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Successful Integration of the Histology Core Laboratory in Translational Research

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Abstract

In a diagnostic setting, the histology laboratory is a key resource for production of quality tissues so the pathologist can make an appropriate diagnosis. In a research setting, the histology laboratory is a valuable resource in providing an excellent quality product for publications and grants for the investigator. Optimal collaboration with research investigators requires that histotechnologists recognize the diverse challenges and opportunities in research. This paper emphasizes the importance of positive interaction with researchers, optimizing professional service for these clients and recognizing key services of histology laboratories in a research setting to maximize success.

Keywords

Histotechnology; Histology; Translational Research; Immunohistochemistry; Histochemical; Pathology; Translational Medicine

INTRODUCTION

In a diagnostic setting, the histology laboratory is recognized as a key asset for the delivery of high quality tissues for the pathologist to make an appropriate diagnosis. From routine processing of tissues to immunohistochemistry problem solving, histotechnologists provide professional experience and support to meet the demands of the laboratory. In a research setting, the histology laboratory is also a key resource to investigators and successful collaboration requires that histotechnologists recognize and adapt to the diversity of challenges and opportunities available in research.

Translational research can generally be defined by the axiom of “bench to bedside” research. The premise of the concept is to take discoveries made in the basic science realm and apply them for clinical access to the patient (1). Along this continuum, research studies are commonly performed in animal models to better understand and validate findings. In fact, it has been reported that approximately 60% of federal grants involve animal studies (2) and the histology lab often acts as a critical resource in this endeavor to evaluate pathologic changes and phenotype. This paper will explore the operational interaction between the histology research laboratory and translational investigators using animal models with the goal of minimizing pitfalls and maximizing productivity (Figure 1).

Client relations

A distinction between clinical and research histology is found in the “client” and their needs. In the clinical realm, the pathologist represents the typical client and their primary goal is that of tissue diagnosis. The pathologist and histotechnologist not only work closely together for the same goal, but often work in the same department. In contrast, the investigator and associated laboratory personnel serve as the client in research and the investigator’s goal is often the comparison of two or more groups of tissues for examination of phenotype or response to treatment. While the researcher may be affiliated with the histology lab, many times they reside in other departments or institutions and are subject to a fee for service in the histology laboratory.

Research investigators are an important resource for revenue generation in the histology laboratory and as such need to be retained through excellent service and quality products. The histology laboratory should set the bar high for retaining clients, which are the daily “bread and butter” for the lab. As in the business world, client satisfaction in the research setting starts when the client brings a project to the lab. A warm greeting gives a great first impression and will serve as a positive foundation for future interactions; all personnel should be regularly trained in this important principle. Lab staff should listen attentively to the client’s requests so as to clearly understand their needs. In this personal service approach, the client must be a priority from initiation to completion of the product. Exceeding the client’s expectations in service, attentiveness, and final product quality will keep clients returning to the lab as well as stimulate word of mouth referrals. These referrals can prove to be better than any billboard advertising that money can buy!

Transparency is another important aspect to client interaction. For instance, sometimes staff members may feel uncomfortable discussing costs with clients when accepting projects into the lab. In this uncertain economy, investigators are looking for a high quality product at a reasonable price. Staff should be comfortable discussing the anticipated project costs, but at the same time display a vested commitment to make the best quality product for the investigator’s lab. Sometimes these factors can be highlighted to the investigator by letting them know that if they have any questions about their project they can contact the laboratory directly. Such openness applies not only to the person dropping off the project, but also to the person ultimately responsible for payment. For example, when a student or technician submits a project, a quick email to both the student and the principal investigator summarizing the submitted projects and estimated costs can prevent significant confusion later should the student not have understood what the investigator wanted or the fee for services. Lastly, transparency is also highly relevant in admitting a mistake immediately when it occurs. While we all dread the inevitable errors (e.g. mislabeling cassettes) and how it is uncomfortable to experience, being forthright and honest at the time of the mistake will avoid larger problems down the road and will give the client further trust in your services.

Professional support

Research investigators are focused in their respective disciplines such as urology, molecular biology or genetics and may not have much experience handling animal tissues or with histologic techniques. At project submission, clients will often discuss relevant scientific aspects of their research and may ask specific questions related to the tissues. This dialogue is an opportunity for staff to give professional advice or direction to improve the project, or even prevent possible failures. For instance, an investigator working on mice may submit formalin-fixed influenza infected lungs for immunohistochemistry of certain leukocyte markers. Because some murine leukocyte markers are damaged/lost during fixation (3), the investigator would be encouraged to use markers proven for their choice of fixation and paraffin-embedded tissues, or collect frozen tissue instead. In our experience, researchers

appreciate professional advice and will seek out additional counsel on future projects which will likely be submitted through the lab.

Financial health

Sound fiscal management is the goal of all histology labs. Accounting for all direct (materials, salaries) and indirect costs (material wastage, etc) in charging for services is essential and intuitive. Regular review of costs and inflationary changes should be done annually to be sure that cost changes do not go unnoticed. While these factors are similar to the diagnostic lab setting, one distinct feature in research is the potential for direct revenue from grants. For researchers who utilize or plan to utilize the histology lab extensively, incorporation of the histotechnologist directly onto grant submissions with salary support and a materials budget is a useful option. Grant support provides a steady stream of revenue for the lab which can minimize seasonal fluxes in business. Importantly, the summation of total support needs to closely match the estimated costs for the duration of the grant. Investigators who frequently use the lab can be approached about such inclusion on future grant submissions. One potential advantage for the investigator is that this portion of the grant budget is not often cut because of the essential duties of the histotechnologists.

Documentation

Documentation is essential for any successful business, including a histology laboratory. When working with investigators, it is important to present that client with a projection of costs for the services you will provide. A written or emailed estimate not only provides a framework for expected pricing as determined by the histology lab, but also serves as a potential addition to a budget for a grant submission. It is important to note for the investigators that the estimate is not a promise, but a projection. Prudent business administrators recognize that one cannot be expected to retain a service price over time given that costs do fluctuate in response to inflation and other factors. Additionally, when writing estimates for multiyear grants one needs to account for price changes. For example, when an estimate is given for a future grant, there needs to be regular/annual inflationary increases in the cost of services and labor that will sufficiently cover real changes in the future. It is useful to retain and date all estimates provided to investigators for reference should their grants become funded. Additionally, rules governing federal grant spending often require that core services at an institution bill grants at the lowest available rate. Because the grant funding and subsequent project may not be submitted to the core for many years after the estimate was made, the histology laboratory should not make “guaranteed” estimates to investigators. In our experience, it is useful to give clients “projections” for future services that include appropriate yearly inflationary increases. We also include a disclaimer stating among other things that the quote is for reference only and the actual costs at the time services are rendered will be the amount billed.

Protocol documentation for research projects is also a necessary and critical component for a histology laboratory. Successfully optimized protocols should be documented by date soon after their work-up with as much detail as necessary. Documentation of protocols is necessary not only for reproducibility in the laboratory, but also for possible publication by the investigator. Frequently reagents are discontinued or new ones come along and the protocol gets “tweaked” for optimization purposes. Citing the approval date of any modified technique used for research tissues will allow identification of the specific protocol even years down the road when new reagents may have been incorporated into a specific protocol. Improperly catalogued current and past protocol information will reflect poorly on the laboratory, especially if it is not readily available to investigators.

Histology research laboratories should strive to have a general plan in place for sharing data with investigators. The details of the plan may be influenced by the organization of the histology lab including availability of electronic records, security access requirements, computer software, proprietary intellectual data, and the histology lab's relationship to the investigator. At some point, investigators will request technical information necessary for publication; however, sharing of a laboratory protocol text that might be directly pasted into a manuscript can potentially be a problem. For instance, if a protocol gets published by one investigator and another investigator tries to publish the same text it constitutes plagiarism and may be red-flagged by software used by some journals. When possible, it is advantageous to give the investigator a published citation of a the protocol used by the lab along with a brief outline of key technical points (commercial source, catalog number, species, dilution, etc.) for adaptation into the manuscript by the authors in their own writing style to avoid plagiarism. Of course when serving as a co-author, the histotechnologist can write and tailor the protocol text to match the style of the target journal. Data sharing can be also influenced by the professional relationship of the histotechnologist to the pathologist. If the pathologist is a director of the laboratory, the pathologist may have access to most investigator data for routine assessment of quality controls or protocol workups. In contrast, when the pathologist is a collaborator of an investigator, he/she typically only has access to the investigator's project. In summary, histology laboratories should have established guidelines for data sharing with investigators and pathologists that match their organizational structure and institutional goals.

Quality Control

A fundamental requirement of quality control in a histology laboratory requires the consistent use of control slides to determine if staining is appropriate to the tissue(s) of interest. In a research setting identification and usage of appropriate control slides cannot be emphasized enough. Specific control slides need to be determined for each species of interest and contain the appropriate positive and negative control tissues for the histochemical or immunohistochemical stain of interest. In our experience, some investigators may not appreciate the full importance of this. For example, we have had investigators ask for a Masson's Trichrome for sections of infected lung looking for fibrosis. They have read in some paper or text that "blue staining" represents fibrosis (i.e. type I collagen). While this is generally true, it is also known that not all blue staining in the lung is fibrosis; a good example is that of airway cartilage which stains a light blue (4). A useful response by histotechnologists in our lab is that "blue staining can represent fibrosis, however other features can stain blue as well, and a pathologist would offer the best interpretation of the staining pattern".

When performing immunohistochemistry specifically, a detailed workup of the procedure is required, whether it be fixative, fixation time, tissue size, antibody dilution incubation times, etc. There are numerous variables when it comes to immunohistochemistry including antibodies, species of interest, tissues of interest, age of species, and even the fixation methods. Each procedure needs to be optimized using the appropriate positive and negative control tissues to assure accurate immunoreactivity before running experimental samples. Sometimes investigators bring "standard" protocols to us for use; however we encourage individual optimization of protocols under our particular laboratory conditions to optimize quality results. This often results in higher quality samples than the investigator had obtained previously. While the investigator may have appropriate tissues for workups on control slides, sometimes it can be difficult to find specific tissues in certain species for controls. Coordinating with a comparative pathology laboratory to bank numerous tissue types from multiple species during routine necropsies is recommended. Certain tissue types can be grouped together in the same block for development of specific

immunohistochemical techniques depending on interests. For example, lymph node, spleen and thymus from a mouse can be put together in the same block for optimizing certain lymphoid markers, such as B220 or CD3. Having an extensive bank of fixed, embedded tissues that is properly cataloged will allow histotechnologists and pathologists to determine which blocks will be adequate control tissues in a quick and orderly fashion.

Another possible example encountered by histology research laboratories is the submission of a large group of samples. These often contain two or more groups of tissues that must be batched together, or as is often the case, broken into multiple batches. Separate batches can create a new variable - the batch effect. While ideally inter-batch variation should be minimal, it can be especially noticed by investigators doing morphometric analysis. It is especially troublesome when all the controls were in one batch and all the treated animals in another batch - thus if there are differences in staining - is it the experimental treatment or the batch effect? There are multiple ways to avoid this including randomization of tissues between the batches, or consistently splitting samples of the different treatment groups evenly amongst the various batches. With these large projects that require multiple batches, it is always best to submit your plan for the batches to the investigator for approval.

It is recognized that the nature and scope of research varies between institutions. Accordingly, many academic centers with animal model based research may not require a good laboratory practice (GLP) compliant environment for a histology research laboratory. However, it is important to remember that when performing some preclinical studies, federal regulations may require GLP compliance. Histology laboratories that are not GLP compliant should aim for GLP practices to maximize consistency and quality for clients.

Pathologist interaction

A key follow-up to quality control in the laboratory is direct interaction with an experienced comparative pathologist. Having a pathologist that works directly with the laboratory allows for quality assurance and a level of precision that will be appreciated by the investigator. As mentioned previously, many research clients are focused in their respective disciplines and may not have much experience with histology and tissue staining. If they do not have easy access to a pathologist they may try to go down the road of Do-It-Yourself-Pathology (5), which can potentially lead to erroneous interpretations as has been reported (2, 6). Ideally the histology research laboratory should be directed by a pathologist experienced in comparative pathology. Serving as director, the pathologist can help to assure that the final products are not only of high quality in terms of tissue preservation and processing, but also serve as a resource for proper interpretation of the tissues. The pathologist can also serve as a resource for the investigator if they have specific questions regarding a tissue, staining protocol or specific laboratory process. Recommendations of the pathologist to the investigator can often result in additional business activity for the laboratory. The histotechnologist-pathologist relationship is an important aspect to a prolific and successful histology laboratory.

Conclusions/Summary

Translational research is an important component for investigations of human disease. The histology laboratory, through their applications and expertise, can be a valuable partner in this endeavor. Optimizing the interaction with investigators can lead to productive growth and sustainability for the histology laboratory.

Acknowledgments

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Figure 1. Schematic showing the typical relationship between the histology laboratory, researcher and pathologist. The histology laboratory often serves as a bridging resource between the researcher and the pathologist for the final goal of tissue evaluation.