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Stem Cell-derived "Mini-brains" Reveal Potential Drug Treatment for Rare Disorder

Using "mini-brains" built with induced pluripotent stem cells derived from patients with a rare, but devastating, neurological disorder, researchers at University of California, San Diego School of Medicine say they have identified a drug candidate that appears to "rescue" dysfunctional cells by suppressing a critical genetic alteration.

Their findings are published in the September 8 online issue of *Molecular Psychiatry*.

The neurological disorder is called *MECP2* duplication syndrome. First described in 2005, it is caused by duplication of genetic material in a specific region of the X chromosome that encompasses *MECP2* and adjacent genes. The disorder displays a wide variety of symptoms, among them low muscle tone, developmental delays, recurrent respiratory infections, speech abnormalities, seizures, autistic behaviors and potentially severe intellectual disability.

It is heritable, but can also occur randomly. *MECP2* duplication syndrome occurs almost exclusively in males. A similar disorder known as Rett (RTT) Syndrome, which involves *MECP2* gene deletions, primarily affects females. Current treatment is largely symptomatic, involving therapies, drugs and surgeries that address specific issues.

As in previous, ground-breaking research with Rett Syndrome patients, senior author Alysson Muotri, PhD, associate professor in the UC San Diego departments of Pediatrics and Cellular and Molecular Medicine, and colleagues took skin cells from *MECP2* duplication patients, converted them into induced pluripotent stem cells (iPSC), then programmed the stem cells to become neurons that recapitulate the disorder more robustly than existing mouse models.

Muotri said analyses of the iPSC-derived neurons revealed novel molecular and cellular phenotypes, including an over-synchronization of the neuronal networks. Interestingly, these phenotypes go in a direction opposite of what scientists had previously reported for Rett syndrome, suggesting that the correct gene dosage is important for homeostasis in human

neurons. More importantly, said Muotri, the finding with human neurons helped direct the next stage, a drug screening, which uncovered a drug candidate – a histone deacetylase inhibitor that reversed all the *MECP2* alterations in the mutant neurons, with no harm to control neurons.

“This work is encouraging for several reasons,” said Muotri. “First, this compound had never before been considered a therapeutic alternative for neurological disorders. Second, the speed in which we were able to do this. With mouse models, this work would likely have taken years and results would not necessarily be useful for humans.”

Muotri said the findings further underscore the potential of stem cell-based models as an efficient method for screening potential drug libraries for the ability to rescue human neuronal phenotypes in a dish. He said his research team would be concluding its preclinical studies in preparation for moving into clinical trials as soon as possible.

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