

TECHNICAL INSIGHTS

DRUG DISCOVERY

TECHNOLOGY ALERT



MICRORNA-BASED DRUG TOXICITY SCREENING FOR THE FIRST TIME

Drug toxicity is one of the major challenges during the drug development process, with 90% failing during development, and also contributes to significant failure rates of clinical trials. Frequent drug failures tend to shoot up drug development costs and also the selling price of the drug once it reaches the market. Added to this, different patients respond differently to drugs, and those patients suffering adverse side-effects of these drugs may end up as dropouts of the trial process, which in turn may complicate the process of meeting the desired clinical end points. Although there are tests used for drug metabolism and toxicity testing, most of them rely on the use of tissue slices. Obtaining them is quite laborious and time-consuming. What is required at this point is a diagnostic test that could be used to study drug toxicity on a molecular level rather than at the tissue level, to accurately and efficiently predict drug response and toxicity in a patient. This would allow researchers to carefully select patients who respond well with the drug compound and also proceed toward successful completion of the trial process.

Recently, small regulatory, noncoding RNAs called microRNA (miRNA) have shown to be useful as biomarkers of a particular disease and that the levels of specific circulating miRNA species may also be useful in detection and monitoring of not only the disease development pathways, but also detect changes that are associated with drug-induced tissue injuries.

A UK-based firm called Systemic has recently launched a drug toxicity screening service into the market, which relies on miRNA profiling to closely monitor potential toxicity of a drug compound during the earlier phases of drug development. It can be used for predictive toxicology as well as investigational toxicity. The service has also been shown to allow assessment of those pathways that may actually lead to development of drug toxicity during later clinical use. The uniqueness of the service lies in the fact that it gives not just a yes/no answer, but also provides critical information for scientists. For example, SistemTOX provides content, context and throughput, all in just one assay. Commenting on the future potential of this innovation, Dr. Verna McErlane, Director of Commercial Operations, International comments told *Technical Insights*, "We certainly envisage that this enabling platform which combines the

selectivity and sensitivity of miRNA, could potentially provide a new "gold-standard" in pre-clinical drug safety testing in the future".

Incidentally, Sitemic are also the first to market with a microRNA- based service to screen for early toxicity and it has been well received within the community as it is understood that assays/tools/technologies that can provide mechanistic insights into how drugs work on the biological system provide a significant leap forward in screening abilities.

Although a very simple test, it is highly informative as it delivers rich knowledge about the basic biological mechanisms, thereby enabling key decision-making throughout the research and development process. By doing so, SitemTOX could significantly reduce research and development (R&D) costs for drug developers, and expedite drug development by eliminating compounds that are too toxic, much earlier during the development process. The SitemTOX test could also be applied to multiple cell lines such as HepG2 and also to stem-cell-derived hepatocytes and cardiomyocytes. The test has already undergone extensive evaluation studies with the company's partners and Sitemic further encourages interested firms that wish to get a deeper understanding of potential drug toxicity, for partnerships so that there can be better clinical trial outcomes.

Taking about future collaborations with potential firms, McErlane said, "Currently Sitemic is a VC funded product development company with CRO activities also. We have a number of on-going strategic collaborations and firmly believe that collaboration is vital in order for us all to deliver robust solutions to the needs of pharma and biotech. Hence Sitemic always keep an open view to collaboration where the relationship is mutually beneficial to both parties."

Drug toxicity is a universal problem that exists not only during the multiple phases of the drug development process, but also continues to exert its presence even after the drug enters the market. Once commercialized, potential toxicity issues may arise as the drug is now exposed to a significantly larger patient population--the result of which may be market withdrawal of the drug. Banning of a commercialized drug not only manifests as a huge income loss for the firm that has developed the drug, but also affects the end-user community, which includes the prescribing physicians as well as the suffering patients who are in need of the drug. On the other hand, if researchers are presented with the ability to fail a drug much earlier, the loss incurred is much cheaper and patient safety is preserved. As per the US Food and Drug Administration's (FDA) estimates, a 10%

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improvement in predicting drug development failure could save the industry about \$100 M, in developing a drug. In addition to cost savings, novel screens such as SistemTOX may also possibly provide drug discovery chemists the opportunity to design drugs by retaining properties related to efficacy while eliminating those related to toxicity.

From the above industry trends, it can be concluded that drug toxicity tests have a significant market potential as they can be applied for testing a growing number of drugs being pursued by several pharmaceutical companies worldwide. Applying such tests during the earlier phases of drug development may aid the firms in shortening their development time, enhancing the safety and efficiency of clinical trails, and also expediting the process of drug approval and market entry.

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