Cleveland Clinic Innovations

Brain-Targeted Allosteric Activators of the α1A-Adrenergic Receptor

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PRODUCT

Small molecule therapy for the treatment of cognition disorders.

INDICATION

Neurocognitive disorders, including Alzheimer's disease.

VALUE PROPOSITION

- High potency compound.
- Blood-brain barrier permeable.
- Expected to have few peripheral side effects.

DEVELOPMENT STAGE

IND-enabling studies.

INTELLECTUAL PROPERTY

Patent Pending.

RELATED PUBLICATIONS

Doze VA, … **Perez DM**. Mol Pharmacology 80(4):747-58, 2011. PMC3187532.

Gupta MK, … **Perez DM**. Molecular Pharmacology, 76(2):314-26, 2009. PMC2713124.

Papay RS, … **Perez DM**. *Curr Res in Pharmacol and Drug Discov,* 4, 2023, 100142. PMC9762201.

CONTACT INFORMATION

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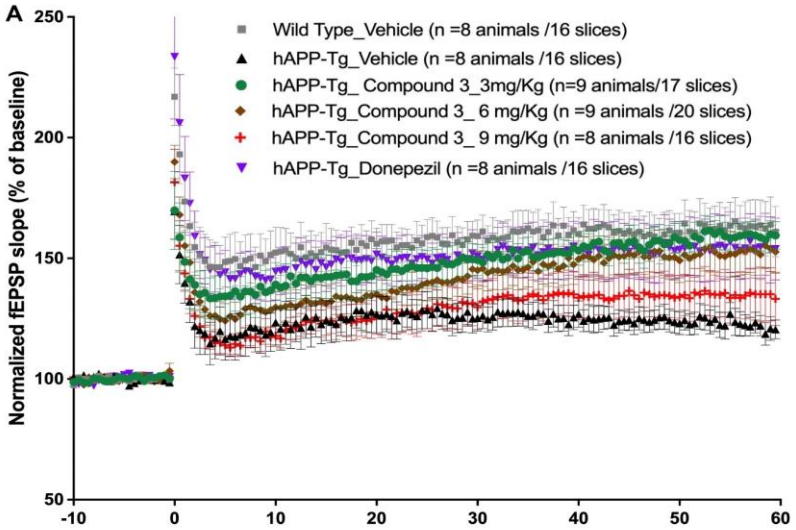
UNMET NEED

- Mitigating neurocognitive decline in degenerative disorders remains a highly unmet need and a great pharmacological challenge.
- Increased α_{1A}-Adrenergic Receptor (α_{1A}-AR) signaling has demonstrated increased synaptic plasticity, neurogenesis, gliogenesis, lifespan and long-term potentiation (LTP).
- ARs are G-Protein Coupled Receptors that bind norepinephrine and epinephrine.

SOLUTION

- Cleveland Clinic researchers have developed first-in-class positive allosteric modulators that bind specifically to the α_{1A}-AR.
- Lead compound (Cmpd-3) improves cognition and rescues LTP and amyloid biomarker deficits in two Alzheimer's disease (AD) mouse models.
- Treated AD mice had increased cognitive scores in the Barnes maze and increased LTP compared to placebo-controls, benchmarked to donepezil and outperformed donepezil at reducing Aβ40 and Aβ42.
- Preliminary DMPK indicates a safe profile with sufficient brain penetrance for QD dosing with full efficacy.
- The team has recently funded and initiated IND-enabling studies that include additional biomarker and target-engagement studies.



*hAPP-Tg+Cmpd-3 at 3 mg/kg (**green**) completely rescued LTP compared to hAPP-Tg vehicle (**black**). hAPP+Cmpd-3 at 6 mg/kg (**brown**) or 9 mg/kg (**red**) also increased LTP. Donepezil, 1mg/kg (**purple**).*