Stem Cells For Drug Dosing And Titration

Personalized Medicine - A New Dimension To The Application

While the early efforts in harnessing the enormous potential of stem cells for treating disease were largely focused on regeneration and the ability to repair damaged tissues in the body, recent advances in this field started driving researchers and clinicians alike to employ stem cells in drug discovery applications, such as novel compound screening, toxicity testing, target identification, disease modeling and personalized medicine development. What makes stem cells such an attractive option for drug discovery studies? The answer is pretty straightforward. Stem cells effectively and faithfully replicate the model of human disease and drug reactions compared to animal models. Using more relevant models of disease for drug discovery while providing financial savings in the long run would also reduce the number of animals required for drug testing.

The effects of physiological changes in patients with ailments like diabetes on pharmacokinetic parameters and the time course of drug response are poorly understood. Even though dosing or titration considerations exist for certain classes of drugs they are not routinely recommended for patients with severe complications. For the majority of drugs, the issue of dose adjustment and drug titration on the basis of patient specific parameters has not been addressed in detail. The effects of altered body composition on the time course of drug response are also not completely understood. hiPSC-derived cells can serve as a surrogate “patient” to anticipate adverse side effects and calibrate optimal dosing/titration of drugs. Personalized medicine wherein hiPSC-derived motor neurons from patients with amyotrophic lateral sclerosis were tested with drugs to augment the limited treatment options is just one of the very many examples to prove the enormous potential of stem cells in drug discovery and personalized medicine.

In the context of existing drug testing platforms, such as animal studies, human clinical trials, animal iPSCs, and ESCs, hiPSCs provide advantages that can augment the current approaches to drug discovery. Stem cells while useful in predictive low-throughput and unbiased high-throughput drug screening can also help discern the biological mechanisms behind drug-drug interactions, an area currently not very well explored. The various advantages stem cells offer over traditional drug discovery approaches makes them a powerful and versatile instrument for the advancement of safe drug discovery and development.

“Dosing is an integral component in being precise with one’s medicine. It’s estimated that somewhere between 30 and 40 percent of the drugs people take do nothing for them. Yet people rarely consider whether their dose could be wrong.”

– Dean B. Joseph Guglielmo, PharmD

Anand Ram Soorneedi
Pharmacist Janel Boyle, PharmD, PhD, who is developing dosing models tailored for children, strongly opines that if you receive the wrong dose or the wrong medication, your results could range from not getting better to feeling worse to even dying. According to the Food and Drug Administration (FDA), more than 700,000 people each year experience serious drug reactions, and more than 117,000 die from them. By contrast, a more precise, individualized dose could boost a drug’s effectiveness against your disease while reducing or eliminating any potential side effects. Using stem cells to calculate the precise dosage and appropriate titration of the drug could one day help circumvent the burgeoning problem of either under or over dosage of drugs.

Understanding the genetics of Drug Induced Hypersensitivity Reactions using stem cells

Understanding genetic susceptibilities to drug responses (i.e., adverse reactions and efficacy) is critical to the implementation of personalized medicine. Genetic variants have been associated with severe adverse reactions to carbamazepine, a common drug used primarily in the treatment of epilepsy and trigeminal neuralgia. In particular, two HLA-related variants (HLA-B*1502 in Asian populations and HLA-A*3101 in Caucasian populations) have been associated with an increased risk of developing Stevens-Johnson (SJS) syndrome and toxic epidermal necrolysis (TEN), two forms of a life threatening skin condition. However, these HLA variants predict only a portion of individuals who will develop these conditions. This suggests that other rare or non-HLA related variants may also play an important role. Scientists at NCTR, in collaboration with scientists at the University of Liverpool (UK) and the Huashan Hospital (China) are performing whole genome sequencing and genetic analysis to identify susceptibilities to carbamazepine-induced SJS or TEN using stem cells. The researchers hope that by identifying additional factors that help to explain variation in patient response, they will be able to better predict in advance who will have an adverse reaction to the drug.
Cayo et al. have established that patient specific iPSC–derived hepatocytes could be used to definitively determine the functional contribution of allelic variation in regulating lipid and cholesterol metabolism and could potentially provide a platform for the identification of novel treatments of CVD. Because hiPSCs can be reprogrammed from easily accessible somatic cell types, such as skin fibroblasts, this raises the possibility of using hiPSCs from GWAS patients as a source of hepatocytes to study the role of specific allelic variants in regulating cholesterol metabolism. In addition, the availability of hepatocytes derived from patients with inborn errors in hepatic metabolism could provide a platform for developing effective drug dosing and titration strategies.
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