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.

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Molecular biomarkers</th>
<th>Molecular targets</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Estrogen and progesterone receptors (ER/PR) on IHC</td>
<td>ER</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Human epidermal growth factor receptor(HER2) on IHC or FISH</td>
<td>VEGF</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Vascular endothelial growth factor (VEGF)-A/ VEGFR2 on IHC or FISH</td>
<td>VEGF</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Epidermal growth factor receptor(EGFR) mutant</td>
<td>EGFR</td>
<td>Erlotinib, Gefitinib</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Protein B-raf (BRAF) mutant</td>
<td>BRAF V600E/K mutant</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Alpha-fetoprotein</td>
<td>VEGF</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Metastatic colorectal cancer</td>
<td>Carcinoembryonic antigen (CEA),EGFR, VEGF</td>
<td>VEGF, EGFR</td>
<td>Bevacizumab, Panitumumab, Cetuximab</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>CEA, CA19-9</td>
<td>Tyrosine Kinase Inhibitors and target of rapamycin (mTOR) Inhibitors</td>
<td>Sunitinib, Everolimus</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>BCR/ABL mRNA on peripheral blood or bone marrow aspirate</td>
<td>BCR/ABL tyrosine kinase</td>
<td>Imatinib</td>
</tr>
</tbody>
</table>

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Pathologists in Pre-clinical Trials

In preclinical research, pathologists can assist to optimize 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 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.

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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.

References


