KDDF
Korea Drug Development Fund

Asset #49

Ramot At Tel Aviv University

Novel Specific Disease-Modifying PERK Activator for Huntington's Disease

Therapeutic Area	Neurology	**Indications**	Huntington's Disease
Modality	Small Molecule	**Development Stage**	Pre-clinical

Overview

Background

- ER stress-induced cytotoxicity is a common mechanism in neurodegenerative diseases.
- The Lederkremer group identified strong ER stress induction in the brain striatum, the first degenerating cells in Huntington's disease (HD).
- ER stress triggers the unfolded protein response (UPR), involving pathways like PERK kinase.
- UPR is initially protective but can become cytotoxic over time; early PERK pathway inhibition attempts failed.
- Lederkremer lab's discovery of low PERK activity suggests a potential for a PERK activator to enhance cellular protection in HD onset.

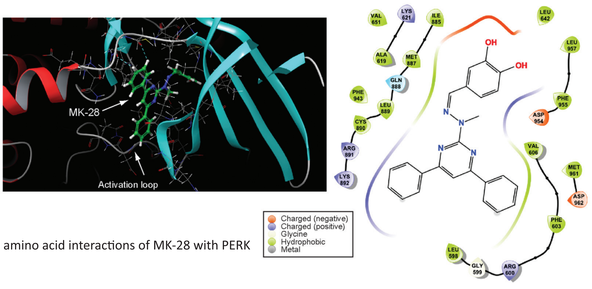
Technology Advantages

- A novel small molecule activator of the PERK sensor of the UPR called MK-28 was developed
- MK-28 showed excellent efficacy - compensates for ER stress induced cytotoxicity and rescues HD cellular and mouse models from cell death
- Motor function is significantly improved and life expectancy is extended in HD mouse models
- MK-28 is specific - selectivity for PERK was shown in a kinase panel with purified components and lack of activity in PERK knockout cells
- MK-28 is a small BBB-penetrating molecule with a favorable pharmacokinetics profile
- MK-28 is non-toxic and safe - tested in vitro and in vivo

Key Data

MK-28 is predicted to interact with the PERK activation loop and its cellular protective effect is PERK-dependent and more potent than CCT020312

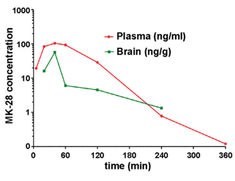
A



Detail of the predicted amino acid interactions of MK-28 with PERK

MK-28 exhibits brain penetrance and improves neurological functions in the R6/2 HD mouse model

B



Pharmacokinetics and BBB penetration analysis show that following 10mg/kg IP MK-28 injection, a maximum concentration of 105ng/ml was determined in plasma. MK-28 exhibits good BBB penetrance with a maximum concentration of 57ng/g

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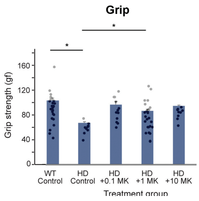
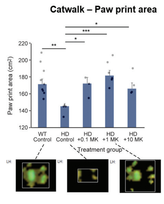


Grip strength test shows significant improvement in motor function upon treatment of R6/2 mice with MK-28. HD mice showed a strong motor deficit, which was significantly reduced with MK-28 treatment (IP 3 times per week, from 3 weeks of age, doses in mg/kg). Test at age of 10 weeks. n=38. Significance *p < 0.05 ANOVA Bonferroni-Holm post hoc.

D



The spreading of the paws on the walkway (paw print area, average of the 4 paws) was strongly reduced in HD mice and restored with MK-28 treatment. Bottom representative images: left hind paw print areas of WT mice compared to untreated HD mice or treated with 1mg/kg MK-28. Test at age of 9 weeks. Significance *p < 0.01 ANOVA Bonferroni-Holm post hoc.

IP Status & Publication(s)

Intellectual Property

Patent Number
US 10723706 B2 (2020.07.28)

Patent Family
PCT, US, EP

Publication(s)

- Ganz at al. (2020) A novel specific PERK activator reduces toxicity and extends survival in Huntington's disease models. Scientific Reports Shacham T, et al. (2023) Efficacy of therapy by MK-28 PERK activation in the Huntington's disease R6/2 mouse model. PREPRINT. Res. Square.