Commentary

Translational Research: Empowering the Role of Pathologists and Cytopathologists

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Research activity is in the core essence of pathology. Advancing our understanding of disease pathogenesis translates into better patient care. Because of their unique position, laboratorians are the best to accurately identify, annotate, and classify research specimens. They also are essential for the accurate interpretation of genomic testing. Currently, cytopathologists are moving to the center of patient care through active communication with clinicians and patients. There are certain research areas in which cytopathologists can be pioneers, such as image analysis, morphology research, and genotype-phenotype association studies integrating morphologic and molecular features. Health service utilization research is another domain in which cytopathologists can excel. Successful research is a journey that necessitates multiple steps. It also involves building expertise in how to overcome obstacles and handle challenges. ***Cancer Cytopathol* 2018;126:831-838.** *© 2018 American Cancer Society.*

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INTRODUCTION

Pathology is a unique specialty that successfully bridges the gap between basic science research and patient management. The core essence of pathology involves a better understanding of the molecular basis and underlying mechanisms of disease risk, initiation, and progression. Advancing our understanding of the mechanisms of disease pathogenesis is translated into exciting new routes for pathologists to pursue. In addition to diagnostic endeavors, another important mission for the pathologists is to help guide treatment decisions, whether by providing predictive biomarkers or highlighting potential targeted therapy based on understanding disease pathogenesis.

THE EVOLVING ROLE OF THE PATHOLOGIST IN PRECISION MEDICINE

The profession of pathology has been evolving over the years. In earlier days, pathology mostly focused on describing the gross features of different organs with lesions identified during dissection. Later on, the use of microscopes further shaped the role of the pathologist. More recently, ongoing advances in immunohistochemistry and molecular analysis have further refined the job of the pathologist to provide additional prognostic and predictive information.[1–3] Another revolutionary milestone came recently with the introduction of concepts of precision medicine and P4 medicine,[4] which is defined as being predictive, preventive, personalized, and participatory (based on active patient participation).[5]

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Although they hold out hope of a significantly improved patient outcome by individualizing a treatment plan based on tumor biology, these new concepts carry a great challenge to the standard-of-care paradigms[6–9] and represent dramatic, revolutionary changes in the role of the cytopathologist. Molecular tests done for patients with different types of diseases are performed in the laboratory. The indication, interpretation, and clinical significance of a molecular test usually require active communication between laboratory team, clinicians, and patients. Consequently, the role of the cytopathologist's role is moving toward the center of patients' circle of care and becoming an active participant in multidisciplinary management teams that include clinicians, biologists, and pathologists, with input from patients.[10]

The exponential growth in companion testing with molecular diagnostics has elicited discussion about the need to develop an integrated *morphomolecular pathology* specialty in which pathologists are equipped with combined molecular and morphologic expertise, enabling them to address the challenge of genomic medicine.[11]

RESEARCH IN PATHOLOGY

An important question is why pathologists should be involved in research. There are several factors that necessitate the involvement of pathologists in research, and the advantages of getting pathologists involved in research include the following:

1. Pathologists are custodians of the tissues and biofluids necessary for research and are the best for accurate annotation for the specimens.
2. A pathology review is needed to ensure the use of accurate and most recent classification of diseases (eg, cancer diagnosis and staging are moving targets).
3. Pathologists have better ability to interpret the results of complicated molecular testing done in their laboratories.
4. Pathologists will enable the selection of optimal tissue for molecular analysis (eg, avoiding areas of hemorrhage and necrosis and avoiding contamination with adjacent normal tissue).
5. Pathologists add a new dimension of research by understanding subcellular morphology (nuclear, cytoplasmic, or membranous, etc) and its correlation with clinical parameters.

Pathologists are custodians of valuable biologic materials, from tissues, to cytology material, to an array of biologic fluids (blood, urine, cerebrospinal fluid, etc). Another important reason is the need for accurate characterization and annotation of the tissues used for research. This includes the use of uniform, up-to-date diagnostic and classification criteria. The presence of a pathologist as a member of the research team is essential for selecting the right area for dissection. In many instances, the lack of pathologists resulted in tissue specimens that were necrotic, full of hemorrhage, or contaminated with normal tissue that seriously affected the analysis. Cytopathologists also have the advantage of being able to correlate the results of biologic analysis with morphology at the cellular and subcellular levels.

PATHOLOGISTS AT THE FOREFRONT OF TRANSLATIONAL RESEARCH

There are certain fields of research that are especially suited for pathologists, including:

1. Biomarker discovery research;
2. Histomorphology and immunohistochemistry-based prognostic markers;
3. Predictive biomarkers (companion biomarker discovery for clinical trials);
4. Health utilization research;
5. Quality-assurance research;
6. Pathology education research;
7. Accurate tumor classification based on molecular analysis;
8. Case reports and case series for rare, unique pathologic entities;
9. Morphologic/biologic correlation research;
10. Big data analysis; and
11. Radiohistomics.

Morphologic research can be a primary field for pathologists and is a low-cost/high-yield option. The power of morphology is observed clearly in the Gleason grading of prostate cancer, which was introduced more than 50 years ago. It relies on morphology to predict clinical outcome. This grading system is still in use to predict prognosis and guide patient management. Other success stories include the Fuhrman nuclear grading system for renal cell carcinoma and using mitotic counts to assess aggressiveness in many cancers.

Another pathology-flavored field of research is the identification of immunohistochemical markers for accurate disease diagnosis and classification. Although morphology is a powerful tool for anatomic pathologists, it is becoming clear in recent years that morphology alone cannot provide accurate disease diagnosis. There are several recently recognized tumors, like the translocation group

of renal cell carcinoma, with morphology that overlaps with known tumor entities. In this regard, immunohistochemical markers would be very useful for accurately identifying such entities.[12] Advanced molecular analysis technologies can change the basis of classification of tumors from morphologic to molecular characteristics.[13]

Searching for prognostic markers is another intriguing field. Clinicopathologic parameters like tumor type, stage, and grade are currently used to predict the outcome of many tumors, but these parameters sometimes lack accuracy.[14] Tumors that appear to be the same might not necessarily behave the same way. There is an urgent need for identifying molecular biomarkers that can be used alone or in combination with other clinical parameters to predict disease outcomes with accuracy. This will significantly improve patient management. Several successful examples exist in the literature. For instance, in a recent study, investigators were able to subclassify papillary renal cell carcinoma into 4 biologically distinct subtypes based on a combination of morphology and molecular markers.[13] Also, assessment of Kirsten rat sarcoma oncogene homolog (*KRAS*), *BRAF*, and mismatch-repair (MMR) status with or without a CpG island methylator phenotype can classify colon cancer into different prognostic subtypes.[15] Dahinden et al demonstrated that using molecular markers improved the performance of morphologic parameters and increased their accuracy in predicting prognosis in patients with kidney cancer.[16]

It also has been demonstrated that new classes of molecules, such as microRNAs (miRNAs), are potential prognostic markers in prostate cancer. These results can pave the way toward refining the Gleason grading system by using adjuvant markers.[17] miRNAs can be measured in tissues using in situ hybridization.

The development of targeted therapy has increased the need for molecular disease characterization to identify biomarkers that can predict treatment efficiency.[9,18,19] Another interesting research domain is searching for morphologic reflections of biologic phenomena. One interesting example is the current advances in pluripotent stem cells and how these can be used for clinical diagnostics.[20,21]

Several platforms and technologies that are needed for translational research already exist as a part of most clinical laboratories in university settings, including polymerase chain reaction analysis, immunohistochemistry, fluorescence in situ hybridization, microarray, next-generation sequencing, and mass spectrometry, as summarized in Table 1.[7,22–39]

TABLE 1. Clinical Laboratory Technologies That Can Be Used for Translational Research

Technology	Example Research Study	References
PCR	• Detection of methylated DNA	Yu 2018[22]
	• Measuring circulating miRNA	Moshiri 2018[23]
Immunohistochemistry	• Combined immunohistochemical scores for cancer prognosis	Cuzick 2011[24]
	• Identification of new proteomic prognostic markers	Grin 2015[25]
Fluorescence in situ hybridization	• miRNA-based tumor classification	Di Meo 2018[26]
	• Cancer prognostic marker	Wu 2018[27]
Microarray	• Tumor classification and prognostic assessment	Feng 2013,[28] Gieseg 2002[29]
	• Identification of miRNA predictive markers	Zhou 2018[30]
	• Detection of multicentric cancer	Lang 2018[31]
Next-generation sequencing	• Cancer prognostic mutations	Real 2014[32]
	• Diagnostic miRNAs	Osanto 2012[33]
	• Prediction of the response to immunotherapy	Bergerot 2018[34]
Mass spectrometry	• Identification of new diagnostic biomarkers	Smith 2014,[35] Zhang 2006[36]
	• Cancer diagnosis and prognosis	Masui 2013,[37] Siu 2009,[38] Vieira de Riberio 2013[39]

Abbreviations: miRNA, microRNA; PCR, polymerase chain reaction.

PATHOLOGY RESEARCH IN THE ERA OF BIG DATA

Big data analysis represents another unique niche for pathologists. The definition of big data is not restricted to the *omics* data produced in research laboratories but also extends to everyday data reported by a clinical chemistry laboratory in a hospital setting and, more broadly, to the information generated in electronic health records. These data can provide a very valuable quality matrix with which to identify health care trends that can shape patient management strategies in different geographic regions, as recently discussed in detail.[40]

The introduction of high-throughput technologies has facilitated a better understanding of cancer pathogenesis at a greater depth and has resulted in a great revolution in precision medicine.[41,42] We are moving into another layer of complexity through integrated analyses of molecular changes at multiple levels for better understanding of the pathways involved in cancer pathogenesis. Thus, it is not surprising that molecular analysis is already part of the routine pathology report. For instance, in metastatic colorectal cancer (CRC), RAS testing currently is routine for patients who are considered for anti-EGFR therapy. Also, KRAS/BRAF and microsatellite instability (MSI)/MMR testing for all patients with newly diagnosed CRC will help in the detection of Lynch syndrome.[15] In addition, it has been demonstrated that MSI/MMR status can predict prognosis[43] and response to 5-fluorouracil treatment in patients with CRC.[44,45]

Furthermore, molecular signatures are expected to improve eligibility criteria for clinical trials to be biology-based instead of the currently used organ-based criteria. This will be an additional task for cytopathologists.[42] Added to this, the introduction of liquid biopsy highlights the increasingly important value of cytology and biofluid materials in the laboratory.[46]

It also has been demonstrated that rapid on-site evaluation and molecular testing of cytologic specimens, such as endobronchial ultrasound-guided fine-needle aspiration specimens, are essential for clinical decision making in patients with lung cancer.[47–50]

It is worth noting that cytologic specimens also are amenable for image analysis. Morphometric image analysis of ThinPrep, liquid-based cytology was helpful in the evaluation of pancreatic disease.[51]

Research is becoming more feasible through freely available databases. These databases contain genomic, transcriptomic, and proteomic analysis information for different cancers, together with their clinical and outcome information. Examples include *The Cancer Genome Atlas* (available at: https://cancergenome.nih.gov/), which enables pathologists and researchers to analyze and validate their molecules of interest in larger data sets.[52,53] Other open-access databases include the GWAS (genome-wide association studies Catalog,[54] ClinGen,[55] and ClinVar.[56]

RESEARCH IN THE ERA OF DIGITAL PATHOLOGY

Digital pathology and image analysis have been used widely in the last few years.[11] Pathologists and residents are welcoming the use of digital pathology in their daily practice,[57] and comparable results have been obtained when the performance of residents using glass slides was compared with the results from digital images.[58] This opened the door for a new dimension of sophisticated image-analysis research, such as genotype/phenotype association analysis and radiohistomics, as detailed in a recent review.[59]

THE ROAD MAP FOR A SUCCESSFUL RESEARCH PROJECT

There are several essential steps that need to be fulfilled for a successful research project, as indicated in Figure 1. The first is to identify the clinically relevant research problem to be addressed. The hypothesis must be clear, and the objective of the research project must have an ultimate impact on patient care. Attending multidisciplinary rounds and participating in conferences, in addition to reading the latest literature in the field, will help frame the research question in a precise way.

An exciting idea is not enough to guarantee a successful research project, because, often times, the devil is in the details. Pathologists will greatly benefit from writing down the anticipated steps in the project and discussing them with senior, experienced colleagues from different angles to polish their research project.

A solid research design is also of a prime importance, including sample size calculation, identifying the right material, and the use of appropriate methodology and controls to address the research question. After obtaining promising results, validation is an essential step, especially for biomarker studies, in which independent validation is strongly encouraged. Another important step to be carefully considered is finding funding for the research project. Targeting the right funding agency is also of prime

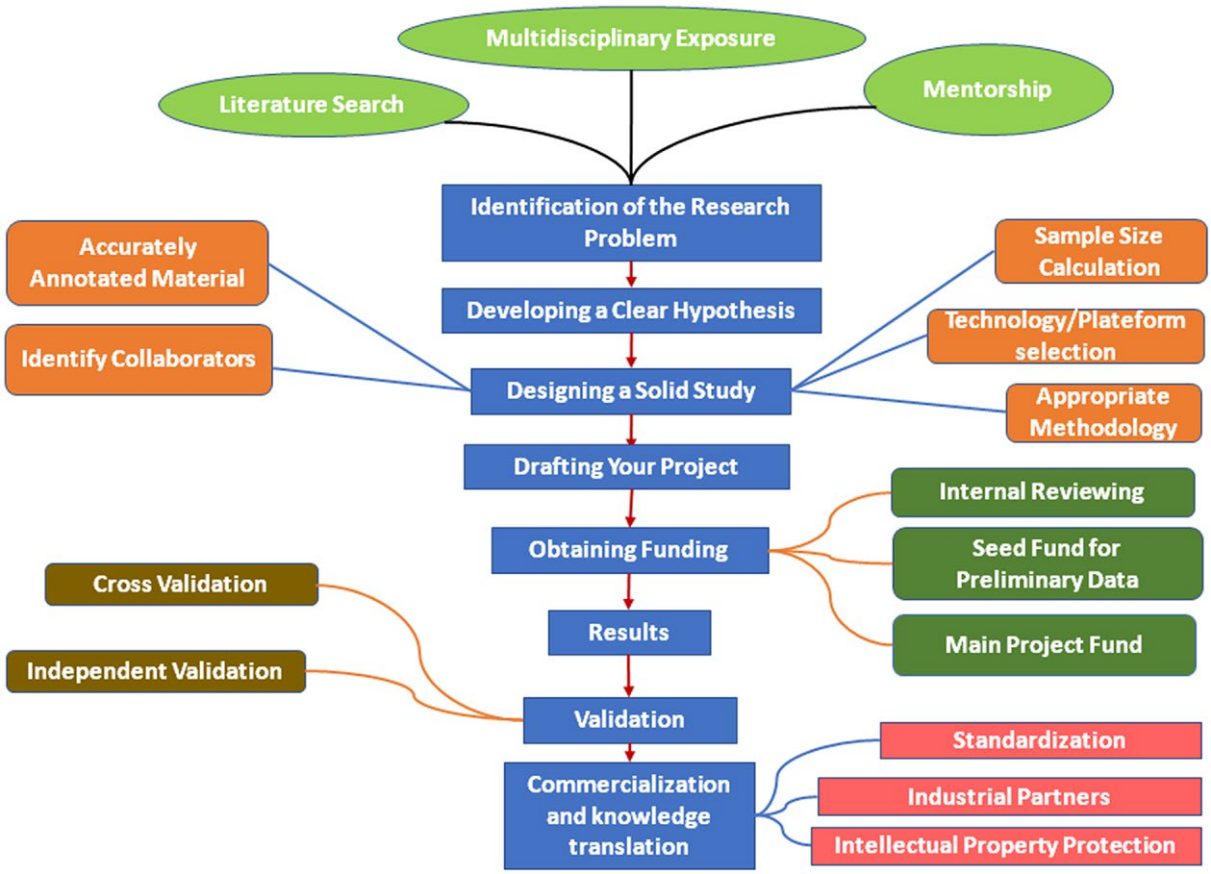

Figure 1. This schematic outlines the basic steps toward a successful research project. It starts with the identification of a clinically relevant research problem and the development of a clear hypothesis. The study design is also of prime importance. Obtaining funding is crucial for continuing successful research. Validation of the results is an essential step toward knowledge translation.

importance. For early stage studies, researchers are more likely to obtain seed funding from local, small-scale organizations to generate preliminary results that will enable them to proceed to full project funding.

HOW TO BE A SUCCESSFUL CLINICIAN SCIENTIST

A few tips for success include focusing on your strengths. In case of a pathologist, this could mean the use of immunohistochemistry and a repository of a biobanked tissues and fluids. Preliminary results are usually essential to apply for larger scale funding. It is also important to realize that developing a research career is a process that needs accumulating expertise. Mentorship is a key toward successful research. In addition, internal review of a research application will have a meaningful, significant impact on improving your research project.

OBSTACLES IN THE ROAD OF SUCCESSFUL RESEARCH

Funding is a challenge for any research project. The increased costs of advanced technologies, in addition to the rising cost of tissue retrieval from biobanks, are not to be taken lightly. There is no magic solution to this. Few helpful ideas include obtaining seed funding to generate preliminary data that will enable a larger scale application to standard funding agencies. Seed funding can be obtained from a local institution or a different specialized organization. It can be also in the form of an in-kind contribution, including space, manpower, or the free use of a platform.

In addition, it can be challenging to extract meaningful information from large, multilevel data. Establishing successful national and international collaborations is key for high-yield research. Careful interpretation of data

is needed, taking into account the heterogeneity of data obtained from different tissues, biologic fluids, cell lines, different tumor subtypes, stages, and grades; and there should be careful consideration of intratumor heterogeneity. Other technical issues to be considered include platform variations, the method of specimen collection and storage, and experimental conditions.[7]

Another important challenge for involving pathologists in research and molecular testing is that many are not familiar with such skills and techniques, which can help them to pursue successful research. To address this problem, we could start with better selection of the candidate to get into the pathology residency program. Having a molecular biology background should be an asset to get into such unique training program. Obtaining knowledge about the morphologic features of the disease is at your fingertips because of the availability of many publically available databases; whereas understanding the molecular basis of the disease, which is essential for solving the mystery of morphologic features, needs a special talent. Candidates with a strong molecular biology background can be positive additions to residency programs to meet this growing and expanding role of pathologists.

Including molecular pathology rotations as a mandatory part of the residency training program is key for better preparation of pathology residents to meet this increasing role of molecular testing in patient care and management. In addition, providing specific training courses in molecular testing for pathologists and pathology residents will definitely help them to be in close touch with this growing field.

CONCLUSION

A successful research project is a multistep process that includes discovery, validation, and then translation to the bedside, which involves standardization, among other steps.[60,61] Although research in pathology may seem like an uphill road with significant challenges, it is and will remain an exciting part of our profession. Those who have taken this path definitely acknowledge the excitement of new discoveries that will add significantly to the health of our patients and community. Being an academic pathologist is not a simple decision; it requires endurance and learning from failures and successes.

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