Stroke drug offers neuroprotection without long term impact on memory and learning

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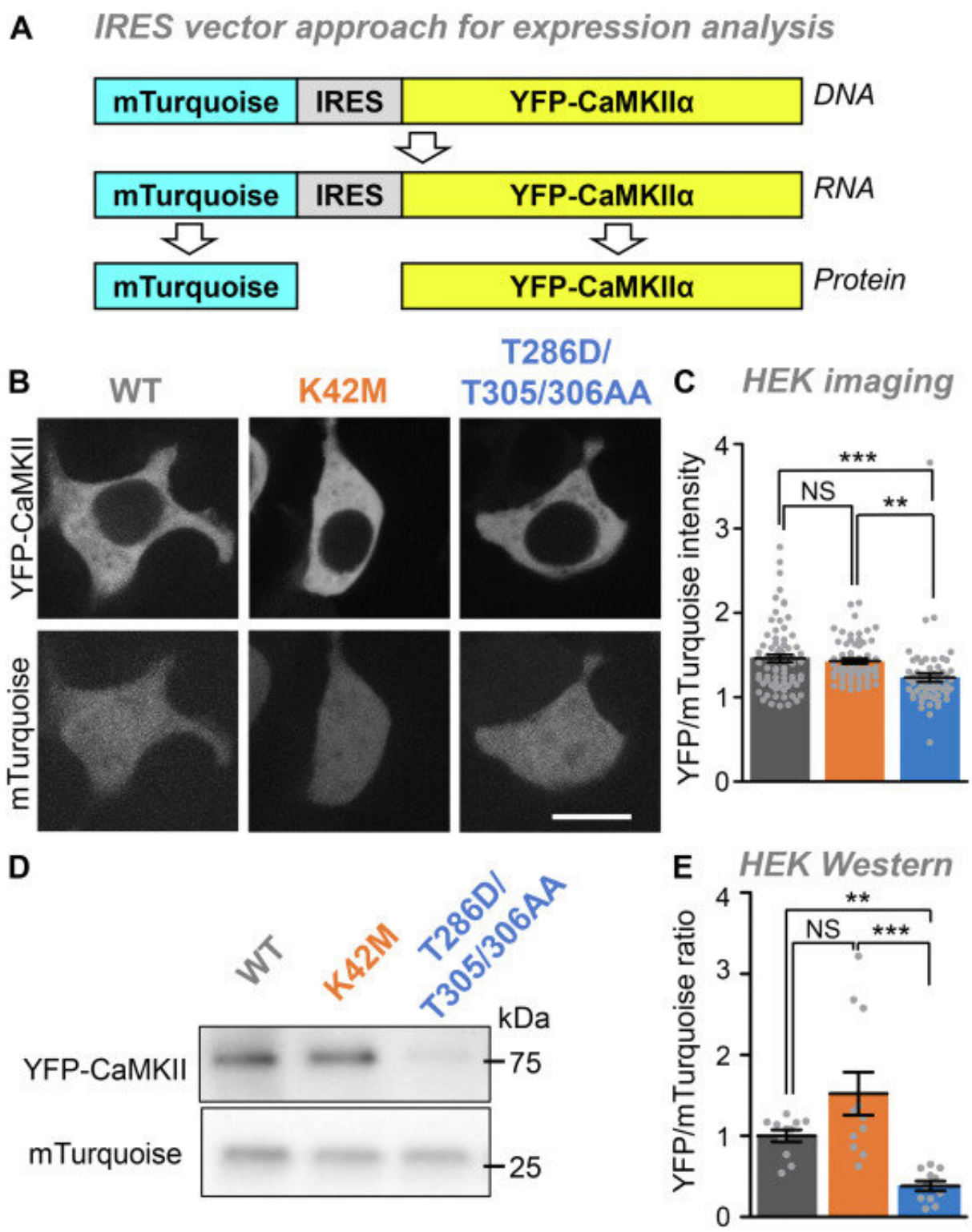

Differential expression levels of CaMKII tool mutants in HEK293 cells. Credit: *Journal of Biological Chemistry* (2023). DOI: 10.1016/j.jbc.2023.104693

A promising new stroke drug that temporarily inhibits a key protein in the brain without causing lasting harm may significantly change the future treatment of cerebral and global ischemia, according to a new study by scientists at the University of Colorado Anschutz Medical Campus.

The study appears in the May edition of the *Journal of Biological Chemistry.*

"We are one step closer to a new stroke therapy," said K. Ulrich Bayer, Ph.D., professor of pharmacology at the University of Colorado School of Medicine and a senior author of the study. "Our research shows that the potential negative side effects were not manifested, while the neuroprotective effects were significant."

Current stroke treatment is largely confined to breaking up blood clots to restore blood flow to the affected region of the brain. But the drug studied here, which was developed on the CU Anschutz Medical Campus, protects brain function itself.

The scientists set out to discover how to target a critical protein called Ca^{2+}/calmodulin-dependent protein kinase II or CaMKII, a central regulator of learning and memory. Long-term interference with this protein was thought to carry a risk of impacting memory and learning ability.

Working with animal models, the team targeted the protein with a neuroprotective peptide known as tatCN19o.

"Our team found that tatCN19o did not affect pre-formed memories and only temporarily interfered with learning for less than an hour," Bayer said.

They also discovered that the drug prevented brain cell damage even at very low doses and when given 30 to 60 minutes after ischemic events.

Study co-author Carolyn Nicole Brown from the CU School of Medicine Department of Pharmacology said the temporary learning impairment with the drug in cases of global cerebral ischemia or stroke would be "highly acceptable even if they were longer lasting than observed here since the treatment is with a single acute bolus of the drug."

"Additionally, the very short duration of the learning impairment could enable even chronic treatments of some conditions," she said, "including Alzheimer's disease, as just one notable example."

Fellow co-author, Nicole Rumian, Ph.D., also in the Dept. of Pharmacology, noted the results support the fact that the protein is involved in maintaining memory, but briefly inhibiting it does not cause long-term amnesia.

Bayer expects further safety studies to be conducted with the drug soon and human trials to begin in about three years.

"As a basic science researcher, I am super excited to see my work reach the clinic within my lifetime," he said.

Neurexis Therapeutics, as the licensee of the technology, is currently advancing the drug through late preclinical development.

More information: Nicole L. Rumian et al, Short-term CaMKII inhibition with tatCN19o does not erase pre-formed memory in mice and is neuroprotective in pigs, *Journal of Biological Chemistry* (2023). DOI: 10.1016/j.jbc.2023.104693

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