Axosim ADC-induced Peripheral Neuropathy Case Study

Summary

Cell culture models have great potential to assess mechanisms of drug toxicology in new pharmaceuticals hitting the market. Antibody drug conjugates (ADCs) are a new powerful pharmaceutical technology that uses the targeting power of antibodies to deliver small drugs to tumor cells. Seattle Genetics, the industry leader in ADCs, pioneered ADCS to improve the lives of those with cancer in a highly targeted manner. In developing this technology, they also needed to assess the mechanisms of side effects caused by ADCs, more specifically peripheral neuropathy in a low cost and time efficient manner. For drug development studies, It is important to catch potentially harmful side effects before Investigator New Drug (IND)-enabling studies begin for FDA approval of the drug. IND-enabling studies are used to secure approval of the first human studies of a newly developed drug, a major step in the clinical trial process.

For this project investigating mechanisms of ADCs-induced peripheral neuropathy they used biotech company Axosim's 2D in vitro cell-culture model using human induced pluripotent stem cells (iPSCs) and human Schwann cells. These cell types were cultured together, and then used to compare the effects of ADCs in the mono and co-culture. Because Schwann cells have been shown to play a role in peripheral neuropathy, they were used in the co-culture model. In this study, neuron length, amount of axonal branching, number of processes, neuron count, and Schwann cell length were assessed between the models. These measures and results showed this co-culture to be an effective assay for assessing causes of peripheral neuropathy from ADCs. This technique successfully showed its potential use in early screening of risk for new therapeutics in the ADCs space.

Quote

"This 2D model with human Schwann cells and iPSCs helps to create a more accurate, and faster developed model than using animal models. This helps to detect adverse effects from drugs like ADCs faster and with more accuracy, allowing them to be released to the general public sooner, and help more lives of those affected by life-threatening diseases."

Esther Trueblood, lead author

Methods & Results

Axosim aimed to develop a model for assessing potential causes of peripheral neuropathy from ADCs through iPSCs and human Schwann cell co-culture. To assess this model's efficacy, these cell types were cultured, and chemotherapeutics and small ADCs molecules were applied for each culture type to assess the mechanisms of ADCs-induced peripheral neuropathy.

Measures of neurotoxicity were conducted next. The co-culture with Schwann cells showed a decrease in neuron count and length, a higher level of neurotoxicity. This decrease in the co-culture including iPSC and Schwann cells points to the bystander effect in causing neurotoxicity, that is that the addition of the Schwann affects neurotoxicity of neighboring cells propagating the neurotoxicity. All in all, this experiment helped to showcase a sensitive high content assay for testing peripheral neuropathy potential using co-cultures. Sensitivity refers to a high likelihood of effect, and high content assays refer to when individual cells are imagined and analyzed with a microscope system that produces a large number of individual cell measurements and data.

Relevance

Tools for ADCs Researchers

This assay provides a tool for assessing peripheral neuropathy and potential causes from ADCs early in drug development, an important aspect to mitigate risk. ADCs provide high therapeutic potential so it is important to know the causes of risk and correct for them early. This assay is beneficial for the ADC space and companies such as Seattle Genetics.

This assay provides great benefit for the makers of ADCs or any drugs with peripheral neuropathy liability in their drug development process. This will allow ADCs to hit the market quicker by mitigating risks and correcting for risks quickly before IND-enabling studies, helping to speed up the clinical trial process. Introducing ADCs into the pharmaceutical market faster provides great benefits to the cancer treatment field by adding new treatments faster with less harm, showing the relevance and benefits of this novel assay.

Metrics

75% faster than animal studies
This helped to speed up the drug development process and correct for risks sooner

75% less expensive than animal model
Using cell culture models saves money in the drug development process, allowing funds to be allocated for more thorough analyses

2D Co-Culture Model of iPSCs and Schwann cells
This allows for a targeted modeled of the nervous system with Schwann cells, a main cell affected by peripheral neuropathy

.