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## ISRIB

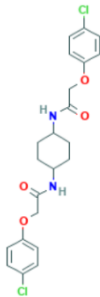
### Evidence Summary

ISRIB may improve cognition, though its effects in Alzheimer's disease are uncertain and could be detrimental. No published reports on its use in humans are available to date.

**Neuroprotective Benefit:** ISRIB may be effective for age-related cognitive decline or certain forms of neurodegeneration, but its effectiveness for Alzheimer's disease is mixed/detrimental based on preclinical studies. No studies have been carried out in humans.

**Aging and related health concerns:** Insufficient evidence exists (only a single preclinical cancer study) whether ISRIB would be beneficial for any age-related disease.

**Safety:** The safety of ISRIB in humans is currently unknown, though there may be toxicity in certain animal models.

<b>Availability:</b> Not available; licensed by Calico	<b>Dose:</b> Unknown in humans	<b>Molecular Formula:</b> C <sub>22</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> <b>Molecular weight:</b> 451.3g/mol  Source: <a href="#">Pubchem</a>
<b>Half-life:</b> 8 hours	<b>BBB:</b> Penetrant in animals	
<b>Clinical trials:</b> None	<b>Observational studies:</b> None	

### What is it?

ISRIB was discovered in a screen for molecules that could prevent the upregulation of ATF4, a protein upregulated by the integrated stress response (ISR) and the unfolded protein response (UPR), two pathways that sense cellular stress signals and react by initiating a number of protective programs ([Sidrauski et al, 2013](#)). PERK, and its effector protein eIF2 $\alpha$ , lie at the intersection of the ISR and the UPR and maintain protein homeostasis in the endoplasmic reticulum (ER). When misfolded proteins accumulate in the ER, PERK phosphorylates eIF2 $\alpha$  which halts protein synthesis, preventing further accumulation of misfolded proteins in the ER. However, protein synthesis is important for learning and memory. ISRIB's specific mechanism is to reverse the effects of eIF2 $\alpha$  phosphorylation.

Studies report an increase in phosphorylated eIF2 $\alpha$  in post-mortem Alzheimer's brains and Alzheimer's animal models. In addition, genetic attenuation of eIF2 $\alpha$  phosphorylation in Alzheimer's mice partially rescues the decrease in protein synthesis, synaptic plasticity, and spatial memory ([Ma et al, 2013](#)). Thus, preventing the phosphorylated eIF2 $\alpha$ -induced brake on protein synthesis might improve memory formation.

ISRIB has a half-life of eight hours in mice and has excellent blood brain barrier penetration ([Sidrauski et al, 2013](#)). However, it is not very soluble and requires significant preparation before treatment in mice.



**Neuroprotective benefit:** ISRIB may be effective for age-related cognitive decline or certain forms of neurodegeneration, but its effectiveness for Alzheimer's disease is mixed/detrimental based on preclinical studies. No studies have been carried out in humans.

Types of evidence:

- One post-mortem study in humans
- Two preclinical studies in AD models
- Four preclinical studies in healthy animals
- Four preclinical studies in other models of neurodegenerative diseases

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

None

Human research to suggest benefits to patients with dementia:

Increased phosphorylation of eIF2 $\alpha$  has been associated with Alzheimer's disease, though it is not known whether inhibiting eIF2 $\alpha$  activation with ISRIB will benefit Alzheimer's patients ([Ma et al, 2013](#)).

Mechanisms of action for neuroprotection identified from laboratory and clinical research

Alzheimer's disease

Two Alzheimer's animal models (one amyloid model and one tau model) were treated with ISRIB (5mg/kg) over one and a half months. In the amyloid model, the dose had to be reduced to 2.5mg/kg due to significant mortality by day eight (the lower dose did not cause significant mortality). Treatment partially restored spatial learning, but not memory, benefits in the tau model when compared to non-transgenic animals. However, there were no learning or memory effects in the amyloid model. Interestingly, ISRIB increased the levels of p-tau in tau transgenic animals. The authors speculate this could be due to an increase in the hyperphosphorylation of tau due to the restoration of protein synthesis ([Briggs et al, 2017](#)).

In another Alzheimer's animal model, a single injection of ISRIB had no effect on cognition ([Johnson and Kang, 2016](#)).

*In vitro*, treatment with ISRIB prevented amyloid-beta-induced neuronal cell death but had no effect on amyloid production ([Hosoi et al, 2016](#)).



### *Healthy young mice*

A single injection of ISRIB in young healthy rodents was able to immediately improve spatial and fear-associated learning ([Sidrauski et al, 2013](#)). One mechanism by which it might improve cognition is by inhibiting mGluR-dependent long-term depression (LTD) in hippocampal synapses which requires eIF2a phosphorylation ([Di Prisco et al, 2014](#)).

### *Healthy aged mice*

One study reported no beneficial cognitive effects of ISRIB (0.1 mg/kg) after a single treatment in aged mice (6-7 months). They reported that potential reasons for differing effects from other studies could be because the study was insufficiently powered, or the types of tests would not be sensitive to ISRIB treatment (Morris Water Maze and contextual fear conditioning). They were unable to identify a marker of target engagement in the brain, so potentially the dose they used could also be too low ([Johnson and Kang, 2016](#)). In another study in aged mice, ISRIB (2.5 mg/kg) treatment over three days reduced the elevation of ATF4 20 days later (suggesting target engagement). Three-day treatment in aged mice also improved cognition in the radial arm water maze (up to three weeks after treatment), increased the number of dendritic spines on hippocampal neurons, and reduced levels of inflammation ([Krukowski et al, 2020](#)).

### *Traumatic Brain Injury*

In mouse models of TBI, injury increased the expression of proteins involved with the ISR. Three daily treatments with ISRIB weeks after injury improved cognition immediately after training and up to one week later. It also improved hippocampal long-term potentiation (LTP) ([Chou et al, 2017](#)). It was also reported that TBI causes an increase in risk-taking behavior in male, but not female, mice. Three-day treatment with ISRIB weeks after TBI reversed this increase in risk-taking behavior (up to 70 days after treatment), reversed the increase in the ISR, and restored synaptic plasticity ([Krukowski et al, 2020](#)).

### *Prion disease*

A drug from GSK targeting PERK (GSK2606414) was able to slow clinical decline in a mouse model of prion disease without affecting prion protein aggregation. However, it was associated with pancreatic toxicity due to on target effects (the unfolded protein response is important for insulin secretion). It was thought that targeting a downstream target in the ISR pathway (namely eIF2 $\alpha$ ) with ISRIB would have the same beneficial effects without the pancreatic toxicity. Indeed, daily oral treatment starting at seven weeks post infection extended lifespan in prion infected mice. It did not have an obvious effect on prion aggregation ([Haliday et al, 2015](#)).

### ALS

In an ALS neuronal cell culture model, [Bugallo et al \(2020\)](#) reported an increase in the unfolded protein response (UPR). They reported that inhibition of the UPR with ISRIB, but not GSK2606414, increased the survival of ALS neurons. The authors speculate that since ISRIB inhibits eIF2 $\alpha$  (which is downstream of PERK, GSK2606414's target) it allowed for the continued translation of ATF4 which could explain the reduced toxicity of ISRIB.

### APOE4 Interactions:

None reported

**Aging and related health concerns:** Insufficient evidence exists (only a single preclinical cancer study) whether ISRIB would be beneficial for any age-related disease.

### Types of evidence:

- One preclinical study in a cancer model

The loss of PTEN (phosphatase and tensin homolog) tumor suppressor and hyperactivation of MYC are associated with about 50% of lethal metastatic forms of prostate cancer. Prostate cancer patients with PTEN loss and high eIF2 $\alpha$  expression showed increased death over a 10-year follow up. In a xenograft mouse model of PTEN loss and eIF2 $\alpha$  overexpression, ISRIB treatment increased lifespan ([Nguyet et al, 2018](#)).

**Safety:** The safety of ISRIB in humans is currently unknown, though there may be toxicity in certain animal models.

### Types of evidence:

- Multiple preclinical studies

In an Alzheimer's animal model, a dose of ISRIB too high (5mg/kg) caused excessive mortality and the dose had to be lowered ([Briggs et al, 2017](#)). An effective, yet non-lethal dose and dosing schedule, has yet to be determined and may depend on the particular disease being treated. Whether long-term treatment with ISRIB is safe is also not yet determined.



**Drug interactions:**

Drug interactions have not been studied; though ISRIB could potentially interact with drugs that have been reported to act on the integrated stress response pathway (e.g., trazodone, [Halliday et al, 2017](#)).

**Sources and dosing:**

Not available; ISRIB is currently licensed to Calico. Doses in preclinical studies which showed some effectiveness were 2.5 mg/kg/day. However, there may be a narrow therapeutic window, as 5 mg/kg/day resulted in increased mortality in an Alzheimer's animal model.

**Research underway:**

Nothing was found regarding ISRIB on [clinicaltrials.gov](#), though presumably Calico is still doing in house studies. Preclinically, it is currently being studied for [Fragile X Syndrome](#).

**Search terms:**

- ISRIB

**Websites visited:**

- [Clinicaltrials.gov](#)
- [Pubmed](#)

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*If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact [INFO@alzdiscovery.org](mailto:INFO@alzdiscovery.org). To view our official ratings, visit [Cognitive Vitality's Rating page](#).*