**A clinical pathologist on every paper… the importance of pathologists in translational medical research**

**Precious Jolugbo**

**3rd Year Medical Student**

**University of Leeds**

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**Introduction**

From bench to bedside, from bedside to back to bench; translational research is a bridge between basic science and clinical applications (1). It was surprising to read that it takes an average of 17 years between scientific knowledge and implementation into clinical practice (2). This is complicated by roadblocks that either prevents basic research from being tested in a clinical setting, or proven intervention from becoming standard practice. Additionally, cultural differences between basic scientists and clinical researchers also play a role in the prolonged period between discovery and utilization (3). However, as commonly known, pathology is the “bridge between basic science research and clinical practice”. There are several essential steps that needs to be fulfilled for the success of a translational research project. This includes but not limited to research generation, appropriate specimen handling and reporting, and introduction of new therapies into routine practice. Pathologists play a key role in each of these steps due to their understanding of basic biology and disease pathogenesis (4).

This essay seeks to discuss the importance of pathologists in translational medical research by disseminating literatures on where translational research meets pathology.

**An overview of translation research**

Translational medical research (also known as “translational research”) has been defined as the interpretation of scientific discoveries made in preclinical in vitro and in vivo experiments into clinical interventions aimed at improving human health (1). Drugs such as bevacizumab (Avastin®) and trastuzumab (Herceptin®) are both examples of translational researchers transforming molecular expertise on specific cancer cells into efficient, tailored therapies (5, 6). To improve health, scientific findings must be converted into practical procedures; those findings begin at the “bench” with basic scientists investigating the disease at a molecular or cellular level before it advances to the clinical level of the “bedside” of the patient (7). Surprisingly, it takes an average of 17 years between scientific discovery and implementation into clinical practice (2). Translational research has, however, proven to be a powerful tool that fuels the process of clinical research as it seeks to bridge the gap between knowledge acquired at the laboratory bench and its application on the clinical bedside.

**History of translational research**

The term “translational research” was established as a Medical Subject Headings (MeSH) term in 2009 (8). However, the concept of “bench-bedside interface” was introduced by the Editor of the New Journal of Medicine in 1968 to describe two papers that demonstrated chronic granulomatous disease of childhood could occur in females (9). Although the term “translational research” first emerged in biomedical journals around 1993, all early publications using the term deal with cancer research (10). “Translational research” was used at this time for research into the identification and evaluation of biomarkers as possible alternatives for cancer prevention research (11). The use of biomarkers was argued to have a significant potential to speed up and reduce the costs of implementing effective cancer prevention strategies.

A pivotal moment in translational research occurred when the American National Institutes of Health (NIH) proposed the Roadmap for Medical Research in 2003 (12). This map aimed to address scientific gaps that hindered the translation of scientific discoveries into improvements in health. This resulted in an exponential increase in translational research in the past two decades (10). To encourage advancements of translational research, numerous large-scale international symposia and conferences have been organised all over the world. At the same time, variety of key journals opened special columns for translational research. Moreover, several organisations have established awards and grants to support the growing scholars involved in translational research. Among these awards are the Clinical and Translational Science Awards (CTSAs) launched by the NIH in 2006 to identify new ways to collectively accelerate the translation of discoveries from the bench to bedside and into communities (13). This continuum can be divided into different phases (*Figure 1)*.



***Figure 1****. Operational phases of translational research (T0-T4). Taken from University of Stanford, Department of Psychiatry and Behavioural Sciences.* [*https://med.stanford.edu/psychiatry/research.html*](https://med.stanford.edu/psychiatry/research.html)*.*

**Phases in translational research**

Initially, 2 phases in translational research were describe: (i) T1 essential scientific advances used to create new disease therapies (“bench to bedside); (ii) T2 research designed to improve the use of developed treatments in clinical and community settings (“bedside to community)”. The second phase was eventually subdivided to include a total of three phases of translational research. Therefore, the latest T1 model represents basic science to clinical science, T2 clinical science to clinical practice, and T3 involves the application of clinical practice to more widespread health improvements (3, 14).

However, closer inspection shows more complexities and the need for several levels of translation, leading to a five phase (T0-T4) definition for translational research (8, 13). A discovery in a basic science laboratory have to be translated into several animal models, non-primate mammals into non-human primates. After this, under the umbrella of T1 translation, clinical researchers must test the clinical applications under restricted clinical conditions through controlled early-stage clinical trials. T2 translation phase requires knowledge from these experiments to be applied more widely through phase 3 trials. Once demonstrated, clinicians have to identify ways to apply these findings to regular patient care (T3). T4 focuses on moving scientific knowledge into the public sector.

**Overcoming challenges faced in translational research**

Translational research comes with its own set of challenges; it includes facets of both basic sciences and clinical research and requires expertise and resources that are not easily accessible in a basic laboratory or an exclusively clinical environment (3). One of the key barriers that have been frequently debated includes the cultural differences between basic science and clinicians and lack of established mechanisms for people from across disciplines to work effectively together (15). Cultural differences between the two groups of researches are generally attributed to lack of communication, differences in education and training, and separate priorities and reward mechanisms (3). On the other hand, mechanisms such as lack of properly trained workforce, lack of appropriate venues for interdisciplinary discussions, and academic disincentives to participation in team research contributes to the barriers (15). Scientists who are interested in understanding human biology and pathology, and clinicians able to understand the methodologies and significance of laboratory findings are the critical components of this workforce. To overcome this barrier, clinicians should be exposed to laboratory research during training, and likewise, basic scientists should be exposed to the clinical setting (3). The integration of these two domains is important for the advancement of translational research.

Interdisciplinary collaborations between basic scientists and clinicians is one of the driving forces of translational research. It is inherently difficult to progress far in translational research without the working in close collaboration with medical fields such as clinical pathologists, medical technologists, hospital administrators and referring clinicians. A quote taken from an editorial piece by Hait (2005) reads “clinicians know all the problems, but none of the solutions; scientists know all the solutions, but none of the problems” (15). Even though this concept has evolved today than it was over 20 years ago, the gap remains significant. However, a branch of medical science that acts a bridge between basic science research and clinical practice is pathology (16).

**What is pathology?**

Pathology is a field of medical science that deals with the study of disease and this use of this information to enhance clinical diagnosis and patient care (17). Pathologists are the custodians of essential biological materials, ranging from tissues to a variety of biologic fluids such as blood, urine and cerebrospinal fluid (16). The two main subdisciplines of pathology are clinical pathology and anatomical pathology; these are later subdivided to cover all the main laboratory disciplines including histochemistry, immunology, molecular diagnosis, clinical biochemistry and laboratory histopathology (18).

Clinical pathology, also known as laboratory medicine, uses laboratory analysis of biologic fluids to diagnose diseases. Its main subdivisions include chemical pathology, haematology and immunology (19). The role of the clinical pathologist is heterogenous, but the essence of the position is to oversee laboratory testing processes and discuss how the findings might influence patient management (20). Clinical laboratory tests allow clinicians and other healthcare professionals to make appropriate evidence-based treatment recommendations for their patients. The process starts with the clinical pathologist designing and validating a laboratory test that answers a clinical question posed by the primary clinician. Following the testing process, the clinical pathologist assists the clinician in evaluating the results, and sometimes providing a recommendation for a future plan of action; this is mostly because clinicians run the risk of insufficient follow-up measures such as further testing if they are unable to properly interpret the test results (18).

Anatomical pathology is somewhat different from clinical pathology. It is a branch of medicine that focuses on examination of tissues and/or organs to provide a diagnosis based on gross, microscopic or molecular examination (21). Anatomical pathology plays a significant role in the diagnosis and management of diseases through its ability to identify abnormalities in tissues and organs. There are two main subdivisions within anatomical pathology: cytopathology and histopathology (22). Cytopathology is the study of disease at a cellular level using a light microscope. A cervical cytology, or commonly known as a Pap smear, is a common cytology tests that checks whether cells in the cervix are abnormal. In contrast, histopathology is the microscopic examination of whole human tissue from biopsy or surgery. Staining of processed histology slides using pigments, or even antibodies (immunohistochemistry) can help identify categories of cells.

Pathology plays a major role in modern medicine. Surveys on the importance of medical laboratory testing in Germany and the USA showed that 60-70% of clinical decisions by specialist clinicians were influenced by laboratory test findings, both in hospitals and outside (23, 24). In addition to their diagnostic skills, pathologists are also needed to aid clinical decision-making, whether by providing predictive biomarkers or identifying potential therapies based on knowledge of the disease pathogenesis (16). Advancements in diagnostic techniques such as polymerase chain reaction and DNA microarrays has now allowed for diagnostic characterization of disease processes at the molecular level (25).

**The role of a pathologist in translational research**

Research activity is the core essence of pathology. Improving understanding of the pathogenesis of diseases translates into improved patient care (16). The integration of pathology into translational research is accomplished in multiple ways, such as the selection of optimal tissue for molecular analysis, and analyses of similarities and differences between human samples and tissue from model systems (16, 17). There are major challenges in translational researcher that can be resolved by a pathologist. One of the challenges is the sampling of obtained tissue specimen for histology and research (17). A pathologist is able to perform gross inspection, processing and sampling extracted tissue for histological examination and potential molecular testing (26). Precise sampling is vital for accurate clinical diagnosis as the heterogeneity of tissues and organs with distinct areas of cancer, necrosis and inflammation can introduce errors. Another challenge is choosing the most appropriate preservation technique for tissue specimen (17). The usefulness of a specimen for histological diagnosis is determined by its preservation. The two main preservation methods are chemical fixation with formalin solution followed by paraffin wax embedding and, snap freezing. The formalin-fixed, paraffin-embedded tissue samples is then microscopically examined to produce thin sections that will subsequently be stained with haematoxylin and eosin (H&E) (27). The clinical diagnostic process in pathology puts pathologists in a unique and privilege position to enable translational cancer research. For example, pathology plays a significant role in the identification and clinical classification of tumours. The discovery and development of targeted therapy of gastrointestinal stromal tumours (GIST) is an example of the use molecular biology in development of specific therapy. Pathologists first recognized a different type of spindle cell tumour in the gastrointestinal tract (28). Biomedical researchers then discovered that majority of these mutations harbour in the c-kit receptors that allow ligand-independent kinase activation. As a result of this discovery, pathologists are now able to utilize immunostaining to characterize c-kit expression in cases of GIST. This aids in the prediction of clinical outcome and supports oncologist in employing targeted therapy (28).

*Biomarkers*

One prime example of translational research in human disease is the study of cancer therapy. A recent review by Provenzano et al provided a comprehensive detail of the importance of pathologists in research (4). Pathologists, in particular histopathologists, have a comprehensive understanding of tumour genetics and disease mechanisms. Therefore, the involvement of pathologists across all stages of research is important, especially in the delivery, interpretation and dissemination of results. Furthermore, the use of morphological subtyping and assessment of biomarkers using immunohistochemistry and molecular techniques equips pathologist with the unique ability to guide correct patient selection. This is especially critical, as unresponsiveness to treatment remains a major concern in the treatment of cancer (29). Therefore, it is highly crucial to use genetic approaches to identify biomarkers which can predict responsiveness to translational cancer therapies. A cancer biomarker refers to a substance or process that suggests that cancer is present in the body (30). It could either be a specific response in the body to the presence of cancer, or a molecule secreted by the malignancy itself. From a clinical point of view, a cancer biomarker may evaluate and measure the risk of developing cancer in a specific tissue or, the risk of cancer progression, or potential response to therapy (31). Most cancer biomarkers are measured either in the blood or in the tumour (30). To optimise usefulness and reduce screening cost, a biomarker should be measured in a body fluid that can be collected using minimally invasive techniques such as blood, urine, sputum or stool. Cancer biomarkers can be categorised into classes based on their clinical application (31). Diagnostic biomarker identifies whether a patient has a specific disease condition. Examples of diagnostic biomarkers for cancers include prostate-specific antigen or PSA (blood based) for prostate cancer, methylated vimentin (stool-based) for colorectal cancer and DNA FISH assays (urine based) for bladder cancer (30). Predictive biomarkers predict response to specific clinical therapies. For example, activation of *HER2* predicts response to trastuzumab in breast cancer (32). On the other hand, prognostic biomarkers aim to inform clinicians about the risk of clinical outcomes such as cancer recurrence or disease progression in the future. The 21-gene recurrence score is a prognostic cancer biomarker which predicts breast cancer and overall survival in node-negative tamoxifen-treated breast cancer (33).

*Biobanking*

Pathologists are key in the biobanking pathway by collecting relevant fresh, frozen and fixed samples for various translation techniques (4). This includes nucleic acid extraction, cell culture and genetic testing. The need for a sustainable supply of well-documented and high-quality human tissue samples is fundamental to human tissue samples (34). Even though *in vivo* and *in vitro* models provide basic scientists an understanding of the molecular structure of cancer phenotype, without testing and validating the same mechanisms in human tissues, the value of such research will be undermined (35). Biobanks, also referred to as tissue banks, is a collection of biological samples for use in research (36). There are several types of biobanks; disease-specific biobanks are collections of tissue materials from patients suffering from a specific disease. Discovery of biomarkers and tailored drug development have been greatly impacted by disease-specific biobanks (37). On the other hand, population-based biobanks gather normal tissue samples from volunteers, mainly to research the correlations of different environmental or genetic factors for diseases in large and diverse populations (37). Biobanks greatly impacts translational research, as it provides a database of a wide variety of tumour types and normal tissue, thereby allowing the research teams to access high quality samples (34). The sustainable supply of high-quality biologic specimens therefore decreases experimental bias and adds value to the outcomes of clinical research. Between 2006 to 2010, approximately 500,00 people recruited has their blood, urine and saliva samples collected alongside their detailed health information into the UK biobank project. Already more than 140 project applications from researchers have been submitted for the utilization of this resource (34). The impact of biobank infrastructure is phenomenal. The availability of clinical bio-specimens for validation and optimization of new assays is one of the potential obstacles for bio-markers development (38). It is important to note that variations in the collection and storage capabilities of different biomarkers is one of the major causes of errors in biomarker discovery and translational research. Therefore, the existence of a large single source of biologic materials therefore ensures optimal quality for the underlying research (34).

**Concluding remarks**

Pathology plays a significant role in the success translational research. Pathologists are able to provide insights into sampling of tissue specimens, biomarker discoveries, and support future studies through their involvement in biobanks which all drives translational medical research. Even though translational research comes with its own sets of challenges, adequate steps taken to integrate pathology into translational research during training will surely reap a tremendous benefit.

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