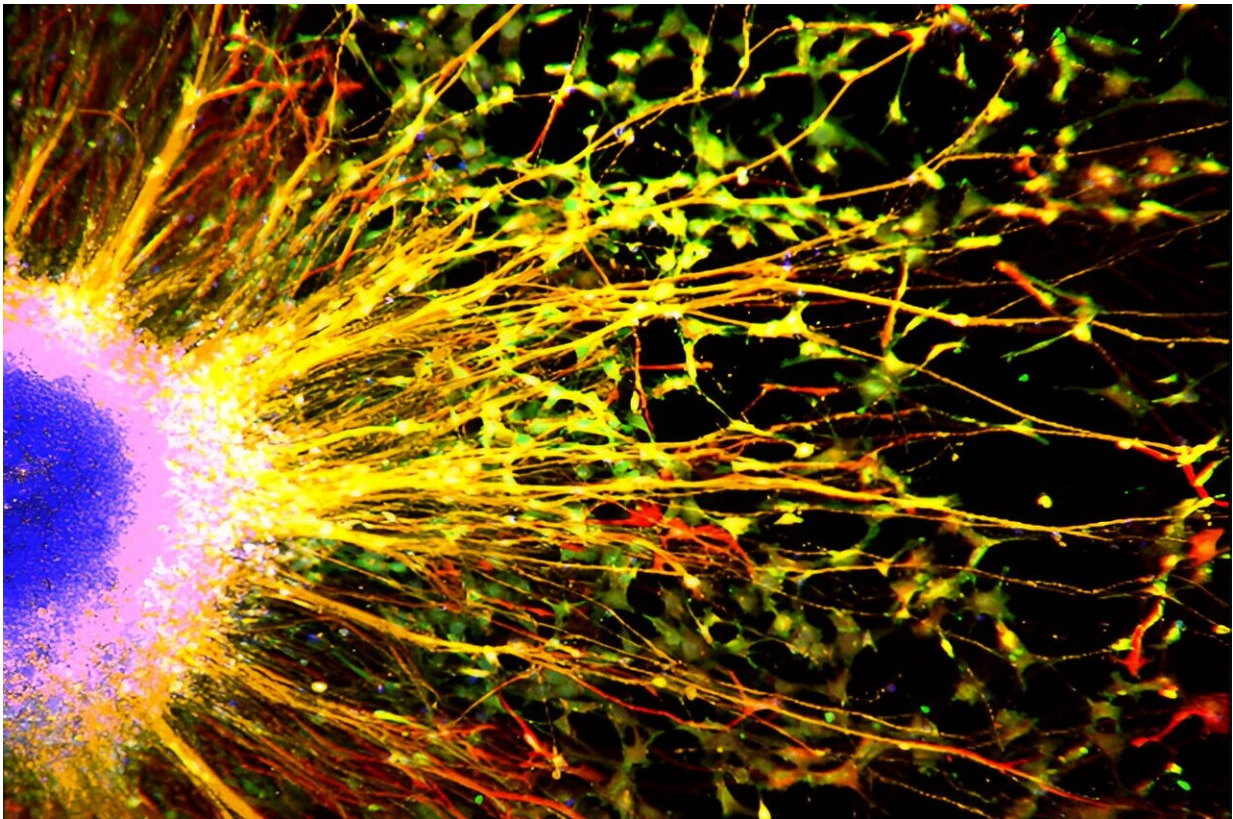


Cancer drug could ease cognitive function for some with autism

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A representative culture from a brain organoid in which the gene MECP2 — causative in Rett syndrome — has been "knocked out," as shown through a fluorescent microscope. Because the culture was treated with experimental cancer drug ADH-503, new synapses formed. Credit: Muotri Lab/ UC San Diego Health Sciences

An experimental cancer drug could make thinking easier for individuals with Rett syndrome, a rare disorder linked to autism, according to new research from the University of California San Diego—a discovery that could lead to therapies for patients with other neurological conditions.

The findings, published July 25 in [Stem Cell Reports](#), highlight the role of [microglia](#)—a type of white blood cell found in the central nervous system—in the formation of the human brain.

While such cells have been better studied in neurodegenerative disorders like Alzheimer's disease, [amyotrophic lateral sclerosis](#) (ALS) and multiple sclerosis, "very little information has existed on their role in early stages of neural development" because access to fetal tissue is limited, said Pinar Mesci, Ph.D., the study's lead researcher. Now employed elsewhere, she completed work on the project while at the university.

In a bid to better understand their function, Mesci instead used [brain organoids](#)—"mini brains," essentially, that mimic the developing brain of an embryo—grown from skin-derived stem cells of consenting patients. Such organoids were created from individuals with Rett syndrome—a disorder primarily found in females that features loss of speech, purposeful use of hands, mobility and muscle tone, among other symptoms—as well as from neurotypical individuals.

Mesci then added healthy microglia to the Rett syndrome [brain organoids](#) and found that the functioning of synapses—where neurons connect and communicate—was "rescued." This occurred due to the restoration of phagocytosis, a process by which microglia—sometimes referred to as the "janitors" of the central nervous system—ingest and destroy foreign substances like bacteria and dead cells, keeping the brain and spinal cord tidy. The process also involves "pruning" of synapses, which optimizes brain function.

Researchers also found that the synapses of typical neurons experienced impaired functioning when Rett syndrome microglia were introduced, further confirming the role of the immune cell in brain function and development.

"If the brain's 'janitors' are not working, problems start to arise," said UC San Diego School of Medicine professor Alysson Muotri, Ph.D., senior author and director of the university's Sanford Stem Cell Institute's Integrated Space Stem Cell Orbital Research Center.

Faulty microglia make cognition even harder for Rett syndrome patients, who already contend with fewer and impaired synapses and dysfunctional astrocytes due to a loss of function in the MECP2 gene, implicated in other types of neurodevelopmental conditions as well.

Microglia with loss of MECP2 function "are not as good at pruning synapses and shaping the [neural network](#)—they don't do a good job," Muotri said.

The team then tested a battery of existing drugs on the microglia, to see if any might restore phagocytosis. They found one: ADH-503, also known as GB1275—an experimental oral pancreatic cancer medication that also reduces the number of immune-suppressing cells that enter a tumor. The drug serves as a regulator of CD11b, a protein involved in phagocytosis, among other processes.

Other studies on Rett syndrome have highlighted potential therapeutic targets. But none so far have identified a potential treatment involving human microglial cells.

By the time Rett syndrome patients are diagnosed, it's too late to repair and not currently possible to replace faulty neurons, the primary issue in the disease. "But by focusing on other cell types—and potentially finding

drugs that improve how they work—we might improve the environment for those neurons and ease functioning for patients," Mesci said. "That's what I'm excited about."

Jonathan Kipnis, Ph.D., professor of pathology, immunology, neurology, neuroscience and neurosurgery at Washington University School of Medicine in St. Louis and director of its Brain Immunology and Glia Center, said the new research "nicely demonstrates" microglia as a potential therapeutic target in Rett syndrome.

"I hope this work will 'move the needle' and bring the Rett community back to neuroimmunology," Kipnis said. "Understanding neuro-immune interactions in this complex disease may not only provide new insights into the disease biology, but also develop novel approaches to attenuate its progression."

The research represents the first successful integration of human microglia into Rett syndrome brain tissues *in vitro*—a model that may prove superior to mouse models.

The researchers hope the study "opens doors for therapies," not only for those with Rett syndrome, but for those with other neurodevelopmental and neurodegenerative disorders in which microglia play a role.

"That's my wish," Mesci said, "that we can improve quality of life."

More information: University of California, Human microglial cells as a therapeutic target in a neurodevelopmental disease model, *Stem Cell Reports* (2024). [DOI: 10.1016/j.stemcr.2024.06.013](https://doi.org/10.1016/j.stemcr.2024.06.013). [www.cell.com/stem-cell-reports ... 2213-6711\(24\)00193-0](https://www.cell.com/stem-cell-reports/2024.06.013)

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