Docket #: S20-116

Brain-Penetrant Neurotherapeutics to Rebalance Excitatory and Inhibitory Signaling

Stanford researchers in Dr. Thomas Montine's lab have developed a series of small molecules that cross the blood-brain barrier, modify neurotransmitter metabolism, and globally suppress excitatory brain signaling. The lead compound has activity in mouse models of brain diseases known to derive in part from excitatory neuron hyperactivity, including levodopa-induced dyskinesia (LID), Alzheimer's disease, and a form of inherited epilepsy.

Increased excitatory (glutamatergic) neuron signaling is proposed to contribute to many neurodevelopmental, psychiatric, and neurodegenerative diseases. Current attempts to suppress excitatory neuron signaling target individual receptors, a limited approach given broad receptor diversity and adaptation, that often is complicated by psychotropic side-effects.

The Montine Lab's compounds work differently. Neurons take them up, store them, and release them in place of natural glutamate, but they have little or no activity at the receptors those neurotransmitters normally engage. These false neurotransmitter compounds cross the blood-brain barrier, act in an enantiomer-selective manner, and substitute for endogenous neurotransmitter. A promising compound has similar potency as amantadine in suppressing LID in mice but without amantadine's toxicity, restored memory in mouse models of Alzheimer's disease's amyloid ? or pathologic tau overexpression, and was superior to memantine in blocking excitatory neuron injury. A radiolabeled form of one compound also showed rapid brain uptake in mouse PET imaging. Together, these results are promising advances for hard to treat central nervous system diseases.

Stage of Development: In vivo proof of concept

The Montine Lab demonstrated proof of concept in Parkinson's and Alzheimer's disease mouse models, and ex vivo neuroprotection and PET imaging studies in mice.

Applications

- Treatment of central nervous system conditions including neurodevelopmental, psychiatric/behavioral, and neurodegenerative diseases
- PET imaging agents for glutamate-producing or glutamine-transporting cells, including potential cancer detection

Advantages

- New mechanism that changes neurotransmitter metabolism instead of targeting individual receptors
- Globally suppresses excitatory signaling
- Crosses the blood-brain barrier
- No detectable toxicity following 6-month exposure to therapeutic doses in mice
- Enantiomer-selective activity

Publications

- Wawro, A. M., Gajera, C. R., Baker, S. A., Le?niak, R. K., Fischer, C. R., Saw, N. L., ... & Montine, T. J. (2021). Enantiomers of 2-methylglutamate and 2-methylglutamine selectively impact mouse brain metabolism and behavior. *Scientific Reports, 11(1), 8138. https://doi.org/10.1038/s41598-021-87569-1*
- Wawro, A. M., Gajera, C. R., Baker, S. A., Le?niak, R. K., Montine, K. S., Fischer, C. R., ... & Montine, T. J. (2021). Enantiomers of 4?aminopentanoic acid act as false GABAergic neurotransmitters and impact mouse behavior. *Journal of Neurochemistry, 158*(5), 1074-1082. https://doi.org/10.1111/jnc.15474
- Perna A, Zhao J, Gajera CR, Schonemann M, Saw NL, Shamloo M, Montine KS, Garofalo AW, Montine TJ. **(2026)**. Potential glutamatergic and GABAergic false neurotransmitters in models of excitation-inhibition imbalance. *Sci Rep.*, 16(1):23023.

Patents

- Published Application: WO2022216543
- Published Application: 20240115539
- Issued: 12,589,087 (USA)

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