Pharmacological brake-release of mRNA translation enhances cognitive memory

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Translation – full speed ahead

- Translation rate can easily be downregulated by the phosphorylation of the initiation factor eIF2α
  - GCN2: amino acid starvation
  - PKR: viral infection
  - HRI: heme deficiency
  - PERK: accumulation of unfolded or misfolded Protein in the ER
- Find a compound to overcome the phosphorylation effects
Unfolded Protein Response (UPR)

- **PERK**
  (Protein Kinase RNA-like Endoplasmic Reticulum Kinase)
  Dimerization, trans-auto-phosphorylation
  Phosphorylation of eIF2α
  -> slow down of translation

- **IRE₁**
  (Inositol-requiring Enzyme 1)
  Dimerization trans-auto-phosphorylation
  Splicing of XBP₁, called XBP₁s
  -> up regulation of ER-chaperones

- **ATF6**
  (Activating Transcription Factor 6)
  Proteolytic cleavage
  Migration to Nucleus
  -> up regulation of ER-chaperones
Compound screen the needle in the haystack

- Firefly assay: response on ER-stress 187 compounds
- Bi-cistronix ATF4-dGFP-IRES-mCherry: toxicity 77 compounds
- Inhibition of ER stress-elicited induction of endogenous ATF4 via WB 28 compounds
ISRIB
the needle
ISRIB
Keeps translation high
Enhancement of the cognitive memory

"eIF2α+/S51A heterozygote mice display enhanced memory, while induction of the eIF2α kinase PKR in brain pyramidal cells impairs memory (Costa-Mattioli et al., 2007; Jiang et al., 2010)."
Conclusion

- ISRIB causes insensitivity to eIF2α phosphorylation regarding the translation activity.
- Insensitivity to eIF2α phosphorylation seems to have an enhance effect in cognitive memory (in mice).
Side effect
Side effect

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<th>Time (h)</th>
<th>Tg</th>
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- **100 kDa**
  - ATF6 full length

- **70 kDa**
  - ATF6 cleaved
  - ATF6 cleaved (longer exposure)

- **35 kDa**
  - eIF2α total