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Researchers, with stem cells, advance understanding of spinal muscular atrophy

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Cedars-Sinai's Regenerative Medicine Institute has pioneered research on how motor-neuron cell-death occurs in patients with spinal muscular atrophy, offering an important clue in identifying potential medicines to treat this leading genetic cause of death in infants and toddlers.

The study, published in the June 19 online issue of *PLoS ONE*, extends the institute's work to employ pluripotent stem cells to find a pharmaceutical treatment for spinal muscular atrophy or SMA, a genetic neuromuscular disease characterized by muscle atrophy and weakness.

"With this new understanding of how motor neurons die in spinal muscular atrophy patients, we are an important step closer to identifying drugs that may reverse or prevent that process," said Clive Svendsen, PhD, director of the Cedars-Sinai Regenerative Medicine Institute.

Svendsen and his team have investigated this disease for some time now. In 2009, Nature published a study by Svendsen and his colleagues detailing how skin cells taken from a patient with the disorder were used to generate neurons of the same genetic makeup and characteristics of those affected in the disorder; this created a "disease-in-a-dish" that could serve as a model for discovering new drugs.

As the disease is unique to humans, previous methods to employ this approach had been unreliable in predicting how it occurs in humans. In the research published in *PLoS ONE*, to the team reproduced this model with skin cells from multiple patients, taking them back in time to a

pluripotent stem cell state (iPS cells), and then driving them forward to study the diseased patient-specific motor neurons.

Children born with this disorder have a genetic mutation that doesn't allow their motor neurons to manufacture a critical protein necessary for them to survive. The study found these cells die through apoptosis – the same form of cell death that occurs when the body eliminates old, unnecessary as well as unhealthy cells. As motor neuron cell death progresses, children with the disease experience increasing paralysis and eventually death. There is no effective treatment now for this disease. An estimated one in 35 to one in 60 people are carriers and about in 100,000 newborns have the condition.

"Now we are taking these motor neurons (from multiple children with the disease and in their pluripotent state) and screening compounds that can rescue these cells and create the protein necessary for them to survive," said Dhruv Sareen, director of Cedars-Sinai's Induced Pluripotent Stem Cell Core Facility and a primary author on the study. "This study is an important stepping stone to guide us toward the right kinds of compounds that we hope will be effective in the model – and then be reproduced in clinical trials."

Provided by Cedars-Sinai Medical Center