



Opinion

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“Old Drug, New Action” in clinical research



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Opinion

Development of new drug is one of the major projects in pharmaceutical companies. Drug development is known to be cost-intensive and despite extensive efforts, but it is easily masked by the screening system for adverse reactions in clinical practice. Additionally, drug development is a long and costly process while the costs increased particularly in late stages of development in clinical studies. The failure of drugs in late development or after approval is a worst-case to companies. Therefore, many pharmaceutical companies follow a “fail early, fail cheap” approach, as described recently [1], bearing the risk of wasting potentially valuable drugs.

In order to have the reliable data, novel methods were developed such as the range from cellular impedance assay, multiple ion channel effect assay, 384-well high throughput tests for interactions with transporter proteins, multi-electrode arrays (MEAs), mitochondrial toxicity testing, to diverse “omics”-technologies and others, as previously introduced in a review article [2]. Moreover, for setting up the ex vivo models of tissues and organs, tissue-derived cells and cell lines were developed to mimic the in vivo screening. The microphysiological system may also create Organs-on-Chips to provide novel ways for assay of pharmacokinetics, pharmacodynamics, and drug-drug and drug-toxicant interactions as described recently [3]. Otherwise, similar to the recent review [4], each individual’s unique genetic makeup assists the understanding of responses to drugs, and genetic analysis has been applied to patient care in numerous areas; such as, genetic analysis of tumors for cancer therapy.

The epigenetic signature reinforced gene expression may open new perspectives for new biomarkers to the risk groups or patients who do not respond to treatment. Also, it may help the stratification of patients within a personalized medicine framework. Genes encoding drug targets or enzymes and transporters that modulate the absorption, distribution, metabolism, and excretion (ADME) of agent(s) are mentioned as the key factors to regulate the drug response and toxicity. But,

many of these genes are regulated by epigenetic factors. The reversibility of DNA and histone modifications, inhibiting the epigenetic machinery has the potential to prevent the epigenetic diseases. Thus, drugs based on these principles, termed epidrugs, have introduced into clinics. In addition to developing biomarkers for analysis of disease progression and treatment response, the understanding of epigenetic processes has been applied to improve the novel epigenetic treatments for cancer and other diseases. Five epidrugs for treating hematological malignancies have been approved [4]. However, most of them required more budgets in advance.

Another strategy for drug discovery is drug repositioning that is also called as new indications for old drugs. The process of finding new actions of the used drugs outside the scope of the original indication is known as drug repositioning. It saves time and budgets to be a better utilization of sources. It reduces developmental risks because the repositioned drug has already passed the screenings of toxicity and other tests. Thus, once the repositioned drugs enter clinical trials, they compete with the general drugs for efficacy, but not the safety. While safety accounts for approximately 30% of the applied drug failures, it is a marked merit for repositioned drugs. Many academics have found promise in drugs that have long been on the market, named generics whose patents have expired. So the repositioned drugs have the same market potential not less than the new drugs. The repositioned drugs that got the good market returns on the investment; the famous examples are sildenafil (Viagra) and thalidomide [5]. Therefore, drug repositioning is believed as a less time consuming and less costly method. However, it needs the assistance of clinical research to confirm the new efficacy and indication(s).

There are many potential drugs that can be developed as repositioning drugs. Such as: Naproxen for Alzheimer’s disease, Statins for autoimmune disease, and Zileuton from asthma for acne, as described previously [5]. Additionally, metformin has been suggested to treat cancer [6]. Most of them were handled by

professional companies in development. Recently, we found that triamterene can block the TGR5 receptor sites [7]. Triamterene (Dyrenium) is a widely used mild diuretic that reduces potassium ion secretion in distal tubular cells [8]. Takeda G-protein-coupled receptor 5 (TGR5), also known as GPR 131 or M-BAR, is specific for binding of bile acid that has been named as G-protein-coupled bile acid receptor 1 (GPBAR1) in general. TGR5 is expressed around the body. However, the pleiotropic effects of TGR5 activation may result in some adverse reactions, such as pruritus [9] and inappropriate gallbladder filling [10]. Moreover, TGR5 activation may promote cholangiocyte proliferation to increase the risk of cholangiocarcinoma [11]. Recently, TGR5 was shown to be expressed in human gastric cancer [12], although this finding was controversial compared to the data from a previous report [13]. Thus, questions remain regarding the essential role of TGR5 inhibition in clinical applications. It also means that triamterene is suitable to develop in clinical research.

Conclusion

There is no doubt that drug repositioning or “Old Drug, New Action” may provide affordable and new treatment options for both common and rare diseases in the future. “What I like about drug repurposing is that it can solve two issues: improved health-care impact and reduced health-care cost,” says Bruce Bloom. “That’s a big driver for us,” as described recently [14].

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