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Pathologists in Molecular-Targeted Drug Discovery and Development

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Abstract

Pathologists, embracing the expertise in both clinical health care and scientific research system, play an increasing role in molecular-targeted drug discovery and development. In the drug discovery stage, pathologists investigate the pathophysiological mechanisms, identify the potential molecular targets, and lead the translational research for moving these scientific findings to the clinical application. In the pre-clinical trials, pathologists help optimizing the study protocol and participate in the pharmacology and toxicology assays, contributing to moving the drug development forward to the clinical trials. During clinical trials stage, pathologists assist in clinical study protocol design, patient selection and enrollment, sample collection, as well as study endpoint analysis, etc. Overall, pathologists are very important to secure the molecular-targeted drug discovery and development by integrating the histology results and the molecular information. In the future, pathologists are obligated to get ready for their new roles and expand their new responsibilities in molecular-targeted drug discovery and development.

The function of pathologists in the pharmacological industry has been overlooked for a long time. Over the past decades, increasing pathologists are being hired by pharmaceutical companies, majorly because of the rapidly expanding molecular medicine and the increasing recognition of having the pathologists' input in the molecular-targeted drug discovery and development. The pathologists function in the areas of basic research to identify the molecular targets and in the translational medicine for drug discovery by targeting those identified molecular. Additionally, because of their unique expertise in both clinical health care and scientific research system, pathologists are essential in the preclinical and clinical trials for drug development.

Pathologists in Molecular-Targeted Drug Discovery

In the stage of drug discovery, as most basic science researchers, pathologists investigate the pathophysiological mechanisms by performing experiments based on cell line or xenograft models. With their knowledge and expertise in the disease molecular, they identify new molecular biomarkers and assess the effectiveness of the novel compound candidates by targeting those biomarkers. There are a lot of molecular technologies, such as quantitative polymerase chain reaction (qPCR), sequencing of DNA, in situ hybridization, molecular high throughput and profiling, and antibody based immune-fluorescence tissue assays, etc. Plenty of examples have been observed for the molecular targets being applied successfully in the clinics for molecular-targeted therapy or prognosis prediction. This is especially apparent in the field of oncology. For example, in solid tumors, the identification of erbB2/HER2 amplification in breast and gastroesophageal cancer led to the development of anti-HER2 therapeutics (trastuzumab and lapatinib), which inhibits the HER2 protein specifically [1,2]. Additional examples include c-kit and PDGFR alpha mutations in gastrointestinal stromal tumors [3], tyrosine kinase mutations of the EGFR gene in lung cancer [4,5], mutations in the BRAF gene in melanoma [6], or the EML-ALK gene rearrangement in lung cancer [7], all of which have the potential to render tumors extraordinarily sensitive to the specific inhibitors. Part of the currently confirmed gene and protein targets is presented in Table 1. Apparently, pathologists have contributed profound knowledge to the understanding of these molecular alterations in different diseases in recent years.

Pathologists are not only involved in basic science research, they are actually more and more welcomed to join in a translational group. This can be due to their unique advantages of perspective on disease processes and their access to tissue specimens from the operation room in clinical patient care settings. They lead the above identified new targets, especially in tissue specimens, to diagnostic assays development and targeted molecular therapeutics. By doing this, pathologist integrates the advancements in molecular biology with clinical trials. They convey the basic science discoveries and knowledge into clinical applications and move the findings quickly from bench to bedside [8-11]. Clearly, pathologists bridge the gap between scientific research and clinical drug development. Table 1 lists the recently identified molecular targets which have been successfully moved to clinical molecular-targeted drug therapy.

Pathologists in Pre-clinical and Clinical Trialsof Targeted Drug Development

To launch a new pharmaceutical, the therapeutic efficacy and safety

Table 1: List of the identified molecular targets being moved to clinical drug therapy.

Type of cancer	Molecular biomarkers	Molecular targets	Drug
Breast cancer	Estrogen and progesterone receptors (ER/PR) on IHC	ER	Tamoxifen
Breast cancer	Human epidermal growth factor receptor(HER)2on IHC or FISH	VEGF	Trastuzumab
Breast cancer	Vascular endothelial growth factor (VEGF)-A/ VEGFR2 on IHC or FISH	VEGF	Bevacizumab
Lung cancer	Epidermal growth factor receptor(EGFR) mutant	EGFR	Erlotinib, Gefitinib
Melanoma	Protein B-raf (BRAF) mutant	BRAF V600E/K mutant	Vemurafenib
Liver cancer	Alpha-fetoprotein	VEGF	Sorafenib
Metastatic colorectal cancer	Carcinoembryonic antigen (CEA),EGFR, VEGF	VEGF, EGFR	Bevacizumab, Panitumumab, Cetuximab
Pancreatic cancer	CEA, CA19-9	Tyrosine Kinase Inhibitors and target of rapamycin (mTOR) Inhibitors	Sunitinib, Everolimus
Hematological malignancy	BCR/ABL mRNA on peripheral blood or bone marrow aspirate	BCR/ABL tyrosine kinase	Imatinib

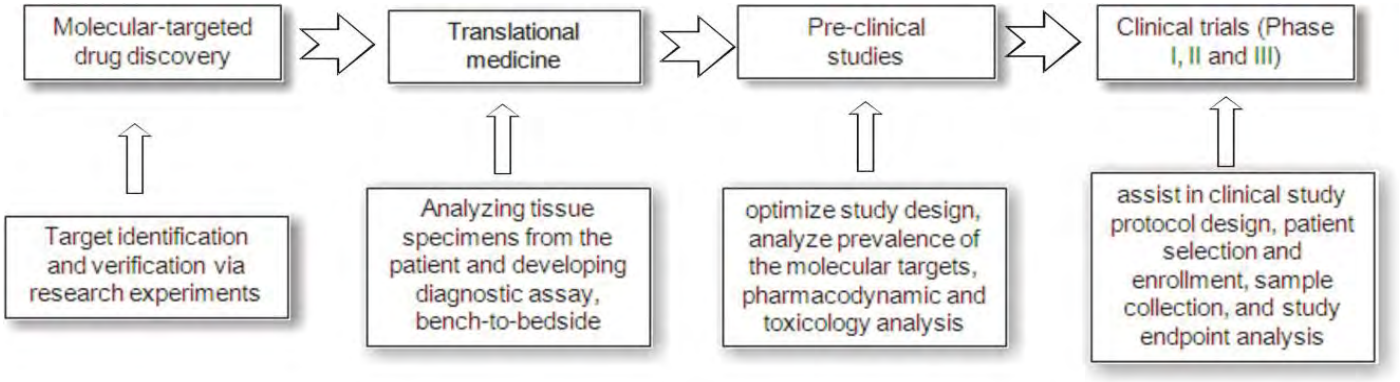

Figure 1: Participation of the pathologist in molecular-targeted drug discovery and development.

has to be secured through the pre-clinical study to clinical trials. Pre-clinical study usually includes pharmacology, pharmacokinetics, and toxicology testing; while clinical trials normally include phase I to III for drug development (Figure 1).Different types of preclinical research may be selected for different products. For all these stages, appropriate anatomical, molecular and chemical pathology analysis is critical for improving drug development, especially molecular-targeted drug development.

Pathologists in Pre-clinical Trials

In preclinical research, pathologists can assist to optimizes study design [12]. Because molecular-targeted therapy works specifically on those defected or mutated biomarkers, careful pathological assessment is essential to characterize and confirm the prevalence of putative drug molecular targets [13, 14]. Additionally, in pre-clinical trials, pathologist also has a key role in the evaluation of pharmaco-dynamic biomarkers [15]. For example, by using *in vitro* human tissue, the phospho-ERK status was evaluated by the pathologists, which provides early pharmaco-dynamic evidence of BRAF-V600 inhibitors [16]. By doing that, the desired biological effects are achieved at the tolerable doses [16]. Clearly, the work of pathologists has been far more than "microscopical analysis" in the pre-clinical trials.

When developing therapeutic molecules, efficacy is nothing without safety. Histopathologists and clinical pathologists play critical roles in the evaluation of toxicology, to predict adverse events before irreversible damage occurs. For the investigation of drug's toxicity, it can be tested both *in vitro* and *in vivo* by analyzing which organs are targeted and whether long-term toxic or carcinogenic effects to the body are existed. As showed in a retrospective study, for 150 chemical compounds, the studies of non-rodents toxicology "predicted" about 63% of toxicities in human, rodents captured about 43%, and both species together predicted about 71% [17]. To achieve this "prediction", pathologists can select the appropriate testing models, evaluate the toxic effects, and eventually help making the ultimate decision of whether a compound can move forward to the clinical. Thereby, with the pathologists' work in toxicology, the safety of the molecular-targeted therapy can be greatly improved.

Pathologists in Clinical Trials for Drug Development

For clinical trials, pathologists can assist in clinical study protocol design, patient selection and enrollment, sample collection, and study endpoint analysis and scoring, etc.

Patient selection and enrollment is one key element for clinical trials, especially for molecular-targeted therapy. Pathologists can design the molecular-based patient selection criteria. They also help to apply these criteria in enrolling the unique group of patients. This consequently leads to a superior responding rate and better clinical outcomes. As suggested in statistics for a given cohort study, a certain intervention results in improved results only in some study samples who possessing a particular biomarker [18]. If this molecular heterogeneity remains unaccounted for, it can make the study power being insufficient [18,19]. The case of HER2-directed antibody trastuzumab is a typical example for illustrating this point. In the patient cohort requiring over-expression of HER2 (IHC score of 2+ or 3+) as inclusion criteria, trastuzumab in addition to chemotherapy leaded to a significantly overall survival benefit (25.1 vs. 20.3 in median survival) [20]. However, without HER2 over-expression being an inclusion criterion, the number of patients to reach a significant survival benefit would be required to be much larger, or even no survival benefit can be observed significantly [21]. Therefore, the pathologists-leaded, targeted-molecular-based patient-selection approach help decreasing the molecular heterogeneity and preventing from the very large sample size for a given cohort.

Sample collection, especially tissue collection, is another critical and very challenging component for different clinical trials. The challenges can be due to the lack of standardization, pre analytic variables, and high cost, etc. In both early and later stages of clinical trials, pathologists contribute their critical expertise such as histopathologic sub classification of the disease, and the feasibility of collecting diversified tissue samples, etc. It is a fact that in large clinical cohort, inadequate or poorly executed sample collection has proven to impact the quality of the data, or even produce disastrous effects. One example is the phase 3 clinical trial for erlotinib. Only 44% had usable slides for immono-histochemistry analysis, with much less usable tissue (31%) for further fluorescence in situ hydridization assessment or sequencing [22]. Therefore, pathologists are indispensible to secure the qualified tissue samples for the downstream analysis.

Pathologists also have a critical role in assessing the study primary endpoint to determine the response of the targeted therapy [23,24]. Different tissues, including peripheral blood mononuclear cells, platelet-rich plasma, skin, and hair, are under investigation as surrogates for tumor tissue, and can be used by pathologists to assess the pharmacodynamic effects of drugs, mainly anticancer agents, in clinical trials. For example, pathologists can assess the therapeutic response in preoperative therapy trials for cancers by using some immediate end points, such as pTNM down-staging, pathologic complete responses, circumferential margin positivity rates or tumor regression grades, and tumor cell density etc. [25,26]. It will be very hard to move the clinical trials forward without the accurate assessment of the histological endpoints by the pathologist.

Future and Perspective

The demand for pathologists is on the rise within pharmaceutical industry due to their expertise in the mechanisms of cellular and tissue response to injury, as well as their critical functions in all stages of the pre-clinical and clinical trials (Figure 1). Pathologists are obligated to integrate the histology results and the molecular diagnostic information to the clinical data so that the patients can get better benefits. In the

future, pathologists will move beyond the realm of diagnosis and mere classification/sub-classification of diseases, and will definitely take the lead in molecular-targeted drug discovery and development.

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