The Challenges and Opportunities of Translational Pathology

Lanjing Zhang[1,2,3,4,*]

[1]Department of Pathology, Princeton Medical Center, Plainsboro, NJ, USA

[2]Department of Biological Sciences, Rutgers University Newark, NJ, USA

[3]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA

[4]Department of Chemical Biology, Rutgers Ernest Mario School of Pharmacy, Piscataway, NJ, USA

Abstract

Translational pathology has not caught up with the quality and quantity of translational medicine. Thus, challenges and opportunities related to translational pathology are discussed here. Pathologists should actively participate in reverse translational research that seeks mechanistic insights to explain clinical findings and/or solve clinical problems. Challenges in translational pathology include ambiguity in defining translational pathology, pathologists' mindsets about translational research, lack of sufficient workforce and immature publication outlets. However, with collective wisdom and support of various stakeholders, we can expand the pool of pathologist scientists, build a translational pathology community and drive innovations in medicine through computational, molecular genetic/genomic and digital pathology approaches.

Keywords

Translational medicine; Translational pathology; Omics; clinical and translational research award

Introduction

The term translational medicine or research was not widely used till early 2000s.[1] Its early use coincided with the model changes in academic health centers and shifts in funding priorities at the National Institutes of Health (NIH) in the USA.[2] At the time, new clinical translational science centers/awards (CTSCs/CTSAs) were established to replace the nearly 40-year-old general clinical research centers (also known as GCRC). The goal of the NIH at the time was to accelerate translating basic discoveries to clinical trials and eventually

*Correspondence to: Lanjing Zhang, Department of Pathology, Princeton Medical Center, 1 Plainsboro Rd., Plainsboro, NJ 08563, USA. Tel: +1-609-853-6833, Fax: +1-609-853-6841, lanjing.zhang@rutgers.edu.

clinical practice. Two bottlenecks of the translation process were identified, which included the link between basic research and clinical trials and the link between clinical trials and clinical practice.[2] Subsequently, bench-side to bed-side translational research was named type 1 translational research, with the latter named type 2 translational research.[3,4] Since that time, the concept of reverse translational research has emerged and focuses on translating bed-side findings into bench-side mechanistic studies.[5] Examples of this include repurposing drugs, patient-driven rapid translation, studies of drug failure and embracing variations in human responses to drugs.[5] Although translational research at large has increased exponentially in size and quality, and continues to do so, translational pathology has not yet caught up with the quality and quantity of translational medicine. Thus, this paper discusses challenges and opportunities that may propel future pathologists and pathology investigators to more focus on this largely understudied area.

Journals in translational research

Forty-five journals with "translational" in the title were identified in the Journal Citation Report® database in January 2022.[6] Among them, 35 were also indexed in the Scientific Citation Index Expanded (SCI-E) with accompanying data regarding the journals' annual citations and Journal Impact Factors® (JIF). This citation data shows that from inception of the translational research concept in early 2000s, the number of "translational" journals has expanded significantly and they have enjoyed rapid growth in their JIF and annual citations (Fig. 1). Strikingly, 8 (42%) of the 19 journals earned their JIF in 2016 or later, suggesting continued and increased interest in translational research. The leading journals ranked by JIF were *Sci Transl Med, Clin Transl Med* and *Trans Res*, while those by annual citations were *Sci Transl Med, Trans Psych* and *J Transl Med.* However, no journals were dedicated to translational pathology or translational research specifically concerning pathology. This finding is very intriguing because it provides pathologists and pathology investigators with new publication opportunities and represents a unique need of publication platform for translational pathology. Therefore, *J Clin Transl Pathol* may help meet the need for a dedicated translational pathology platform. The exponential growth of other translational journals suggests that the new journal will also thrive in the near future, but its success will depend on support from various stakeholders and the team of authors, reviewers, editors and editorial staff. Several non-exclusive opportunities and challenges in translational pathology are detailed below for readers' consideration and to drive further discussion.

Opportunities in translational pathology

There are four primary opportunities in translational pathology, namely reverse translational research, molecular genetic pathology, digital pathology, and machine learning and pathology-related omic data.

Pathologists are always at the intersection of bench-side and bed-side research. They deal with data, including clinical and histological data, on a daily basis. Thus, they can and should bridge the bench-side and bed-side research easily through their ability to provide insights on laboratory tests, molecular genetic diagnostics and histological observations. This is particularly true for reverse translational research because of three main reasons.

First, laboratory tests/data are mostly biochemical in nature. Second, molecular genetic diagnostics provide both molecular and genetic insights for pathogenesis and therapeutics. Finally, histopathological terms by themselves are mostly based on pathogenesis. These data and insights are novel and only available to pathologists. Therefore, if properly equipped, all academic pathology departments are uniquely positioned to carry out reverse translational research. Collaborations with basic scientists in pathology or other departments will nonetheless be required to rigorously design and carry out mechanistic studies driven by pathological observations.

Molecular genetic pathology has advanced significantly in the past decades. An increasing number of new disease entities are now based on molecular genetic alterations. This is particularly true in hematological, bone and soft tissue and urological pathology.[7-9] For example, fumarate hydratase–deficient renal cell carcinoma and microphthalmia transcription factor (MiTF) family translocation–associated renal cell carcinomas are no longer part of type 2 papillary renal cell carcinoma, according to the 2016 edition of the World Health Organization (WHO) genitourinary tumor classifications.[9] A host of emerging molecular genetic/genomic markers have also been discovered and utilized for diagnosing and/or treating sarcomas, lymphomas and leukemias.[7,8] One of the most exciting developments in this area is the discovery of pan-cancer biomarkers (also known as tumor-agnostic markers). These include microsatellite instability , tumor mutation burden and neurotrophic receptor kinase fusions, each of which are rather tumor-specific and have corresponding therapeutics (immunotherapy for the first two markers and NTRK inhibitors for the latter). Thus, one intriguing approach is to investigate signal pathways related to these biomarkers and develop therapies targeted at them individually or in combination. Pathologists may also become more involved in the exploration of future precision medicine and immuno-oncology drug/biomarker combinations, as they are well-placed to lead biomarker-based translational projects, collaborate with and invite clinical colleagues to participate; actively participate in clinical trials and guideline development. In addition, they can build networks with other pathologists and scientists who share the same research and clinical interests in order to share resources, and through these efforts earn trust and recognition from clinical colleagues, who have typically led the development of clinical trials and translational research to date.

The past decades have seen significant growth in the generation of omic data and the number of omic-related studies being undertaken.[10] As a result, a vast amount of data is now available in the public domain. Previous research efforts have shown that machine learning (ML) can help effectively analyze these data and provide unprecedented insights into pathogenesis.[11-13] Of particular interest for the future of translational pathology, it is noteworthy that pathology data remain important contributors to the ML models, while other clinical data may not.[11-13] This combination of computational tools and pathological investigation has led to the development of the field of computational pathology field. The field will thus expand considerably in the near future. Indeed, one review article published in *Lab Invest* on this subject has attracted more than 20,000 views within a year of its publication, and was ranked the journal's top viewed and cited article for the year.[14] As mass cytometry and other high-throughput biological technologies are developed,[15] multi-dimensional *in situ* understanding of disease pathogenesis has become a reality. Proper

interpretation of these data is not possible without input from pathologists, whose medical specialty involves understanding cell-to-cell interaction and cell histology. Next-generation pathologists are therefore encouraged to embrace this opportunity to gain insights from emerging high throughput biological technologies, and synergistically add pathological perspectives.

Whole-slide imaging of glass slides has been implemented in several academic pathology departments in the U.S.A. and will become more prevalent, accessible and affordable in the future.[16] This change in pathology practice will not only influence our daily practice, but represents a totally different perspective on histopathology and pathogenesis at large. The reasons for this include that it will enable us to understand more precisely than before the relationships among various cell types, enable us to quantitatively or semi-quantitatively assess pathological features (e.g., extent of steatosis), and help us gain novel understanding of specific cells' pathological nature using ML tools. Moreover, the development of stain-free or even tissue-free pathological examination will open a new endeavor on how to interpret, analyze and predict cell behavior and the corresponding clinical outcomes of the patients those cells derive from.[17] The success of digital pathology, however, will rely on how willing pathologists' are to adopt these technologies and their ability to nurture favorable attitudes towards its advancement. Digital pathology has the potential to drive innovations in translational pathology and research through its radical deviation from the traditional molecular, genetic and epigenetic doctrine of biology. ML-assisted digital pathology will also enable translational pathologists to look at biological processes through the lens of computational pathobiology and possibly through biophysical perspectives.

Challenges in translational pathology

There are also challenges for translational pathology that are not necessarily unique to pathology, involving collaboration with, and learning from, colleagues in translational medicine, basic sciences and clinical medicine. Instead of acting in a vacuum or limiting research efforts to the familiar environment of the hospital laboratory, adopting a multidisciplinary approach to future research will be likely to yield more meaningful advances. Indeed, multidisciplinary tumor board is a great venue for debate and discussion about current problems in oncology practice. It has thus become an important venue for pathology research ideas. In my view, the major challenges in translational pathology are currently the ambiguity in the definition of translational pathology, the perception of the pathologist's role in translational medicine, workforce issues and a lack of appropriate publication outlets.

The ambiguity in the term translational pathology is likely to derive from the fact that, by its nature, pathology bridges between basic science and clinical practice. Pathological investigators often consider their work to be translational research because they apply basic discoveries to clinical practice (e.g., GATA-3 as a marker for breast and urothelial differentiation).[9] However, it can be argued that human pathological studies mostly, if not exclusively, are works of observational research. Thus, due to the lack of randomization and controls, they are not regarded as producing the same quality of clinical evidence as clinical trials. Nor can they produce the same mechanistic insights as animal or *in vitro* studies,

which are able to investigate the effects of interventions and genetic manipulations. For example, whether and how GATA-3 is involved in the differentiation of breast and urothelial tissue is poorly understood.[9] It is also unclear whether and how GATA-3 can be targeted as a treatment for breast and urothelial cancers. This highlights that pathological investigator must conduct additional studies to truly "translate" their works into clinical practice or from basic sciences.

Another challenge is the mindset of pathologists and their perception of their own role and responsibilities in translational medicine, which are arguably more modest at present than they could be. To address this challenge, pathologists should adopt a new mindset and become more active in translational research, as described above. In addition to applying for extramural research funding, pathologists should also consider cultivating collaborations with oncologists involved in sponsored clinical trials, pursuing pathology/biomarker driven clinical trials, and even engaging directly with trial sponsors as principal investigators.

An important part of the translational research workforce is physician scientists. However, there is currently a nationwide shortage of physician scientists, including pathologist scientists, who are facing ongoing challenges such as financial burdens, low success rates for research funding applications, payment disparity (physicians versus physician scientists) and insufficient institutional support.[18] Pathologist scientists are probably the most severely impacted by these challenges, and urgent action is needed, to assist physician scientists, with specific measures already having been proposed.[18] Indeed, M.D.-Ph.D. graduates mostly chose internal medicine (26.1% of all), pathology (13.6%), or pediatrics (12.9%) for their residency training than other specialties.[19] However, those who chose pathology would report spending less time on research activities than those chose internal medicine or pediatrics.[19] Therefore, pathology residency programs and academic departments must collectively spearhead solutions to increase medical graduates' interest in pathologist scientist track and, more importantly, provide support to help them succeed in developing into the next generation of pathologist scientists. For example, the Johns Hopkins Hospital, Baltimore, MD has reportedly started offering a physician-scientist research track as one of their 6 novel tracks of pathology residency training, with some success.[20]

Many pathologists do not have sufficient training to achieve academic success, contributing to problems with the available pathologist scientist workforce. Many aspects of becoming an independent investigator are rarely taught or mentored during residency or fellowship training, including laboratory management, time management, grantmanship, grant application strategies, network building and work-life balance. Moreover, there is a lack of training for pathologists in how to engage, interact with and obtain funding from the healthcare industry. These issues can leave interested and passionate pathologist scientists burnt out, causing them to leave the field at a young age, possibly even earlier than is the case in other areas of physician science. Problems like these call for actions to effectively help young pathologists fulfill their dreams of becoming physician scientists.

As described above, there are currently no journals dedicated specifically to translational pathology. One of the reasons for this may be the lack of a clear definition of translational pathology, as described earlier. Moreover, many journals actually focus on pathogenesis,

but considers their publications as translational. Furthermore, pathology is a relatively small medical specialty, as can be seen by the fact that JIFs of leading pathology journals are lower than those of other medical specialties (e.g., internal medicine, cardiology and oncology). Thus, it is likely to be more difficult to attract articles and establish a journal in translational pathology than other specialties. Finally, many scholars and editors are not convinced of the need or importance of translational pathology. It is noteworthy that the *Journal of Pathology, American Journal of Pathology, Laboratory Investigation* and *Modern Pathology* all have published works in translational pathology, while their main focus remains basic science. The launch of *J Clin Transl Pathol* will in my view provide a welcome niche for translational pathologists and nurture pathologists and pathological investigators interested in this developing field. It is possible that additional journals may be launched that cover translational pathology in the future.

Conclusions

Pathologists not only play a pivotal role in patient care, but serve as a driving force to bridge basic science and clinical practice. We will certainly contribute to type 1 translational research (bedside to clinical trials) and type 2 translational research (implementing research to clinical practice). More importantly, we can and should actively participate in reverse translational research that seeks mechanistic insights to explain clinical findings and/or solve clinical problems. Reverse translational research and pathology can efficiently and effectively transform how we understand pathogenesis and therefore how we practice medicine. We should be aware of the challenges involved in translational pathology, including ambiguity in defining what translational pathology is, the perception of the pathologist's role in translational medicine, the lack of sufficient workforce and immature publication outlets. However, through sharing our collective wisdom and obtaining support from various stakeholders we can expand the pool of pathologist scientists, successfully build a translational pathology community, and drive innovations in medicine through the use of ML, molecular genetic/genomic approaches and digital pathology.

Funding

Abbreviations:

CTSCs/As	Clinical and translational science centers/awards
JIF	Journal Impact Factors®
NIH	National Institutes of Health
MiTF	Microphthalmia Transcription Factor
ML	Machine learning
SCI-E	Scientific Citation Index Expanded

WHO   World Health Organization

References

[1]. Marincola FM. Translational Medicine: A two-way road. J Transl Med 2003; 1(1):1. doi:10.1186/1479-5876-1-1. [PubMed: 14527344]

[2]. Crowley WF Jr, Gusella JF. Changing models of biomedical research. Sci Transl Med 2009;1(1):1cm1. doi:10.1126/scitranslmed.3000124.

[3]. Tuot DS, Diamantidis CJ, Corbett CF, Boulware LE, Fox CH, Harwood DH, et al. The last mile: translational research to improve CKD outcomes. Clin J Am Soc Nephrol 2014;9(10):1802–1805. doi:10.2215/CJN.04310514. [PubMed: 24970870]

[4]. Tuttle KR, Tuot DS, Corbett CL, Setter SM, Powe NR. Type 2 translational research for CKD. Clin J Am Soc Nephrol 2013;8(10):1829–1838. doi:10.2215/CJN.00130113. [PubMed: 23620444]

[5]. Shakhnovich V. It's Time to Reverse our Thinking: The Reverse Translation Research Paradigm. Clin Transl Sci 2018;11(2):98–99. doi:10.1111/cts.12538. [PubMed: 29423973]

[6]. Journal Impact Factor, Journal Citation Reports Science Edition. Clarivate Analytics; 2021. Available from: https://clarivate.com/webofsciencegroup/solutions/journal-citation-reports/. Accessed January 15, 2022.

[7]. Wei S, Siegal GP. Small Round Cell Tumors of Soft Tissue and Bone. Arch Pathol Lab Med 2022;146(1):47–59. doi:10.5858/arpa.2020-0773-RA. [PubMed: 33635948]

[8]. Zhang W, Yao J, Zhong M, Zhang Y, Guo X, Wang HY. A Brief Overview and Update on Major Molecular Genomic Alterations in Solid, Bone and Soft Tissue Tumors, and Hematopoietic As Well As Lymphoid Malignancies. Arch Pathol Lab Med 2021;145(11):1358–1366. doi:10.5858/arpa.2021-0077-RA. [PubMed: 34270703]

[9]. Jia L, Deng FM, Kong MX, Wu CL, Yang XJ. Common Diagnostic Challenges and Pitfalls in Genitourinary Organs, With Emphasis on Immunohistochemical and Molecular Updates. Arch Pathol Lab Med 2021;145(11):1387–1404. doi:10.5858/arpa.2021-0107-RA. [PubMed: 34673910]

[10]. Liu DD, Zhang L. Trends in the characteristics of human functional genomic data on the gene expression omnibus, 2001-2017. Lab Invest 2019;99(1):118–127. doi:10.1038/s41374-018-0125-5. [PubMed: 30206311]

[11]. Feng CH, Disis ML, Cheng C, Zhang L. Multimetric feature selection for analyzing multicategory outcomes of colorectal cancer: random forest and multinomial logistic regression models. Lab Invest 2021. doi:10.1038/s41374-021-00662-x.

[12]. Deng F, Huang J, Yuan X, Cheng C, Zhang L. Performance and efficiency of machine learning algorithms for analyzing rectangular biomedical data. Lab Invest 2021;101(4):430–441. doi:10.1038/s41374-020-00525-x. [PubMed: 33574440]

[13]. Wang J, Deng F, Zeng F, Shanahan AJ, Li WV, Zhang L. Predicting long-term multicategory cause of death in patients with prostate cancer: random forest versus multinomial model. Am J Cancer Res 2020;10(5):1344–1355. [PubMed: 32509383]

[14]. Cui M, Zhang DY. Artificial intelligence and computational pathology. Lab Invest 2021;101(4):412–422. doi:10.1038/s41374-020-00514-0. [PubMed: 33454724]

[15]. Spitzer MH, Nolan GP. Mass Cytometry: Single Cells, Many Features. Cell 2016;165(4):780–791. doi:10.1016/j.cell.2016.04.019. [PubMed: 27153492]

[16]. Aeffner F, Zarella MD, Buchbinder N, Bui MM, Goodman MR, Hartman DJ, et al. Introduction to Digital Image Analysis in Whole-slide Imaging: A White Paper from the Digital Pathology Association. J Pathol Inform 2019;10:9. doi:10.4103/jpi.jpi_82_18. [PubMed: 30984469]

[17]. Neary-Zajiczek L, Essmann C, Rau A, Bano S, Clancy N, Jansen M, et al. Stainfree identification of tissue pathology using a generative adversarial network to infer nanomechanical signatures. Nanoscale Adv 2021;3(22):6403–6414. doi:10.1039/d1na00527h. [PubMed: 34913024]

[18]. Jain MK, Cheung VG, Utz PJ, Kobilka BK, Yamada T, Lefkowitz R. Saving the Endangered Physician-Scientist - A Plan for Accelerating Medical Breakthroughs. N Engl J Med 2019;381(5):399–402. doi:10.1056/NEJMp1904482. [PubMed: 31365796]

[19]. Brass LF, Akabas MH. The national MD-PhD program outcomes study: Relationships between medical specialty, training duration, research effort, and career paths. JCI Insight 2019;4(19):133009. doi:10.1172/jci.insight.133009. [PubMed: 31578310]

[20]. Wake LM, Allison DB, Ware AD, Hooper JE, Baras AS, Bloch EM, et al. Pathology Residency Program Special Expertise Tracks Meet the Needs of an Evolving Field. Acad Pathol 2021;8:23742895211037034. doi:10.1177/23742895211037034. [PubMed: 34485688]
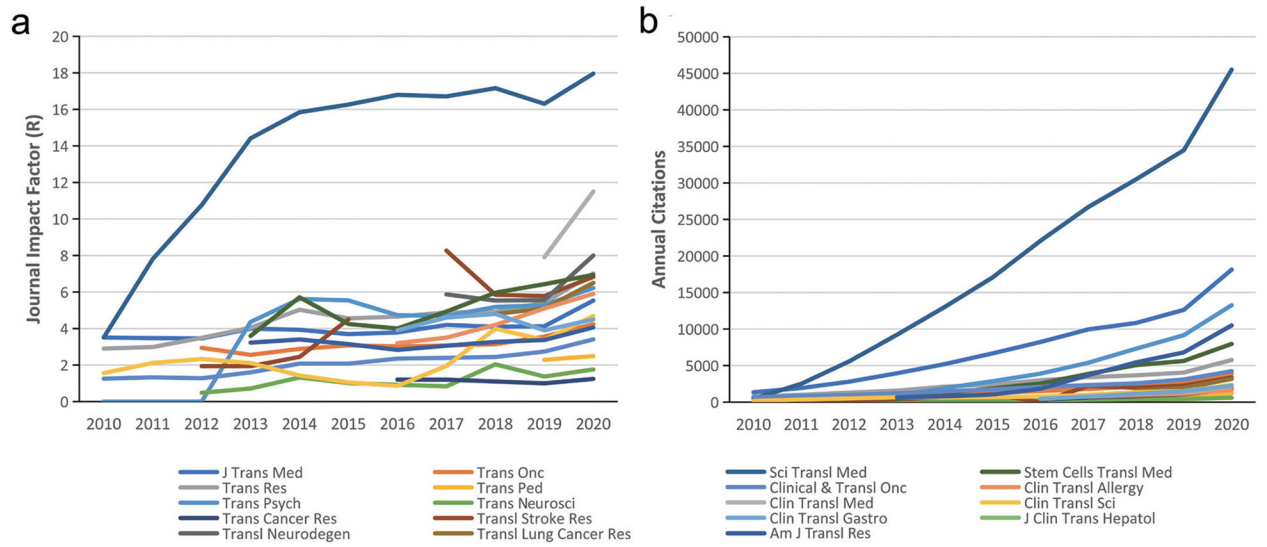
Fig. 1. Changes in Journal Impact Factors and citations of selected journals focused on translational research, 2010–2022.
(a) The Journal Impact Factor® increased in more than half of the 19 selected journals focused on translational research. (b) Annual citations increased in all of the selected journals.