AI Expedites Motor Neuron Analysis and Screening in ALS Research

By Corinna Singleman, PhD December 19, 2024

Visualization of motor neuron electrical activity using a high-density microelectrode array. [Satoru Morimoto]

Developing motor neurons from stem cells taken directly from amyotrophic lateral sclerosis (ALS) patients offers new hope for better understanding and treatment of the fatal neurodegenerative disorder. Researchers at Keio University, Japan, led by Hideyuki Okano, PhD, now report a new method for culturing functional spinal lower motor neurons (LMNs) from induced pluripotent stem cells (iPSCs) with high induction efficiency, while significantly shortening the time required to produce functional neurons.

"We aimed to develop a streamlined and robust approach that would accelerate ALS research and enable large-scale drug screening for this devastating disease, particularly in sporadic ALS patients," corresponding author, Satoru Morimoto, PhD, shared with *GEN*.

Details of the new methodology and analysis were published in *Stem Cell Reports* under the title, "Swift Induction of Human Spinal Lower Motor Neurons and Robust ALS Cell Screening via Single-Cell Imaging."

Morimoto's team has a strong desire to find a cure for ALS, a challenging disease to study as more than 90% of cases are sporadic, leading to high heterogeneity in the patient population. In order to effectively study the disease, researchers "need to analyze a large number of cases to compensate for individual differences," he said.

The resulting LMNs were found to have replicated ALS-specific pathologies, such as the abnormal aggregation of TDP-43 and FUS proteins. The team confirmed functionality of the LMNs using a multi-electrode array (MEA) system to measure firing activity and network activity, which were found to be similar to mature neurons.

Further analysis of the cultured LMNs showed that in addition to maintaining ALS cellular markers, the LMNs had reduced survival rates compared with healthy cells, mimicking ALS motor neuron responses.

"Our approach provides a robust platform for studying ALS-specific cellular vulnerabilities and offers unprecedented opportunities for drug screening," the authors wrote. This study shows reproduced ALS phenotypes in LMNs. A study published in 2023 by the team used the same method for inducing cells showed a positive correlation for clinical drug response. However, the present study did not directly assess "whether the severity of the phenotype correlates with the patient's clinical progression."

Using AI to improve outcomes

"The main challenge was to achieve high induction efficiency in a short time while maintaining cell purity and overcoming heterogeneity for large-scale multi-sample analysis," Morimoto told *GEN*. Further, "it was necessary to establish reliable single-cell analysis technology to accurately assess the phenotype of the induced motor neurons and eliminate cells other than LMNs."

The researchers utilized machine learning and AI-driven image analysis techniques for live imaging and single-cell tracking to assess the morphology and viability of LMNs and to exclude non-LMN cells from analysis. Morimoto's team used AI to "enhance automated analysis by improving the accuracy and efficiency of identifying cellular phenotypes, detecting subtle changes, and predicting disease progression."

"It has been very rewarding to see how our methods have streamlined a previously labor-intensive process, making ALS research more accessible and

Continuing research will include further exploration of the LMNs to model ALS cell response to drug treatments. Morimoto has three major goals ahead, namely to "elucidate the pathomechanism of sporadic ALS; develop the most appropriate drug for each individual patient with sporadic ALS; and use iPS cell-derived neurons as biomarkers for patients."

The Japanese study offers a pathway to better understanding and treatment of ALS and potentially other neurodegenerative diseases. Their technique opens doors for large-scale analysis and drug screening, but it has its limitations requiring real-time monitoring systems and reducing variability. Morimoto pointed out to *GEN* that "automating cell growth and analysis requires ensuring reproducibility and maintaining the delicate conditions required for neuronal differentiation while being scalable."

On a positive note, Morimoto shared his pride in the study and team stating, "One of the most exciting things about this project has been witnessing the interdisciplinary collaboration within our team, combining expertise in stem cell biology, time-lapse imaging, and machine learning."

Morimoto is on a mission to "continue to work with collaborators around the world to find a cure for ALS."

News | Amyotrophic lateral sclerosis | Artificial intelligence | Cell biology | Induced pluripotent stem cells | Machine learning | Neurons | Phenotype