Potential treatment target for drug-resistant epilepsy identified

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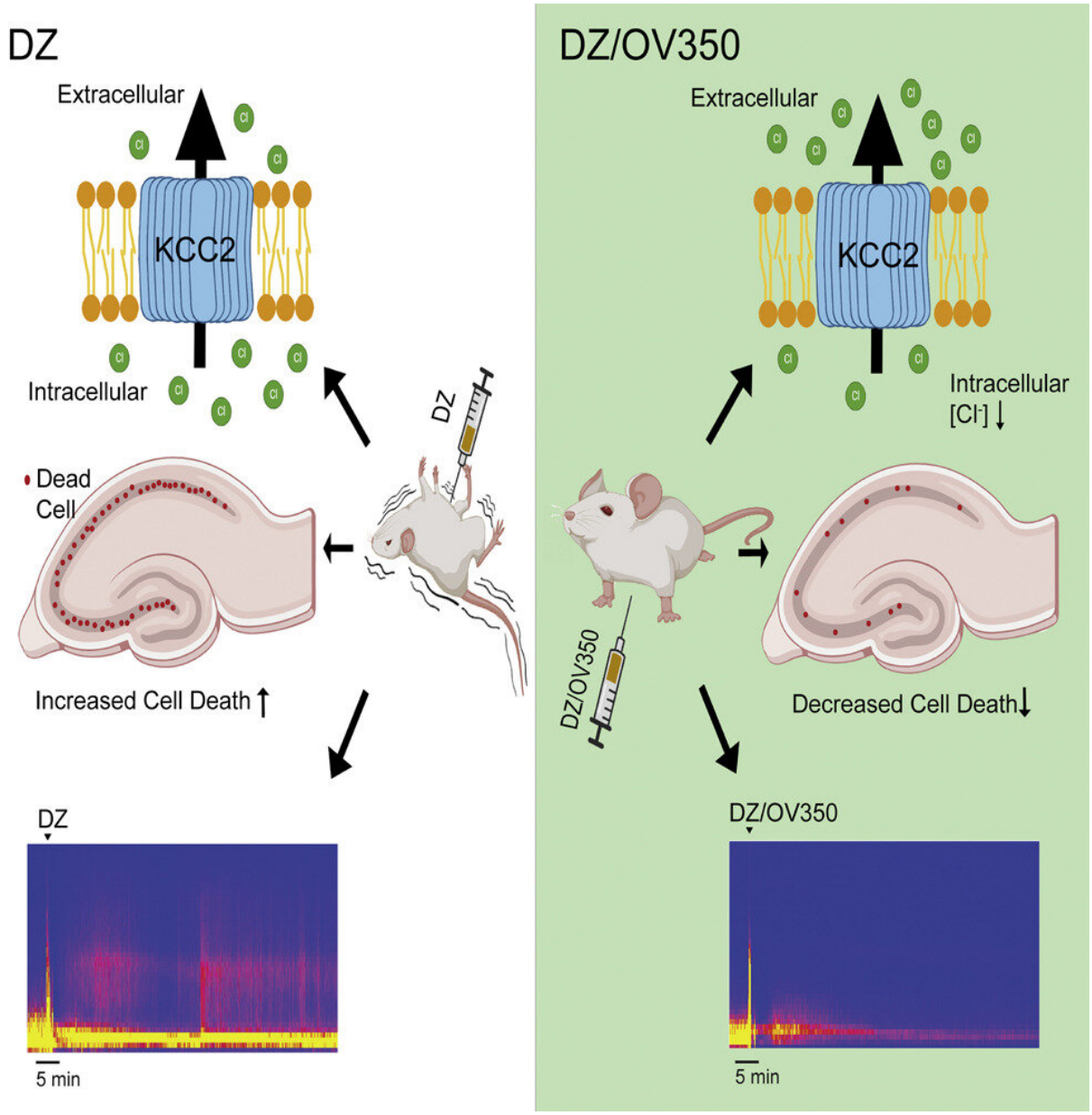

Credit: *Cell Reports Medicine* (2023). DOI: 10.1016/j.xcrm.2023.100957

Researchers at Tufts University School of Medicine and colleagues have identified a small molecule that may help treat people with epilepsy whose condition has become resistant to the benzodiazepine drugs usually used in managing seizures. The research, conducted in laboratory cells and rodents, was published online March 7 in *Cell Reports Medicine*.

Uncontrolled epilepsy can lead to frequent and prolonged seizures lasting five minutes or more that can cause brain cell damage and even death. The condition affects an estimated 3.4 million people in the U.S. and millions more worldwide.

Epilepsy occurs when the intricate, delicate balance of signaling by neurons in the brain malfunctions, causing neurons to fire too much and trigger seizures. Benzodiazepines slow down the messages traveling between neurons.

"While seizures can frequently be controlled with medications, up to 30 percent of those with epilepsy develop drug resistance after a period of time," says study co-first author Krithika Abiraman, a scientist in the Department of Neuroscience at Tufts University School of Medicine.

The scientists were looking for targets in the brain that could restore normal signaling. They focused on a potassium chloride co-transporter called KCC2. In the normal brain, KCC2 helps pump chloride out of nerve cells, which helps brake neuronal overfiring.

"Previous research in both rodents and humans had shown that low KCC2 levels and activity in the brain is linked to drug-resistant and

prolonged seizures," explains Shu Fun Josephine Ng, co-first author and a scientist in the Department of Neuroscience. Both Ng and Abiraman work in the laboratory of Stephen Moss, professor of neuroscience at the School of Medicine, program faculty at Tufts Graduate School of Biomedical Sciences, and corresponding author on the study.

Collaborators at AstraZeneca screened more than one million compounds to identify a family of compounds that might be able to affect the activity of KCC2 in the brain.

The scientists tested one of the compounds in that family—Compound 350—and observed that in combination with benzodiazepine, the Compound 350 reduced seizure activity in rodents with drug-resistant seizures.

"We also observed that mice treated with the benzodiazepine and Compound 350 had lower cell death in the brain than those treated only with the benzodiazepine," said Ng, adding that this was most likely because rodents treated with both drugs were not having as many seizures.

"The small molecules we have identified have the capacity to be developed as first-in-class drugs to alleviate drug-resistant epilepsies and neurodegenerative disorders," says Moss. "In collaboration with Ovid Therapeutics, these compounds are now under clinical development."

More information: Rebecca Jarvis et al, Direct activation of KCC2 arrests benzodiazepine refractory status epilepticus and limits the subsequent neuronal injury in mice, *Cell Reports Medicine* (2023). DOI: 10.1016/j.xcrm.2023.100957

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