Docket #: S20-116

Enantiomers of Glutamic Acid Derivatives as Neurotherapeutics

Stanford scientists in Dr. Thomas Montine's lab have discovered a series of glutamic acid derivatives that penetrate the blood-brain barrier and modify metabolism of neurotransmitters with the potential to treat a number of neurological conditions, including neurodegenerative diseases and psychiatric conditions.

An imbalance of glutamatergic (excitatory) and GABAergic (inhibitory) neurotransmission contributes to a broad range of neurodevelopmental, psychiatric, and neurodegenerative diseases. Current treatments that attempt to modify the action of neurotransmitters usually target their receptors and have yet to effectively treat many of the conditions that scientists know to be related to excitatory-inhibitory imbalance.

This technology developed in the Montine lab includes a series of small molecule compositions that are enantiomers of glutamic acid derivatives and instead influence neurotransmitter metabolism to modify excitatory versus inhibitory brain signaling. These molecules penetrate the blood-brain barrier and act in an enantiomer-selective manner, showing low toxicity. The Montine lab recently has shown that one of these enantiomers reverses the motor deficits in two different mouse models of Parkinson's disease (both toxin and transgenic models), and reverses the working memory deficit in a transgenic mouse model of Alzheimer's disease. These properties and this novel therapeutic strategy make this compound series extremely promising for the treatment of a number of previously intractable diseases of the central nervous system.

Stage of Development
The Montine Lab has investigated metabolic stability, brain uptake and other biochemical properties of the compound; in vitro and in vivo. They are now focused on cell and animal based experiments.

Applications

- Treatment of central nervous system conditions including neurodevelopmental, psychiatric/behavioral, and neurodegenerative diseases

Advantages

- Proven penetration of blood-brain barrier
- Low toxicity
- Enantiomer-selective activity on neurotransmitter metabolism
- Targets metabolism of neurotransmitters instead of their receptor engagement, representing a novel treatment strategy
- Broad range of potential applications for previously intractable diseases characterized by disregulation of the central nervous system

Publications

- Wawro, Adam M., et al. "Enantiomers of 2-methylglutamate and 2-methylglutamine selectively impact mouse brain metabolism and behavior." *Scientific Reports* 11.1 (2021): 1-13.
- Wawro, Adam M., et al. "Enantiomers of 4?aminopentanoic acid act as false GABAergic neurotransmitters and impact mouse behavior." *Journal of Neurochemistry* 158.5 (2021): 1074-1082.

Patents

- Published Application: WO2022216543
- Published Application: 20240115539

Innovators

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