Press release

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Polku Therapeutics' novel compound blocks memory loss after repeated mild traumatic brain injury in preclinical model

A landmark study published in *Experimental Neurology* demonstrates that Polku Therapeutics' proprietary prolyl oligopeptidase (PREP) ligand prevents long-term memory impairment in a model of repeated mild traumatic brain injury (TBI) – a major risk factor for chronic traumatic encephalopathy (CTE) and other neurodegenerative conditions.

The research, led by Polku's scientific co-founder Professor Timo Myöhänen at the University of Helsinki, shows for the first time that targeting the PREP–PP2A pathway can counteract the damaging cascades triggered by repeated head impacts.

Unmet need in brain trauma

Each year, up to 60 million people worldwide suffer traumatic brain injuries. Even so-called mild concussions, especially when repeated, can lead to lasting cognitive deficits, dementia, mood disorders, and in severe cases CTE. Today, there are no approved therapies to prevent the chronic consequences of head trauma.

Breakthrough findings

In the new study, mice subjected to five repeated mild TBIs developed significant cognitive deficits when tested three months later. Treatment with Polku's PREP ligand immediately after each injury blocked the emergence of these deficits.

Further analysis revealed that PREP ligands reduced markers of neuroinflammation and cellular senescence that is linked with premature aging and neurodegeneration. It also normalized a synaptic plasticity regulator, critical for memory and cognition, that is shown to be dysregulated after brain trauma. Collectively, these effects suggest PREP ligands can intervene early in the biological cascades that drive long-term damage after repeated head injury.

Towards disease-modifying therapies

"This is the first demonstration that a small-molecule PREP ligand can protect against the cognitive decline seen after repeated concussions," said **Professor Timo Myöhänen**, senior author of the study, and co-founder of Polku Therapeutics. "By targeting fundamental mechanisms like PP2A activation and astrocyte reactivity, our compounds offer a potential route to disease-modifying therapies for TBI and tauopathies."

The findings build on Polku Therapeutics' platform of PREP–PP2A modulators, which are also under investigation in models of Alzheimer's disease and other neurodegenerative disorders.

Broad implications
The results open new therapeutic possibilities not only for patients suffering from traumatic brain injury, but also for high-risk groups such as athletes, military personnel, and others exposed to repeated concussions. Preventing long-term damage after TBI would reduce enormous personal and societal costs associated with dementia, mood disorders, and loss of productivity.

About the study
Uhari-Väänänen J, Eteläinen T, Zuo C, De Lorenzo F, Kilpeläinen T, Myöhänen TT. *A prolyl oligopeptidase ligand blocks memory deficit in a repeated mild traumatic brain injury model*. *Experimental Neurology*, 2025.
https://doi.org/10.1016/j.expneurol.2025.115454

About Polku Therapeutics
Polku Therapeutics is a Finnish biotechnology company developing first and best-in-class small-molecule therapies targeting the PREP–PP2A pathway to treat neurodegenerative disorders. By modulating fundamental protein–protein interactions that control tau phosphorylation, autophagy, and cellular resilience, Polku aims to deliver disease-modifying treatments for CNS conditions.

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