorepositories, scientists are able to analyze vast amounts of clinical information about a patient's health and diseases. Biorepositories can assist researchers to identify and validate ways to deliver drugs, identify how diseases progress and vary, and determine how different groups of patients respond to drugs. There are examples of how biospecimens can accelerate cancer research. Through the use of well-characterized and well-preserved tissue samples, a drug called trastuzumab (Herceptin®) was developed for the treatment of a genetically linked form of breast cancer. Another drug called Gleevec® was originally developed for the treatment of Chronic Lymphocytic Leukemia, a form of blood cancer, but researchers found through the analysis of biospecimens collected from different tumor types that it also can be used for treatment of gastrointestinal stromal tumors and is now FDA approved for that purpose (National Cancer Institute, 2015).

As the use of biorepositories increased, it created more collaboration among institutions and the establishment of large national databases. The existence of these large dispersed databases

prompted the need for centralization at both the local institutional as well as the national level (Ginsburg, Burke, & Febbo, 2008). This led to the creation of the "next generation" biorepositories (Fullerton, Anderson, Guzauskas, Freeman, & Fryer-Edwards, 2010). The next generation biorepository will provide great scientific benefits to the medical community but there are many challenges associated with its implementation. The new initiatives and research governance can make the establishment and maintenance of biorepositories very difficult. Institutions have to deal with many ethical and regulatory issues in the areas of privacy, institutional review, informed consent and data stewardship. In the area of privacy, anonymization (personal information codification but with the secured retention of information linking the data to the subject) is no longer sufficient to protect the privacy of the participants. As such, institutions are required to provide extreme measures to control and retain coded identifiers with innovative approaches to data security and oversight of the research. Consistent approaches to institutional review across institutions are essential with regard to the cooperative understanding of the use and management of data. It is critical that alternative methods of obtaining consent for biorepository participation allow an on-going involvement of research subjects by developing ways of re-contacting the participants through the use of various communication tools. Stewardship of data should be carefully observed and institutions are mandated to adopt the defined research governance mechanisms. Applying standardized specimen and data collection procedures mitigates the process for obtaining and properly preserving high quality specimens (Hullseik, George, & Brown, 2011). In addition, a centralized Institutional Review Board approval is necessary to ensure consistency and expeditious access to the samples. Institutions have a moral obligation to protect trial participants and to establish a system in which samples that are donated are carefully maintained, monitored and used in the most efficient way.

Major Challenges Facing Biorepositories

Setting up a quality management program is one of the major challenges in creating and maintaining a successful biorepository. It has been shown that the most extensive impediment to the effective use of biorepositories is the lack of standardization in maintaining high-quality biospecimens. Institutions are faced with ethical, legal and policy issues on many different aspects involving quality assurance and control, informed consent and privacy protection, access and ownership of specimens. Providing administration and management structure that can address these major issues is difficult and challenging. The National Cancer Institute (NCI) established the Biorepository Coordinating Committee (BCC) and the Office of Biorepositories and Biospecimen Research (OBBR) which provided standardized procedures addressing the operational, ethical and legal aspects of establishing and maintaining biorepositories. They also provided best practices used by biorepositories around the country.

Some of the operational and research challenges that a biorepository faces are personnel, equipment and shipping of samples. The complex operations of the biorepository require that staff have specialized skills and experience. As such, personnel turnover is a major concern. The cost of losing trained employees is very high in terms of dollars and productivity. The biospecimens are stored under controlled temperature and any equipment breakdown such as a power failure will jeopardize the integrity of the samples. This is also true with the bioinformatics systems that

support the databases which maintain the sample records. There are cases when biospecimens are shipped and there are regulatory considerations when shipping biospecimens. A biorepository should follow domestic and international transport regulations imposed by the International Air Transport Association. All biorepository personnel are certified to receive, handle, package and distribute human infectious substances and biohazardous materials. Occupational Safety and Health Administration (OSHA) regulations on toxic and hazardous substances are consulted to determine whether a substance requires a hazardous label. Shipping breakdowns such as mislabeling of samples or improper packaging can cost large amounts of money and the loss of valuable research resources to the institution.

Biorepositories can also face difficulty in acquiring samples from participants. One of the common reasons why a person would want to participate in a study is the lack of generally accepted therapy or the partial effectiveness of the experimental therapy available to patients. Participating in a clinical study might offer the patient a new alternative to standard treatment before it will be available to the public. For example, Chronic Lymphoma Leukemia (CLL) is a type of cancer and although many patients suffer from this disease, patient participation in the study is limited. For some people with CLL the disease grows slowly and they don't seek treatment until the disease is in its advanced stages. This contributes to the limited number of patients willing to participate in the study. Many patients do not know they have CLL. The progress of the research is dependent upon the number of samples collected and the frequency of donation. In addition, the collection of samples at different times is imperative to examine longitudinal changes at the various stages of the disease. Limited resources such as nurses/staffing and scheduling conflicts present difficulties and missed opportunities for patients to participate. Coordination of patient visits can be a challenge as some patients do not live locally and their availability is limited.

The last but not least of the major challenges is securing continued financial support to sustain the long term operations of the biorepository. Managing a biorepository requires infrastructure that usually involves different sources of support. It requires financial flexibility to meet emerging research needs. Institutions need to be creative in finding funding sources to continuously support the infrastructure of its biorepository not just for a limited time but also for the long-term commitment. The funds can come from grants, institutional support, philanthropic sources, and fees for service known as recharges or a combination of the sources. A recharge mechanism that allows recovery of costs becomes fundamental to sustain an effective biorepository. Other strategies such as seeking funding from grateful patients or from philanthropic resources can be a major source of funding. Many donors are willing to donate funds to research such as cancer due to personal experiences and many believe it is a great cause to support.

A financial analysis needs to be done to insure that at least initially the core facility will be adequately funded to conduct its business. Questions to ask are how long the apparent funding sources will be available, will the funding be sufficient to maintain a reasonable level and quality of service, what fees will be needed and how will they be charged, and are there hidden costs such as equipment maintenance, specialized instrumentation, webpage development.

Evaluation of the Success of the Biorepository

There are many ways to evaluate the success of individual biorepositories. It can be done by examining the number of users over time, number of publications citing the biorepository, dollar volume of business, users' satisfaction surveys, and the overall results of operations. A biorepository can be considered successful if it can provide high-quality biospecimens while meeting the strict guidelines of the federal and institutional regulations involving the operational, legal and ethical aspects of running a biorepository. Biorepositories offer opportunities to researchers to expand the treatment of cancers through personalized medicine. It is changing how they think about cancer and how care should be delivered to the patients. Researchers are focusing more on not just getting the diagnosis right but also taking it further to characterize the tumor more specifically so treatments can be custom tailored to the patients. The true success of biorepositories can be measured by the advances made in scientific research as evidenced by reports citing biospecimens that led to greater treatment options available to patients.

MCC and the Regulatory Process

MCC is an Organized Research Unit (ORU) of the University of California and a major clinical department of UCSD Health Sciences, where interdisciplinary research is conducted to translate scientific discoveries from the laboratory to the cancer patient. The mission of the MCC is to translate promising scientific discoveries into new and better options for the prevention, diagnosis and treatment of cancer and for the amelioration of pain. Its mission is pursued by supporting principal investigators to conduct clinical trials and other primary research to find the most advanced treatments for cancer. The MCC is structured into six formal research programs focusing on different areas of cancers. It provides comprehensive care to cancer patients in a way where multi-disciplinary teams work together to decide the best course of treatment. The MCC Biorepository resource plays a vital role in supporting this mission. It is used by many Cancer Center members who collaborate on various types of cancer research. The MCC Biorepository relies on Treating Teams which consist of physicians, case managers, and medical assistants who recruit patients that are willing to donate samples. The patient identification can start as early as when a cancer patient schedules an appointment. A patient who showed interest in donating samples can be sent a consent form electronically or by mail. The patient can then fill out the form at home and would be ready to participate at the time of appointment. In most cases, personal contact and communication with the Treating Team can prompt study participation of the patient.

The consent process varies from patient to patient. It could take between 15 to 40 minutes to complete. The consent form is lengthy; it consists of five pages with the addition of five more pages of HIPAA form and the Experimental Subject Bill of Rights.

There are different types of samples collected (blood in the form of serum, plasma or buffy coat; urine, saliva and tumor tissue) and depending on the type of sample, the collection, preparation and distribution of samples varies. The collection for blood, urine and saliva takes place in OSHA approved space. The tumor collection is performed during surgery and done in operating rooms. Once pathologists have processed the tissue collected samples are stored in -180° C

liquid nitrogen tanks. The samples are made available to MCC principal investigators or outside research collaborators.

At MCC, the Clinical Trials Office oversees hundreds of trials across all types of cancers and all phases of drug development. Patients who agree to participate in any clinical trial are educated about the study and go through the informed consent process. Once tissue donors are identified, samples are collected from consented patients and the clinical information on the subject is de-classified and coded to protect privacy. The informed consent document addresses the following:

- The patient's right to refuse biospecimen donation. Their refusal to donate should not in any way influence their treatment or eligibility to participate in the clinical trials.
- Explanation of why particular biospecimens are being sought and why human research participants are being asked to participate.
- The source of the biospecimens that will be collected for research.
- The custodian of the biospecimens and the role of the custodian.
- Documentation to support how the biospecimens will be used and whether they will be used in research other than the initial intended purpose.
- Statements about whether biospecimens will continue to be stored and shared as long as they are potentially useful for research.
- Assurance that biospecimens are respectfully destroyed when no longer useful for research, or transferred to another established resource in accordance with the terms of the informed consent.

The consent form represents agreement to donate blood and urine samples, access to medical record and potential to participate in future cancer studies. The informed consent form specifies that the samples are to be used for the conduct of research to better understand cancer diseases. Early diagnosis is momentous in the treatment of cancer. Patients are given the option to withdraw from participation at any time.

MCC has a Protocol Review and Monitoring Committee (PRMC) which provides oversight in monitoring the data integrity and safety of clinical trials conducted at the Cancer Center. The Committee reviews the data and safety monitoring plan of clinical trials that addresses the participant's safety, data validity, risks and complexity of the clinical trial and proposed compliance with confidential and adverse event reporting requirements. In addition to the PRMC, the Clinical Trials Office, the Data and Safety Monitoring Board and the Cancer Center Quality Assurance Manager provide complementary review, monitoring and auditing functions during the various stages of the clinical trial. This is done to ensure that maximum protection and ethical treatment of human participants are in place.

Another regulatory component is the Institutional Review Board which is under the UCSD Human Research Protection Program (HRPP). The Program oversees ethical and regulatory policies and procedures involving research on human subjects. The policies and procedures were written in accordance with federal policy on the Protection of Human Subjects (DHHS Policy 45 CFR Part 46, FDA Policy 21 CFR Parts 50 and 56). The main function of the HRPP is to

review research protocols and determine to approve or disapprove, require modifications, propose amendments based on assessment of the risks and potential benefits of the research and whether or not the rights and welfare of human subjects are adequately protected. The HRPP also has the authority to suspend or terminate a study already activated. The IRB process adds another layer of protection to cancer studies to ensure that investigators securing the use of human samples have full institutional approval.

Creation of the MCC Biorepository and Tissue Technology Resource

One of the most important steps in creating a biorepository is determining funding sources to support the facility. There are also many other challenges related to managing a biorepository system that services all stages of research. There are a vast number of samples that have been collected from cancer prevention studies and many early detection trials and observational studies. As the grants supporting these trials end, funding for maintaining the biorepositories is not available (Goodman, Thornquist, Edelstein, & Omenn, 2006). Funding for a biorepository can come from different sources. The National Cancer Act officially established the Cancer Center Programs in 1971. The Act implemented a standard funding mechanism known as the P30 Cancer Center Support Grant or CCSG. The CCSG is awarded to institutions for successfully meeting a spectrum of rigorous standards associated with scientific and organizational merit; the highest and most difficult designation to achieve is comprehensive cancer center. The Moores Cancer Center is one of 41 designated comprehensive cancer centers in the country. As an NCI-designated Comprehensive Cancer Center, it conducts research activities in basic laboratory, clinical, prevention, control and population based-research into a broad-spectrum transdisciplinary cancer research enterprise. It receives funding from NCI to support its research infrastructure including senior and program leaders, staff investigators, planning and evaluation, administration, shared resources and clinical trials.

The biorepository is one of the shared resources at MCC. It was established as a developing shared resource within the NCI funded Cancer Center Support Grant (CCSG) in 2006. For the 2013 core grant renewal, histology services were combined with tissue collection and storage to create the Biorepository and Tissue Technology Resource (BTTR). The BTTR provides different types of samples including plasma, serum, RNA stabilized buffy coat, urine, viably frozen tumor samples and paraffin embedded tumor slides with associated clinical information to investigators with Institutional Review Board (IRB) and Cancer Center Banking Committee approved protocols. Samples are collected over time from consenting subjects and clinical information is de-identified to protect privacy. The blood and urine samples are collected and frozen and coded with a unique study number for data storing. The data consist of time of collection, diagnosis of the tumor stage and site, clinical outcome and other demographical information. Patient information is de-identified as much as possible and the data are safeguarded with multiple levels and layers of security. Encryption is required for all health related personal data. Access to clinical annotation is determined based on need as outlined in each investigator's protocol.

The priority of the BTTR is pure banking so it tries to maximize collection of samples from nine clinics at MCC involving Gastrointestinal, Genitourinary, Lung, Head and Neck, Melanoma,

Gynecology and clinical trials. Pure banking is between 85-90% versus 10-15% for investigator initiated procurement. The Shared Resource Leader evaluates the biospecimen requirements for PRMC, the Physician Assistant develops the protocol, and then it gets submitted to IRB. The BTTR has a general biobanking IRB protocol to cover most applications with delinked data. Faculty members need an IRB protocol only when they need delink data.

The MCC BTTR is partially funded by the NCI Cancer Center Support Grant, institutional support and also by a recharge mechanism. The University of California, San Diego (UCSD) allows a research unit such as the Cancer Center to develop a recharge mechanism to recover costs incurred by charging a fee to investigators seeking tissue but it must follow strict policies and procedures. There must be a need for the good or services to be provided by the activity. The benefits, including relative prices and quality of the proposed activity must be weighed against the benefits of obtaining similar goods or services from commercial sources or other University sources. Goods or services should not be sold to the general public unless the goods or services are unique or sales will not compete with commercial sources. Both the recharge mechanism and institutional support are essential in sustaining the operations of the BTTR. Without them, the Shared Resource cannot exist because the CCSG covers only a portion of the costs of operation. There are cases that some Shared Resources can function with only the CCSG and the recharge but the BTTR requires institutional support at this time in its development. It is very expensive to operate and the revenue from the recharge is limited. The early volume of business is not enough to support the operations and increasing the prices of the services is not a viable solution.

Collaborative Efforts of the BTTR

Collaboration plays an important role in research. It helps researchers from different disciplines share knowledge and resources. The federal government has created grants specifically to incentivize researchers. There are many benefits to collaborations and many discoveries have risen from the collaborative work of researchers. Collaboration can also help achieve greater economies of scale, improve productivity and increase competitive advantage.

In 2012 the Moores Cancer Center, Sanford-Burnham Medical Research Institute and Salk Institute joined together to form the NCI Cancer Center Council (C3) in the San Diego area to increase collaboration, leverage their collective talents and resources as well as garner more use of the Shared Resources, particularly the BTTR. C3 focuses on enhancing inter-institutional sharing of a unique core facility at each center. The MCC Biorepository and Tissue Technology Core is being used by C3 members and facilitates collaboration of research in cancer.

Role of the Finance Administrator in Establishing and Managing the Biorepository

Finance Administrators play a key role in establishing and managing the biorepository. The Finance Administrators understand the business operations and processes involving accounting, finance, marketing, economics, statistics and human resources. They can affect the effectiveness of the recharge facility because they specialize in a specific area in which they have knowledge and experience. The Finance Administrators are responsible for establishing a viable rate structure, managing the billing and payment, financial tracking, utilization reports and annual

business plans. In addition, their role is to effectively communicate business status and activities to Shared Resource leaders and those that are tasked with decision making. Because recharges need to break even, finance administrators can assist and influence the Shared Resource leaders in making important decisions that can maximize the effectiveness of their operations and integrate practices that can sustain the business.

Establishing the Rate Structure

Core facilities may or may not have recharges. If the core facility is a component of a multi-project program grant and services only the investigators of the grant, then there is no need for a recharge. However, if the facility is larger than the grant or institutionally based, it will need a recharge both to control utilization as well as to meet budgetary needs. Establishing a recharge involves performing market analysis. The benefits including relative prices and quality must be compared to the benefits of obtaining the services or goods from commercial sources or other university sources. There must be significant current and continuing demand and the services to be provided must be unique and specialized. It is critical to insure that all fixed and variable costs are covered and that there are no hidden or uncovered costs. Costs assigned to the activity must be essential to the purpose for which the activity was established. Personnel costs should be carefully analyzed to ensure that appropriate percent efforts are included in the rate calculation. For the BTTR rate calculation, we made sure that personnel performing the duties such as physicians and lab technicians involved in consenting and sample collection are factored in the fee structure. The fund balance will be operated on a break even basis although some activities are allowed to accumulate a surplus or deficit within the amount as determined by the institution. At UCSD the recharge facility is allowed to carry a surplus or deficit equivalent to two-month expenses. When calculating the opening rate, consideration should be given to adjusting the rate later to reflect the actual current volume of business.

Determining the Rates

There are a number of factors to consider in calculating the initial fee schedule. These include the level of anticipated business, any funding gap, availability of a subsidy from a grant or the institution, and source of users, including internal and external, which may lead to a tiered rate schedule. Tiered rates are implemented to reflect the type of users of the facility: Cancer Center member, non-Cancer Center member or non-UCSD member. Cancer Center participating members are eligible to use the Cancer Center Shared Resources at subsidized rates relative to other users due to the funding provided by the Cancer Center Support Grant. The criteria for participating membership are below:

- Have a salaried or non-salaried faculty appointment at UCSD, and
- Hold an NIH RO1 cancer-related grant or equivalent peer-reviewed grant, or
- Have recent publications that are relevant to cancer, or
- Have a Cancer Center leadership role to organize an essential activity or service, as appointed by the Center Director, or

- Have an extensive collaboration with other peer-reviewed Cancer Center members, or
- Be leading investigator-initiated Cancer Center clinical trials or accruing considerable numbers of patients (at least 5 per year) to such trials, or
- Systematically assisting in the procurement of clinical specimens for cancer-related research

Once a rate is established it should be used for at least one year to gauge if it meets the budget needs. Users resist constant changes in rates since they need to be budgeted in grants and other funding mechanisms. However, the initial rate is seldom the long-term rate because the first rate is projected, not actual business. An analysis of the rate should be conducted after one year to see if the rate is sustainable or needs to be modified based on the facility's output.

The MCC Biorepository receives a minimal amount of grant funding and its operations are mainly funded through a recharge mechanism that involves charging fees for providing services to both university and non-university users. The process of establishing a recharge system at UCSD requires different layers of institutional approval. It starts with the development of a rate structure. UCSD employs strict costing principles and the development of the rate structure must adhere to policies and procedures. A viable rate structure is crucial in sustaining the business operations of the MCC Biorepository.

Below is a step-by-step process in establishing the rate structure.

1. Develop a faculty survey to assess the need for the biorepository core
2. Perform a market analysis to ensure that the price and quality is competitive
3. Identify potential Core Leader(s)
4. Explore financial options for supporting the service
5. Determine if a recharge is needed
6. If the recharge is needed, determine if a subsidy is available and how much
7. Restructure the tiered rates based on the subsidy
8. Analyze options to determine optimal approach

Calculate the recharge rates:

1. Determine the specific services that will be offered
2. Determine the percentage use of each service
3. Decide if the recharge is an hourly rate or a service unit rate
4. Project the billable units for members, non-members, and non-university

Calculate the personnel expenses

1. Determine staffing and the level of support required
2. Calculate the salaries and benefits based on projected effort and fringe benefit rates
3. Project the member usage based on faculty survey and biorepository leader estimates
4. Multiply the salaries and benefits by the member usage percentage
5. Deduct the subsidy to arrive at the net member expense

Calculate the non-personnel expenses:

1. Determine all essential costs required to provide the service (i.e. laboratory supplies, equipment depreciation, equipment service agreements, staff training)
2. Calculate the non-personnel expenses by multiplying each cost with the member usage percentage
3. Deduct the subsidy to arrive at the net member expense

The total personnel and non-personnel expenses are summed to arrive at the total projected expense to be recovered both with and without subsidy.

Calculate the tiered rates:

- The member rate, also known as the subsidized rate, is calculated by dividing the Total Net Member Expense by the member projected billable hours/units
- The non-member rate, also known as the base rate, is calculated by dividing the Total Recharge Expense by the non-member projected billable hours/units
- The non-university rate is calculated by adding the overhead rate to the non-member rate

In Tables 1A and 1B, the rate is constructed for a serum sample, one of the many services provided by the biorepository. The rate is calculated by accounting for the personnel, consumables, service agreements and equipment depreciation costs that allow the biorepository to perform the serum sample service unit. The facility receives a subsidy from the Cancer Center Support Grant, thus the rate structure is tiered, with a Cancer Center member rate, a non-member rate and for external users, a non-UCSD user rate. The same methodology can be used to calculate an hourly rate for a specific type of service using billable hours instead of units.

Table 1A. Rate Calculation by Unit of Service: Serum Sample

Personnel	% Effort	Salary & Benefits	Total Recharge Expense	Percent Usage by Members	Member Expense	Less Subsidy	Net Member Expense
Shared Resource Leader	1%	$ 200,000	$ 2,000	96%	$ 1,923	$ 962	$ 962
Staff Research Associate IV	10%	$ 85,000	$ 8,500	96%	$ 8,173	$ 4,087	$ 4,087
Staff Research Associate III	5%	$ 65,000	$ 3,250	96%	$ 3,125	$ 1,563	$ 1,563
Staff Research Associate II	5%	$ 50,000	$ 2,500	96%	$ 2,404	$ 1,202	$ 1,202
Total Personnel			$ 16,250		$ 15,625	$ 7,813	$ 7,813
Lab Supplies			$ 1,350	96%	$ 1,298	$ -	$ 1,298
Equipment Depreciation			$ 1,500	96%	$ 1,442	$ -	$ 1,442
Total Non-Personnel			$ 2,850		$ 2,740	$ -	$ 2,740
Total projected expenses to be recovered			$ 19,100	-	$ 18,365	$ 7,813	$ 10,553

Billable Units	Percent Usage	Projected Billable Units	Proposed Rate	
Members	96%	500	$21	$10,553 divided by 500 units
Non-members	4%	20	$37	$19,100 divided by 520 units
Non UCSD users	0%	0	$53	$37 plus the 45% overhead rate
	100%	520	Units (Samples)	

Table 1B. Rate Calculation Summary: Serum Sample

Revenue:	
Revenue-Member	$10,553
Revenue-Non-member	$734
Revenue- Non-UC User	$0
Total Revenue	$11,287
Expenses:	
Salaries & Benefits	$16,250
Supplies & Other Expenses	$2,850
Total Expenses	$19,100
Less: CCSG Subsidy	$7,813
Plus: Differential Income Transfer	$0
Total Net Expenses	$11,287
Net Profit (Loss)	$0

The MCC Biorepository provides a wide range of services and each type of service requires a separate rate calculation. Using the methodologies described above, the following catalog of services is provided to investigators:

Table 2. Biorepository Catalog of Services

Item Code	Item Description	Unit Cost
BR0001A1	Serum per sample (250 uL) - Member	$21.00
BR0001B	Serum per sample (250 uL) - Non-Member	$37.00
BR0001C1	Serum per sample (250 uL) - Non-University	$53.00
BR0003A1	Plasma per sample (250 uL) - Member	$21.00
BR0003B	Plasma per sample (250 uL) - Non-Member	$37.00
BR0003C1	Plasma per sample (250 uL) - Non-University	$53.00
BR0004A1	Buffy Coat per sample (150 uL) - Member	$23.00
BR0004A2	Buffy Coat per sample (150 uL) - Non-Member	$40.00
BR0004C1	Buffy Coat per sample (150 uL) - Non-University	$58.00
BR0005A1	Urine per sample (500 uL) - Member	$21.00
BR0005B	Urine per sample (500 uL) - Non-Member	$37.00
BR0005C1	Urine per sample (500 uL) - Non-University	$53.00
BR0010A1	Saliva - Member	$40.00
BR0010B	Saliva - Non-Member	$72.00
BR0010C1	Saliva - Non-University	$105.00
BR0011A1	Solid Viable Fresh Tissue Per Subject - Member	$120.00
BR0011B	Solid Viable Fresh Tissue Per Subject - Non-Member	$170.00
BR0011C1	Solid Viable Fresh Tissue Per Subject - Non-University	$247.00
BR0015A1	Solid Fresh Frozen Tissue Per Vial (50 mg) Member	$24.00
BR0015B	Solid Fresh Frozen Tissue Per Vial (50 mg) -Non-Member	$36.00
BR0015C1	Solid Fresh Frozen Tissue Per Vial (50 mg) - Non-University	$52.00
BR0018A1	Xenografted Viable Freeze Tumor Per Vial - Member	$103.00
BR0018B	Xenografted Viable Freeze Tumor Per Vial - Non-Member	$140.00
BR0018C1	Xenografted Viable Freeze Tumor Per Vial - Non-University	$202.00

Implementing the Recharge Account

In order to implement a recharge account, a flexible automated database system is strongly recommended. It should be capable of handling the internal and external billing, recording of revenue and expenditures and utilization of members, non-members and non-university users and offer other advanced features such as online registration. At MCC, an in-house Microsoft Access database was developed to provide the financial infrastructure needed for the recharge account. When using the facility for the first time, the Principal Investigator has to register online. The online registration is the first step in gathering information from the user. It asks specific questions that will determine which rate to apply based on established criteria for different users. The system keeps the entire record by creating a profile and an account number for each customer. Once the registration has been approved, the user can submit their request to the respective facility. The laboratory personnel will generate a requisition form which requires the internal user to provide an account number to be charged for the service. The account is validated in the system first before the work can be started. For an external user, a Purchase Order has to be placed.

Billing the Services

Having an automated billing system is necessary in operating a recharge system. The core facility can generate hundreds of transactions in a month and this can only be handled effectively and efficiently using an automated billing system. There are two types of billings generated from the system; one is used for internal users and the other for external users. For billing the internal users, the system generates a file that has all the accounting information that can be downloaded into the university information financial system. This process is simple and fast and it can be done with a click of button. All calculations are done by the system including data merging and copying from the sources and application of different formulas to get the desired results. For the external billing, the invoice generated contains all data provided to the customer such as the bill amount and date, terms of payment, description of items and other related account information. Two copies of invoices are generated; one is sent to the customers and the other is sent to the UCSD Accounting Office for recording.

Payment Processing

Payments are processed for internal billing when the transactions are downloaded to the financial system which then post to the ledgers on a monthly basis. For external billing, payments are recorded by the UCSD Accounting Office when checks are received. The system generates an Aging Report so that accounts receivable are monitored and collected.

Financial Tracking

Managing the finances of the biorepository is very challenging. It should be viewed and managed as a small business with a varied funding and customer base. The revenue and expenditures need to be monitored monthly both at the level of the facility and centrally by a Research Administrator from the Cancer Center to ensure that the fund balance does not result in a surplus or deficit

since the budget should be maintained at no gain/loss basis. There are a number of commercial products available to manage the utilization and finances of the facility; MCC has an in-house shared resource database to accomplish this. The system provides for internet registration for service, electronic internal billing, and electronic utilization tracking describing the service, user, fee and time of service.

In tracking the revenue and expenses of the biorepository, it is crucial to watch for seasonal or monthly perturbations such as an annual service contract, severance pay for a terminated employee, or the loss of a user's grant. While any of these will have a negative impact on the monthly financials they may be one-time aberrations. It is also possible that more permanent revenue or expense changes will require modifying the service fee, either upwards or downwards. When changing the fee adequate notice should be sent to the research community so investigators can adjust their grant budgets accordingly. Six months is a fair lead time.

Table 3. Biorepository Fund Report

ACCOUNT	BALANCE FORWARD 7/1/2014	YTD INCOME 9/30/2014	YTD EXPENSES 9/30/2014	YTD BALANCE 9/30/2014	PROJECTED INCOME 6/30/2015	PROJECTED EXPENSE 6/30/2015	PROJECTED BALANCE 6/30/2015
Biorepository Recharge	$2,840	$26,366	$27,948	$1,258	$86,098	$83,844	$3,512
CCSG Subsidy	$1,200	$52,440	$13,410	$40,230	-	$40,230	-
Differential Income	$955	-	-	$955	$4,800	-	$5,755
Equipment Account	$30,000	-	-	$30,000	$1,500	-	$31,500
GRAND TOTAL	$34,995	$78,806	$41,358	$72,443	$95,398	$124,074	$43,767

Recharge is allowed to have a surplus/(deficit) if the amount is within 2 months of annualized expenses.
Differential Income generated from outside revenue recorded annually and can be used by the Department
Equipment Account is recorded annually and used for replacement or purchase of new equipment

In Table 3, the biorepository recharge account is projecting a balance of $3,512, which is within the policy since the amount is below the average 2 months of annualized expenses, which is $4,658. The differential income account has no limit and can be used as discretionary. The equipment account is restricted to new or replacement equipment.

Utilization Reports

Utilization reports are essential to the core facility especially if subsidies from grants are used to calculate the rates. At MCC, almost all of the core facilities including the Biorepository receive subsidies from the Cancer Center Support Grant. As such, it is necessary that we provide utilization to the National Cancer Institute to report how facilities are being used by the Cancer Center members. The MCC database can produce multiple types of utilization reports and graphs. It can generate reports at a specific time frame by Principal Investigator, Account or Index numbers, Item Codes or Service Types. Accurate reporting of utilization is a must because it can assist leaders and managers in evaluating the performance of the facility.

The MCC Shared Resource Database can produce different types of utilization reports:

Utilization Report by Principal Investigator (PI)

This report lists PI names, their membership status as of the end of reporting period, the number of samples used and the percent usage. For the calendar year 2014, there were a total of 20 PIs that used serum samples from the Biorepository. The projected utilization was overestimated during start up. Projected utilization used for the rate calculation was 520 samples; however, the actual utilization for the reported 12-month period was 360 distributed samples. This is not unusual in the early stages of a core facility's development. It occurred due to multiple reasons. In this case, our faculty survey generated more prospective interest than the initial unitization. It happened because the faculty were expecting to conduct experiments that did not take place, the facility was not fully stocked with tissue samples because the requested samples were not yet acquired, the patient samples were more difficult to collect due to underestimating the staffing required to obtain consent and there was not a sufficient number of patients with the tumors being sought.

Table 4. Biorepository Utilization by PI, 01/01/2014 – 12/31/2014 (Actual)

Full Name	Member as of Report End Date	Serum Samples	% Usage
PI #1	Yes	30	8.33%
PI #2	Yes	28	7.78%
PI #3	Yes	7	1.94%
PI #4	Yes	20	5.56%
PI #5	Yes	13	3.61%
PI #6	Yes	17	4.72%
PI #7	Yes	15	4.17%
PI #8	Yes	22	6.11%
PI #9	Yes	30	8.33%
PI #10	Yes	12	3.33%
PI #11	Yes	18	5.00%
PI #12	Yes	43	11.94%
PI #13	Yes	22	6.11%
PI #14	Yes	10	2.78%
PI #15	Yes	26	7.22%
PI #16	Yes	12	3.33%
PI #17	Yes	11	3.06%
PI #18	No	6	1.67%
PI #19	No	8	2.22%
PI #20	No	10	2.78%
Grand Total		360	100.00%

Total Member Usage	93.33%
Total Non-Member Usage	6.67%
Grand Total	100.00%

Notes:

The projected utilization in the Rate calculation was 520 but the actual utilization was 360

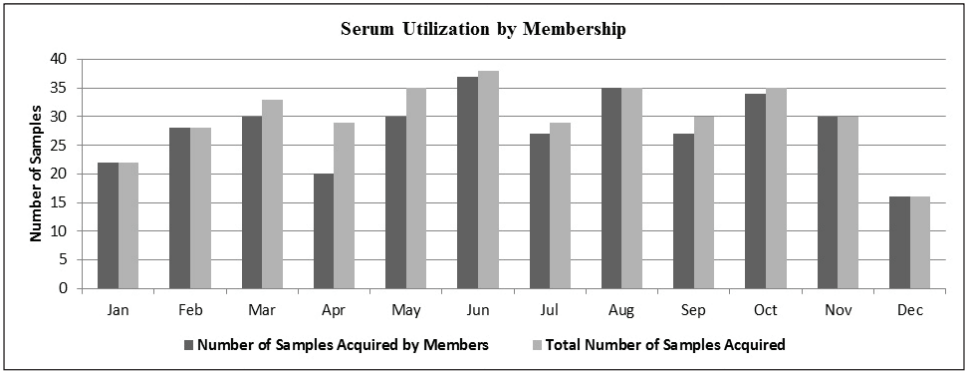
The projected member usage in the Rate Calculation was 96% but the actual member usage was 93.33%

Utilization by Membership

This report lists the member versus the non-member utilization per month for serum samples acquired by the 20 Principal Investigators for the calendar year 2014. Total number of serum samples acquired by members were 336 versus total number of serum samples acquired by non-members were 24. Total number of serum samples acquired by all members was 360.

Table 5. Serum Utilization by Membership

Calendar Year 2014	Number of Samples Acquired by Members	Number of Samples Acquired by Non-Members	Total Number of Samples Acquired
Jan	22	0	22
Feb	28	0	28
Mar	30	3	33
Apr	20	9	29
May	30	5	35
Jun	37	1	38
Jul	27	2	29
Aug	35	0	35
Sep	27	3	30
Oct	34	1	35
Nov	30	0	30
Dec	16	0	16
Total Serum Samples	336	24	360

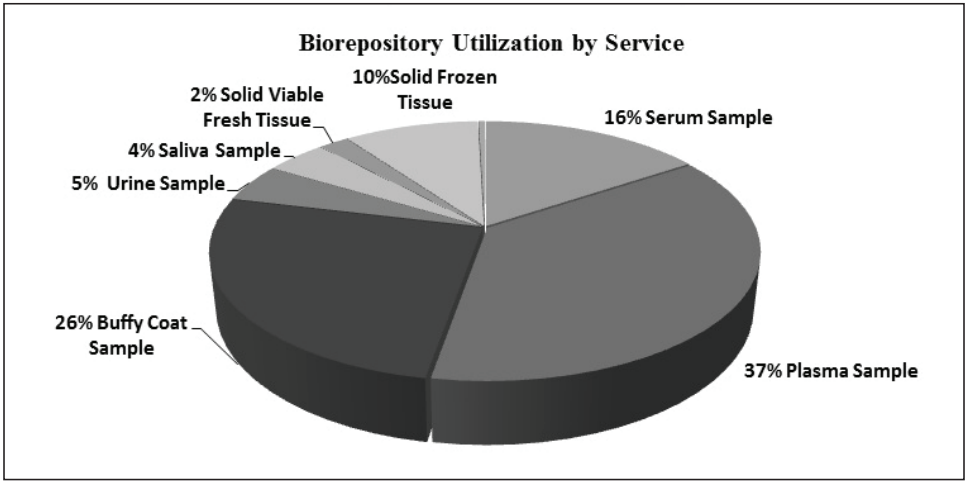


Utilization by Service Type

This report lists the utilization of all the services offered by the Biorepository Shared Resource.

Table 6. Serum Utilization by Service

Service	Samples	Percentage
Serum Sample	**360**	**16%**
Plasma Sample	**850**	**37%**
Buffy Coat Sample	**596**	**26%**
Urine Sample	**110**	**5%**
Saliva Sample	**100**	**4%**
Solid Viable Fresh Tissue	**48**	**2%**
Solid Frozen Tissue	**219**	**10%**
Xenograph Viable Freeze Tumor	**10**	**0%**
Total	**2293**	**100%**



Surveys

Conducting surveys is one of the most meaningful areas of measurement in research. A good survey can identify issues that can be addressed by the BTTR to improve its services. It can be used as a benchmark to help establish a baseline from which the BTTR can gather information as to whether target population needs are met. Surveys can pave the way to a successful marketing program that can enhance the business.

Marketing

Marketing is a critical aspect of running a biorepository. Without marketing, the business may offer the best products or services but none of the potential customers may be aware and the business may not be given an opportunity to grow and succeed. For the BTTR to succeed, the product or services it offers must be known to potential users. A good marketing program that gives BTTR the best chance is a healthy mix of different forms of marketing such as website development, public relations, print advertising, and showings at special events like scientific retreats and seminars.

Annual Business Plan

An annual business plan is vital in order to consistently grow the business. It creates a road map for where the business is going. It does not necessarily guarantee success, but crafting the annual plan and course of action improves the odds in favor of the business. A good business plan should set goals that are achievable. Preparing a business plan can reveal business strengths and weaknesses and it can also paint realistic action or steps to be taken for achieving the desired outcomes. It is good business practice for the BTTR to have an annual business plan that includes a description of the services provided including any changes forecasted for the coming year, the current staffing and any changes, and the next year's budget including a breakdown of each revenue source, the projected utilization, and plans for the next year. This report is prepared at the start of the academic fiscal year by the Shared Resources Manager and the BTTR Director. It is then approved by the Associate Director for Shared Resources. The Business Plan may include projected changes in technology requiring new instrumentation or personnel with specific skills. It may include the termination of services that are either no longer sought or those that can be better provided elsewhere (see Appendix 1 for the BTTR Business Plan).

Performance Review

Performance review is probably one of the most disliked tasks but it is also one of the most important steps in maintaining a core facility. Performance reviews provide a look at how the facility is doing based on performance measures or indicators. It allows the facility to focus on improving the different aspects of their operation and how it can progress toward its business goals. Without these indicators and guidance, it would be very difficult to attain its full potential.

It is necessary to have an annual performance review of the biorepository and this can be performed at a number of levels. The research administrator is primarily concerned with managing the administrative and financial aspects of the facility including service fees and budget. Client satisfaction based on timely delivery of service, up-to-date technology and quality output are monitored by a peer group—the Shared Resources Oversight Committee (SROC) at the Moores Cancer Center—that is chaired by the Cancer Center Associate Director for Shared Resources. The SROC is composed of research division leaders of the Cancer Center. It meets quarterly to review the performance of cores and discuss the need for new cores. Each core is required to present its performance to the SROC annually. The presentation is both a projection

of future use and a progress report on the past year. There is a discussion period following each presentation. The SROC is also responsible for developing core facility governing polices that are crafted and carried out by research administrators. The success or failure of a shared resource program depends on the choice of appropriate institutional policies and requires an effective institutional governance regarding decisions on staffing, existence and composition of advisory committees, policies and of defined mechanisms of reporting, budgeting and financial support of each resource (De Paoli, (2009).

Lesson Learned

We know that the need for readily accessible, quality controlled human tissue is vital to cancer research and we believe that we can establish and maintain a flexible and dynamic Biorepository and Tissue Technology system. The establishment and maintenance of the BTTR posed many challenges. It was a complex undertaking and we learned many valuable lessons in the process. There were lessons learned involving personnel and hiring the right skilled staff but the most significant experience was gained in the process of establishing the rates. We overstated the projected usage for many of the different types of services. The early usage has been lower than expected and as a result the recharge did not generate enough revenue to cover the cost of operations. While the lower volume affected the anticipated revenue, the higher projected utilization had the offsetting benefit of creating a lower initial fee based on the rate setting methodology described herein.

This caused us to rely more on institutional support. We chose not to increase the rate at this time because we want to offer low prices as an incentive to increase usage. We also learned that we do not have enough staffing to obtain consent from participants and we are not capturing all prospective donors. We are hiring additional staff to mitigate this issue. We discovered that we do not have the samples that researchers want and we believe that this will be addressed with the increased staffing. We need to improve collaboration of the Finance Administrator and educate the laboratory researchers about the business aspects of operating the recharge system. We now know that operating the BTTR will require continued institutional support, at least temporarily. Finally, MCC is committed to support the BTTR because it considers this as an investment that will pay off in the long run. We are looking at more proactive steps to increase business by advertising, conducting faculty surveys and performing market analyses to meet the competition.

Summary

The significance of biorepositories in the biomedical research field has been established and proven to enhance and advance the future treatment of many diseases, but the creation and maintenance of a biorepository involve risks. One of the major risks is that there may be a limited number of patients that are willing to participate in the tissue collection. The success of the facility will highly depend on the number of samples collected, the quantity of tissue donation as well as the utilization by researchers to whom a fee will be charged. Moreover, there are many challenges in maintaining the different aspects of the biorepository system. The operational aspects which involve the collection, processing, storage, retrieval and distribution of specimens, management of clinical data, quality assurance and control can be handled by providing a system

capable of complying with standard operating procedures to ensure that the integrity of samples are safeguarded at all times. The development of the informatics infrastructure is essential in this endeavor. Likewise, the legal and ethical aspects including custodianship, informed consent, and privacy protections for individuals who donate biospecimens can be addressed by having an effective Protocol Review and Monitoring System and Institutional Review Board.

Establishing and maintaining a biorepository is expensive and it requires not only commitment and support from the institution but also a strong administrator that can manage the business aspects of it. One of the major challenges remains adequate funding to support the resource. The best way to address this is to develop a recharge system so it can be operated as a business. Developing a good rate structure, continuously monitoring the financials, preparing an annual business plan and reviewing performance will contribute to a successful biorepository.

Authors' Information

Sonia Ashley has over 30 years of accounting and managerial experience both in public and private sectors. She is the Director of Business Operations for the Moores Cancer Center and has been for over 15 years. She has experience managing core facilities and setting up rate structures for all of the core facilities at the Center. As the Director, she manages contract and grants exceeding over 90 million and in-charge of Human Resources responsible for over 500 employees. She made both short and workshop presentations with SRA on the management of core facilities.

Ira Goodman has over 40 years of contract and grant administration experience. He is currently the Associate Director for Administration for the Moores Cancer Center. He manages the administrative services that facilitate research, patient care and clinical research. He participates in the design and strategic planning for the Center, financial and human resources management, oversight of information systems development, program planning, space and facilities. He is an expert in setting up and managing core facilities and has presented workshops and presentations at SRA.

Correspondence concerning this article should be addressed to:

Sonia Ashley
Moores Cancer Center
University of California, San Diego
3855 Health Sciences Drive #0658
La Jolla, CA 92093-0658
scashley@ucsd.edu

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Appendix 1

MOORES UCSD CANCER CENTER
Biorepository and Tissue Technology Shared Resource (BTTSR)
Business Plan FY 2013-14

Director: Scott VandenBerg, MD PhD **Co-Director: Richard Schwab, MD** **Co-Director: Nissi Varki**

Service Profile
The BTTSR provides for the acquisition, multi-modality processing, and archiving of well-annotated human biospecimens that is seamlessly integrated with histology and tissue analysis services. Three major activities are provided by this shared resource: 1) the biorepository for human tumor specimens that are acquired during diagnostic and therapeutic procedures from consented subjects with associated blood, urine (when applicable), and CSF (when applicable), and that are linkable to clinical and diagnostic and made available to MCC investigators; 2) tissue histology and technology for state-of-the-art molecular morphology/biomarker applications, and 3) histopathologic expertise for validation of diagnostic parameters on biorepository specimens, and assistance in the interpretation of human and mouse tissue pathology. Each major activity is coordinated by an expert faculty co-director. Dr. Vandenberg (STT), an experienced pathologist, is overall Director of the BTTSR, Dr. Schwab (STT) oversees the biorepository clinical affairs and sample collection and distribution, and Dr. Varki (STT) oversees the histology and tissue technology applications in human samples and animal models. The BTTSR assists in the formulation of targeted prospective collections for clinical trials or for translational research projects directed at biospecimens that need specific parameters, in addition to routine tissue collection during diagnostic or therapeutic procedures. Tissue technology includes multi-label immunohistochemistry, multiplexing immunofluorescence, and *in situ* hybridization in addition to analytical microscopy for molecular morphology, including spectral imaging. The state-of-the-art laser-capture microscopy in the tissue technology resource provides an important resource for performing genomic/expression profiling and proteomics on tissue sections with complex tumor cell heterogeneity and complements the biomarker discovery capabilitiesperformed in this facility.

Integrated Services of the BTTSR
Biospecimen Oversight
- Acquisition of human biospecimens – solid tissue, blood, plasma/serum
- Processing, storage and custodial archiving
- Tissue quality assurances/specimen identification
- Database system integrated with Velos via *e-sample* module
- Management of biospecimen use & distribution via NCI best practices

Biospecimen Processing
- Whole blood processing for cells/serum/plasma
- Viable tissue processing/short term culture
- Freezing tissue (Liquid N2)
- Tissue fixing/processing with multiple modalities
- Microtomy of frozen and embedded tissue
- Optimization/standardization of existing biomarker assays
- Development of new biomarker assays/analytical molecular morphology

Interpretation of Tissue Parameters
- Expert histopathologic analyses/diagnostic conformation for human and mouse tissues
- Immunohistochemical/immunofluorescent assay validation and evaluation

Collaboration
- Consultations related to tissue preservation/histology
- Experimental design in projects for tissue histology
- Development of robust database elements using *e-sample*
- Core for tissue banking and specimen tracking, extraction of de-identified data related to distributed specimens for research data warehousing

Staffing:
Sharmeela Kaushal – Biorepository Lab Manager MaryAnn Lawrence – Histology Research Associate
Jimmy Salinas – Biorepository Research Associate Amanda Gifford – Histology Research Associate

Financial Plan:

Income Source	Budget 2013-14	2013-14 Percent
CCSG	$217,409	20%
Charge Backs	$380,000	36%
Institutional Support	$464,090	44%
Other (from Grants)	0	0
Total Operating Budget	$1,061,499	100%

Projected Utilization:

Histology Service	Volume
Assay Handling	1,254
Tech Time	1,517
Pathology Consultation	51
Special Stain	2,918
Paraffin Section	43,959
Paraffin Block	15,444
Frozen Section	14,620
Other Consultation	2,168
Serial Sections more than 25	72
Routine Stain	9,440

Biorepository Service	Volume
Serum	320
Plasma	350
Buffy Coat	300
Urine	225
Tumor Tissue	64
Normal Tissue	5

Plans for the Year:
The BTTSR is targeting these 3 areas for continuing and future development of services.
(1) Innovative application of dual ISH/IHC labeling using the ACD RNAscope® technology which preserves optimal histologic detail. The ACD technology is especially valuable when a biomarker has no available antibody probes or when expression levels are especially low. The capability to perform dual ISH/IHC labeling on the same tissue section is a significant enhancement of localizing complex biomarker phenotypes.
(2) The capacity for routine viable cell processing/short-term culturing of tumor cells to include tumorosphere cultures, 3D matrix cultures, transwell and tissue slice cultures under standard CO2/room-O2 conditions. In addition culture conditions with lower O2 conditions (1-6%) will be available for the various culture modalities. The Biorepository will minimize time between human tissue acquisition from the OR/day surgery suites and placement of viable cells in lower oxygen environments. Real-time videography (with brightfield/interference contrast or fluorescent illumination of monolayer cultures for ≤72 hours under normoxicor 1-6% O2 is also being developed as a resource within the facility.
(3) Optimization of LCM technology with respect to isolating analytes from subpopulations of tumor cells that represent small percentages of overall tumor populations but may exert profound biological effects on tumor growth, therapeutic responses, recurrence or invasive progression, of from subpopulations of viable cells in heterogeneous tumor cell cultures grown under variable O2 concentrations.

Unit Director Signature _____
Cancer Center Director Signature _____