A Personalized Model to Fight Epilepsy

GliaPharm has developed an innovative model to test targeted treatments for epilepsy, particularly in the context of GLUT1 deficiency syndrome.

The Swiss biotech company GliaPharm, in collaboration with the Geneva Haute Ecole du Paysage, d'ingénieurie et d'architecture (HEPIA), has created a groundbreaking experimental model based on human cerebral organoids. Published in the journal *Frontiers in Neuroscience*, this system replicates key features of epileptic brain activity, enabling the evaluation of personalized treatments. An initial trial demonstrated the efficacy of GliaPharm pipeline molecule in treating epilepsy linked to GLUT1 deficiency syndrome, offering new therapeutic perspectives.

GLUT1 deficiency syndrome (GLUT1-DS) is a rare genetic condition caused by mutations in the gene that encodes the GLUT1 protein. This protein functions as a specific transporter that allows glucose to enter the brain. In patients with this syndrome, the brain's ability to transport glucose is significantly impaired, especially in astrocytes—cells responsible for supplying neurons with energy.
The resulting energy hypometabolism in the central nervous system leads to epileptic seizures, among other symptoms. "At GliaPharm, we have developed molecules capable of stimulating glucose utilization by astrocytes, potentially addressing dysfunctions linked to cerebral energy hypometabolism, such as epilepsy," explains Charles Finsterwald, Chief Scientific Officer and co-founder of GliaPharm.

Overcoming the Limitations

Despite the urgent need for targeted treatments, traditional models, such as mice, present significant limitations. "Mice fail to accurately replicate human epileptic mechanisms, making it difficult to develop effective therapies," says Finsterwald. To address this challenge, he and his team turned to a promising alternative: cerebral organoids, three-dimensional cultures derived from human stem cells.
They developed organoids from induced pluripotent stem cells (iPSCs) obtained non-invasively from human skin samples. These cells are then reprogrammed in vitro to differentiate and form functional clusters of brain cells. "The advantage of organoids is their ability to recreate human neuronal circuits and the surrounding glial cells, such as astrocytes. They also pave the way for personalized medicine: one patient, one organoid," notes Pierre Magistretti, founder and chairman of GliaPharm's scientific advisory board.

The model is enhanced by a system of microelectrodes and a perfusion chamber developed by Luc Stoppini's lab at HEPIA. This unique setup enables real-time monitoring of neuronal activity and simulation of specific conditions, such as glucose deprivation or drug application. "We can precisely adjust glucose levels to recreate hypometabolism and observe its effects on epileptic activity," adds Finsterwald.

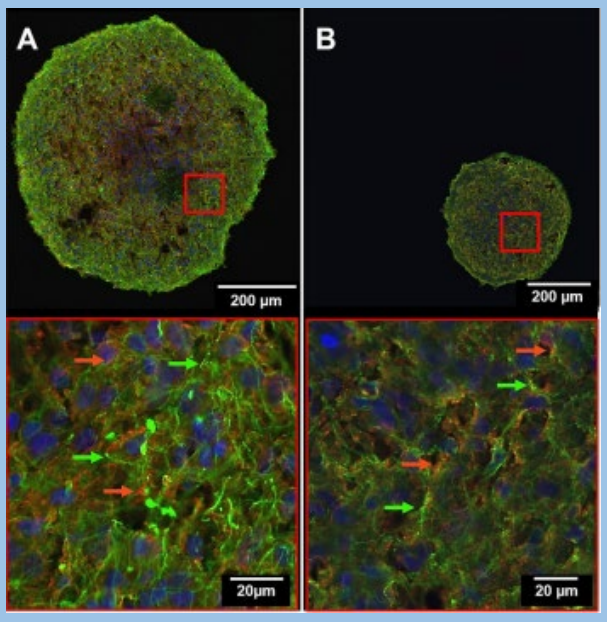

Illustration:

Human cerebral organoids allow potential treatments for epilepsy testing. *The two top images show brain organoid from healthy volunteer (left) and GLUT1-DS patient (right). Bottom images show zoomed-in view where neurons (red) and astrocytes (green), the two main cell types that compose the organoid, are distinguished with fluorescent staining.*

Promising Initial Results

The platform was tested using organoids derived from GLUT1-DS patients and healthy donors. Analyses revealed distinct characteristics: GLUT1-DS organoids exhibited reduced cell density, smaller size, and heightened epileptiform activity, mirroring key features of the disease in humans.

When testing a molecule developed by GliaPharm, researchers observed a significant reduction in epileptic seizures in the pathological organoids. "These results demonstrate the potential of our model to test innovative therapies and validate their efficacy before clinical trials," says Finsterwald enthusiastically.

Beyond epilepsy, this technological platform opens the door to research and development on other brain diseases, whether or not they involve metabolic or epileptic disturbances. "We now have a tool to explore personalized treatments, not only for epilepsy but also for other central nervous system disorders," concludes Finsterwald.

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