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Three Series of Chemical Inhibitors: Targeting ER Stress to Combat Neurodegenerative Disorders

Stanford researchers have developed a novel therapeutic approach for neurodegenerative diseases by targeting endoplasmic reticulum (ER) stress in neurons using CHOP inhibitors, with significant potential for development into first-in-class neuroprotective drugs for neurodegenerative diseases.

Neurodegenerative diseases are characterized by the progressive loss of structure or function of neurons, leading to debilitating and often fatal outcomes. Despite extensive research, we currently lack neuroprotection therapies that effectively halt or reverse neurodegeneration. There is an urgent need for novel treatments that can protect neurons. We previously found that neuronal ER stress may lead to neurodegeneration and mitigate ER stress, potentially slow or prevent the progression of neurodegenerative diseases.

To develop ER stress modulators, Stanford researchers have developed a chemical series comprising of CHOP inhibitors, which confer neuroprotection by modulating ER stress in neurons. Previously, Stanford researchers had uncovered the crucial role of neuronal ER stress as a critical factor in neurodegeneration in glaucoma patients. These studies demonstrated that modulating neuronal ER stress pathways by inhibition of CHOP provides significant neuroprotection in glaucoma animal models. Leveraging these findings, Stanford researchers performed cell-based HTS assays to screen chemical libraries and identified potent CHOP inhibitors,. Further structure-activity relationship (SAR) studies identified more potent analogs of the lead compound to modulate ER stress. In summary, a chemical series of- CHOP inhibitors are identified based on the core-structure of the lead compound, which can be further developed for neuroprotectants. thus to have the potential to be developed into first-in-class neuroprotective drugs for patients suffering from glaucoma and

other neurodegenerative diseases.

Stage of Development:
Research - in vitro cell-based assays and in vivo mouse glaucoma models. The next steps involve developing the lead compounds into drug candidates and further optimizing the structure of these compounds to identify the most potent, safe, soluble ones with ideal PK/PD profiles for drug development.

Applications

- First-in-class neuroprotective drugs for treating neurodegenerative diseases
- Glaucoma treatments
- Targeted therapy with broad applications
- Provides a platform for the development of future neuroprotective agents
- Can be integrated into personalized medicine strategies

Advantages

- Pioneering neuroprotectants for treating neurodegenerative diseases
- Potential to significantly improve patient outcomes and advance the field of neuroprotection.

Publications

- **Related publications:**
- Differential Effects of Unfolded Protein Response Pathways on Axon Injury-Induced Death of Retinal Ganglion Cells. *Neuron.* 2012 Volume 73, Issue 3, 9 February 2012, Pages 445-452. doi: 10.1016/j.neuron.2011.11.026. PMC3278720
- Rescue of Glaucomatous Neurodegeneration by Differentially Modulating Neuronal ER Stress Molecules. *Journal of Neuroscience.* 2016 May 25;36(21):5891-903. DOI: 10.1523/JNEUROSCI.3709-15.2016. PMC4879204
- Neuroprotection by eIF2?-CHOP inhibition and XBP-1 activation in EAE/optic neuritis. *Cell Death Dis.* 2017 Jul 20;8(7):e2936. doi: 10.1038/cddis.2017.329. PMC5550873

- Maprotiline restores ER homeostasis and rescues neurodegeneration via Histamine Receptor H1 inhibition in retinal ganglion cells. *Nature Communications.* 2022 Nov 10;13(1):6796. DOI: 10.1038/s41467-022-34682-y PMC9649812

Patents

- Published Application: WO2025212515

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