Repurposed drugs targeting the unfolded protein response to prevent neurodegeneration in dementia

https://www.neurodegenerationresearch.eu/survey/repurposed-drugs-targeting-the-unfolded-protein-response-to-prevent-neurodegeneration-in-dementia/

Principal Investigators

Professor Giovanna Mallucci

Institution

University of Cambridge

Contact information of lead PI
Country

United Kingdom

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Repurposed drugs targeting the unfolded protein response to prevent neurodegeneration in dementia

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Alzheimer's Society

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2

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Research Abstract

We recently discovered the mechanism by which protein misfolding leads to neurodegeneration in prion
disease. The pathway involved is a generic cellular pathway, a branch of the unfolded protein response (UPR)
that controls protein synthesis at the level of initiation of translation. Rising levels of misfolded

prion protein
cause sustained over-activation of the PERK-eIF2? branch of the UPR in neurons resulting in an uncompensated decline in global translation rates, synaptic failure and neuronal death. Reduction of eIF2?- P
levels by genetic manipulation or by pharmacological inhibition of PERK by GSK2606414, rescue vital
translation rates and prevent neurodegeneration and clinical disease in prion-infected mice. The small
molecule ISRIB is similarly protective. There is increasing evidence that UPR dysregulation is a central
process in protein misfolding neurodegenerative diseases, and that maintaining translation levels is essential
for neuronal health. Raised levels of PERK-P and eIF2?-P occur in the brains of patients with Alzheimer's,
Parkinson's, Frontotemporal dementias and related diseases. The pathway is also implicated in learning and
memory; manipulation of eIF2?-P levels boost cognition in wild type mice and restore memory deficits in AD
mouse models. Raised levels of eIF2?-P are associated with neurodegeneration in a tauopathy mouse model,
which we have also prevented by treatment with PERK inhibitor. However, progressing these compounds to
clinical use has been impeded by pancreatic toxicity of GSK2606414, and poor solubility of ISRIB. This led us
to screen known drug libraries for inhibitors of the UPR in C. elegans and cell lines with better therapeutic
qualities. Two compounds, trazodone and dibenzoylmethane, were found and tested in prion disease and
displayed efficacy without toxicity. Trazodone is an antidepressant that could be repurposed for the treatment
of dementia, while dibenzoylmethane is a naturally occurring compound with low toxicity. The aim of this
application is to test these compounds in models of tauopathy and Alzheimer's disease, to determine their
greater relevance to dementia and to strengthen the case for repurposing these compounds for new
therapeutic treatments.

Further information available at:

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