262 eIF2B inhibition prevents neurodegeneration

Asset Overview

Product Type	Small molecule
Indication	Neurodegenerative disorder
Current Stage	Lead Identification / optimization
Target(MoA)	Binding to eIF2B Non-covalent binding at the Protein interface
Brief Description	• The researchers developed a chemical inhibitor of the ISR, ISRIB, reverses the attenuation of eIF2B by phosphorylated eIF2α, protecting mice from neurodegeneration and traumatic brain injury. ISRIB is not toxic to the pancreas and significantly extends survival in animal experiments • ISRIB is not toxic to the pancreas and significantly extends survival in animal experiments
Organization	The Alborada Drug Discovery Institute

Differentiation

□ **Eukaryotic initiation factor 2 (eIF2α)**

- eIF2α is part of a wider integrated physiological response to maintain proteostasis in the face of ER stress
- The dysregulation of which is increasingly associated with a wide range of diseases, particularly neurodegenerative disorders
- High levels of eIF2α cause sustained translational repression leading to catastrophic reduction of critical proteins, resulting in synaptic failure and neuronal loss

□ **Inhibition PERK branch of the unfolded protein response (UPR)**

- Mostly used PERK inhibitor GSK2606414 and GSK414, is apparently not specific and some of the side effects attributed to this drug in vivo, can be a result of its off-target activities including pancreatic toxicity
- The researchers developed treatment with the small molecule ISRIB, which restores translation downstream of eIF2α

□ **Advantages of ISRIB treatment**

- ISRIB penetrates the blood–brain barrier and reduces ATF4 levels and partially restores protein synthesis rates
- Fine-tuning the extent of UPR inhibition and subsequent translational de-repression uncouples neuroprotective effects from pancreatic toxicity
- In any case the survival of pancreatic tissue is marked advantage of partial inhibition of the ISR

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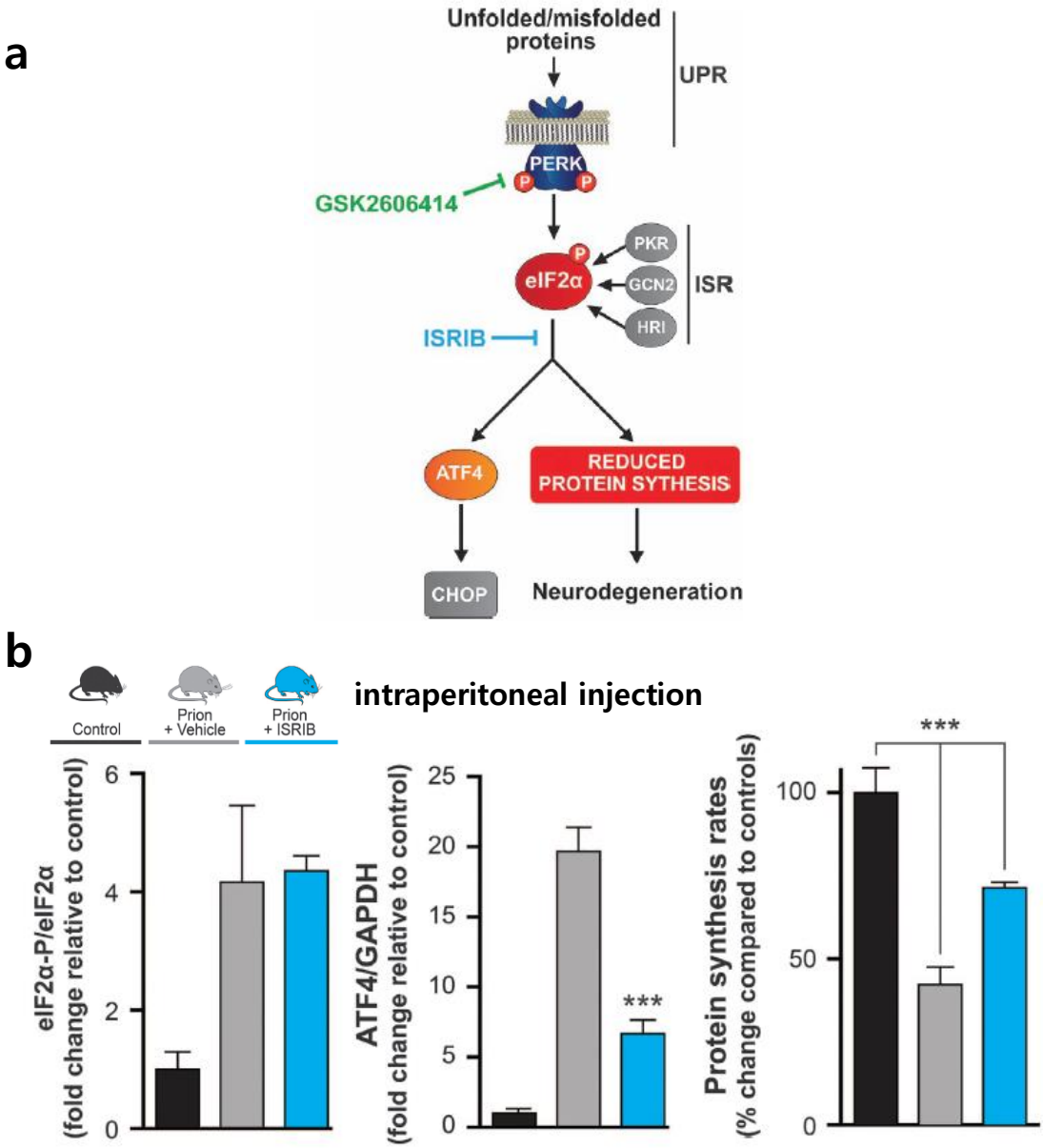
Key Data

PERK branch of the UPR and ISRIB restores and survival in prion-infected animals



(a) Scheme of the PERK branch of the UPR. Unfolded proteins activate PERK, which phosphorylates eIF2α. This represses translation at the level of initiation.(b) ISRIB restores translation in prion-diseased mice, downstream of eIF2α phosphorylation. ISRIB treatment (blue bars) lowers ATF4 levels while leaving eIF2α-P unchanged in prion-diseased mice when compared with vehicle treated (gray bars) animals, confirming its site of action downstream of eIF2α-P. Representative immunoblots of hippocampal lysates and bar chart quantitating relative levels of proteins in three independent samples are shown.

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Key Data

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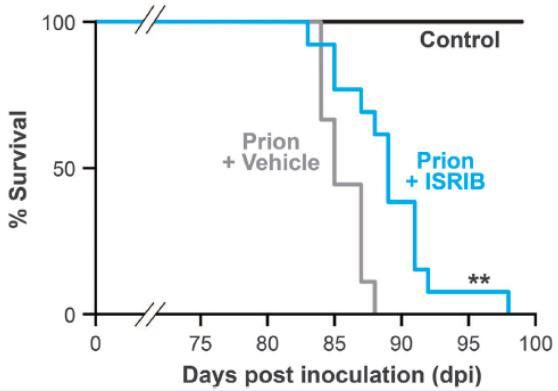
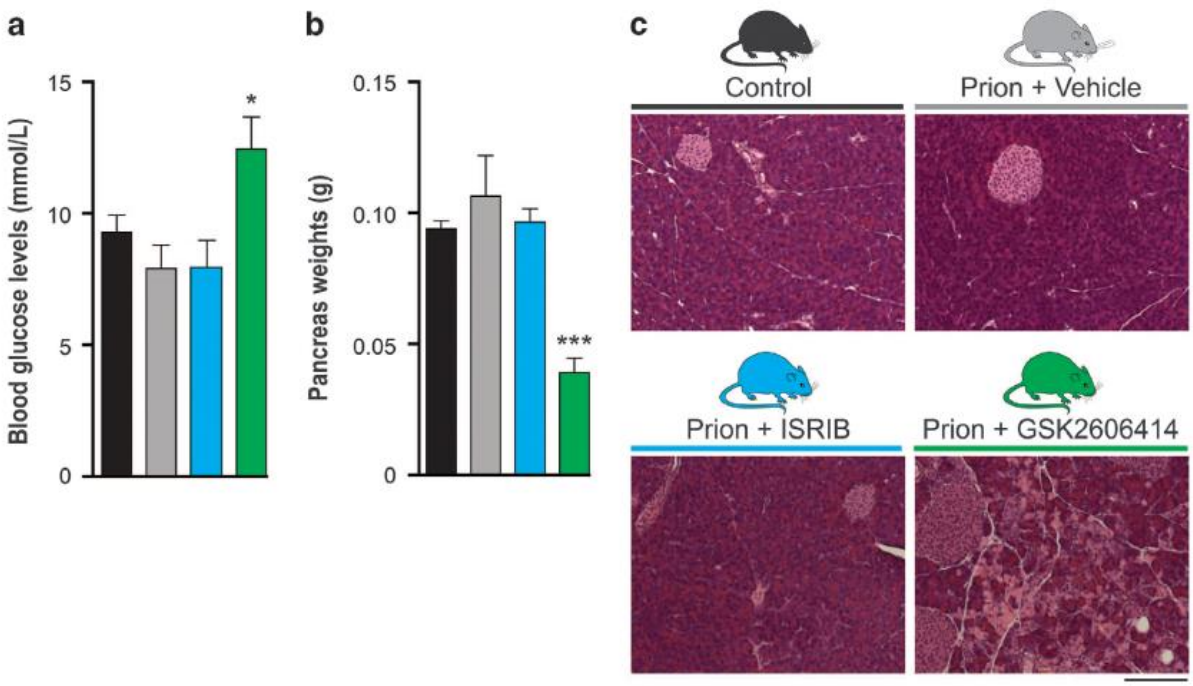


ISRIB treatment significantly extends survival in prion-infected animals compared with vehicle-treated mice. Kaplan–Meier plot, controls n=9 (black bar), vehicle n=9 (gray bar), ISRIB treated n=12 (blue bar).

ISRIB is not toxic to the pancreas, unlike GSK2606414.



(a) GSK2606414 treatment (green bar) mildly raises blood glucose levels compared with control (black bar),vehicle-treated (gray bar) and ISRIB-treated (blue bar) mice (n=6–9 for each group). GSK2606414 treatment leads to a significant reduction in pancreas weight, while ISRIB treatment has no effect (n= 3–6 for each group).

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

Contact Information

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