Translational Inhibition of Neurotoxic Aggregating Proteins Leads to Efficacy in Alzheimer's and Parkinson's Patients

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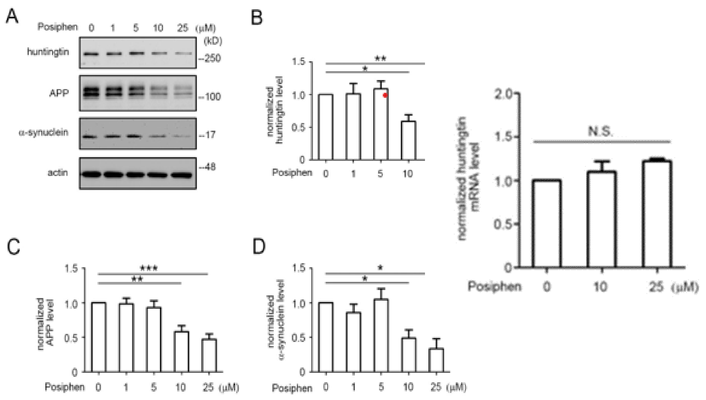
Introduction

Overexpression of neurotoxic proteins drives downstream events that dysregulate axonal transport, lead to inflammation, nerve cell death, and loss of function. By inhibiting the translation of neurotoxic aggregating proteins - amyloid precursor protein, tau, alpha-synuclein etc., ANVS401 restores axonal transport, lowers inflammation and protects nerve cells from dying. Thereby, ANVS401 shows efficacy in two double-blind, placebo- controlled clinical phase 2a studies in AD and PD patients.

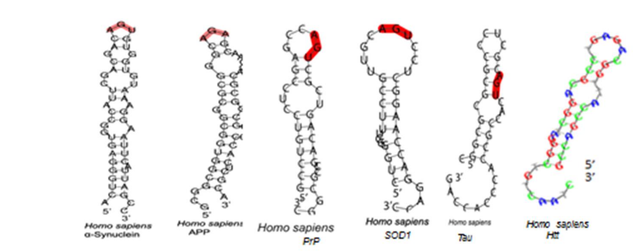
ANVS401 is a Translational Inhibitor of Neurotoxic Aggregating Proteins (TINAP)



In an unbiased assay - SILAC Metabolic Labeling (stable isotope labeling using amino acids in cell culture) – we looked for protein expression affected by ANVS401. We found huntingtin protein, APP and a-Syn were downregulated. Indeed, western blots confirmed that ANVS401 inhibits the translation of these neurotoxic proteins without affecting their mRNA levels.

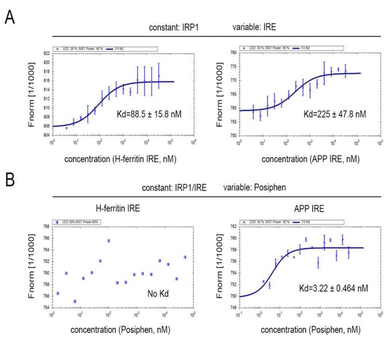
ANVS401 facilitates the binding of IRP1 to the atypical IREs in neurotoxic proteins

1. Neurotoxic aggregating proteins have the atypical IRE domain in the 5" UTR of their mRNAs.



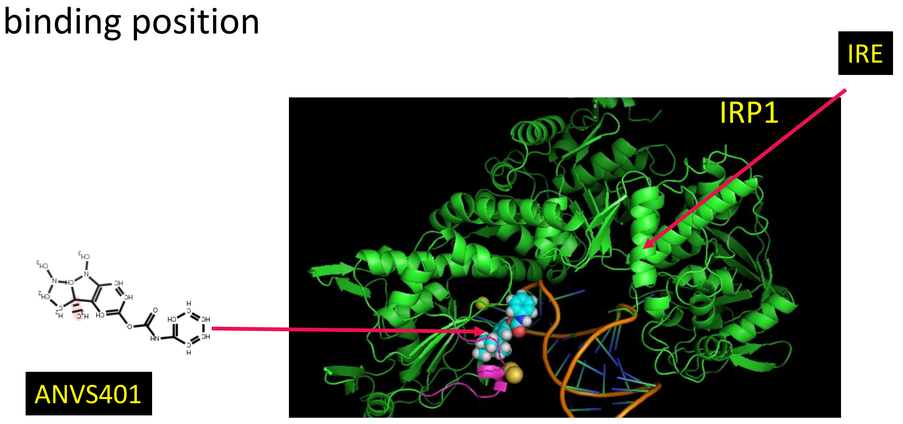
The Iron-responsive elements (IREs) are 30-nucleotide long RNA motifs containing the CAGUGN sequence (the classic IRE motif) and can form special stem-loop structures.

2. ANVS401 specifically binds to atypical IREs but not the typical IREs

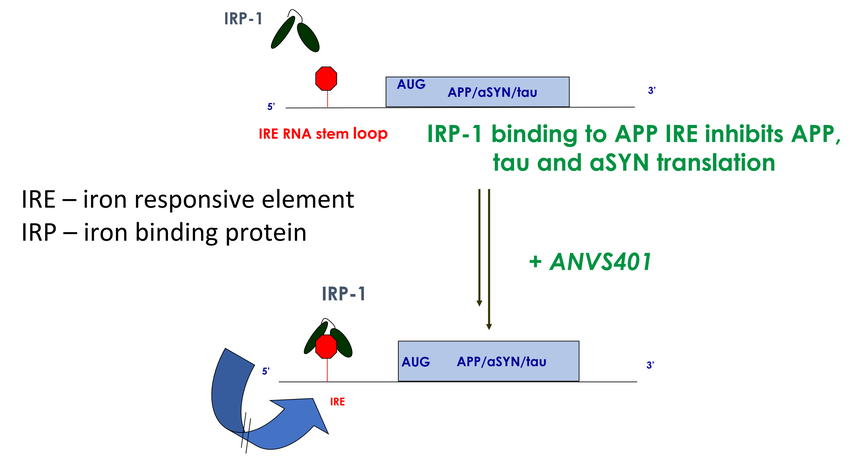


Microscale thermophoresis showed both APP (atypical IRE) and Ferritin (typical IRE) can bind to IRP1 (Iron Regulatory Protein 1) but only APP & IRP1 complex can bind to ANVS401.

3. Molecular model of how ANVS401 locks IRP1 in the RNA binding position



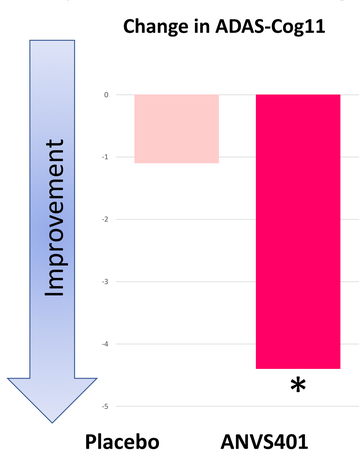
4. ANVS401 potentiates the binding of IRP1 to the atypical IREs



ANVS401 shows efficacy in Phase2a trials of both AD and PD patients

We conducted two phase2a clinical trials one in Alzheimer's (AD) and one in Parkinson's (PD) patients. In part 1 of this double-blind, placebo-controlled study, 14 early to moderate AD and 14 early to moderate PD patients were recruited. They were given 80mg ANVS401 or placebo per day for 25 days. In part 2, an additional 40 early to moderate PD patients were randomized into 5mg, 10mg, 20mg and 40mg ANVS401 dose groups.

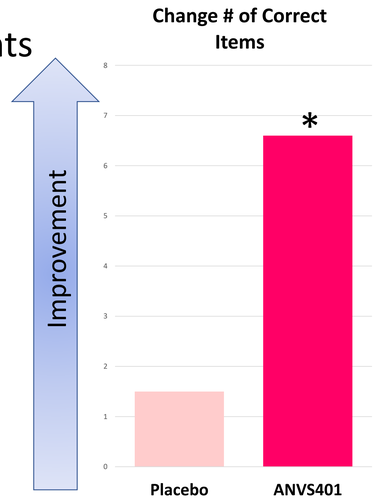
1. Improves ADAS-Cog 11 in AD patients



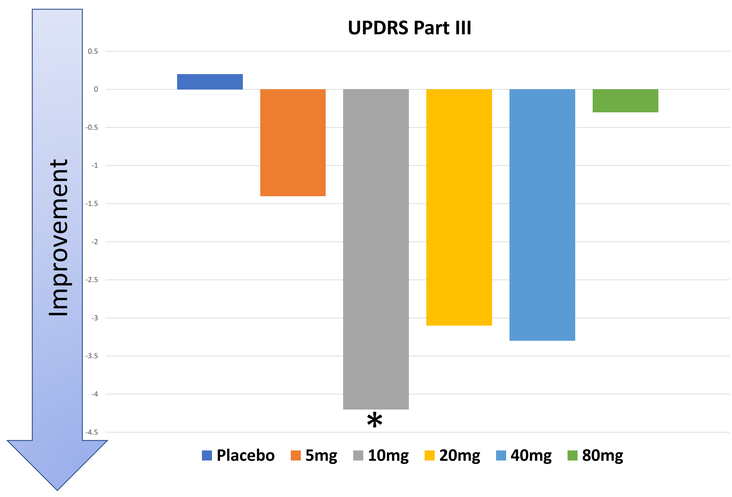
80mg ANVS401 treated patients showed 4.4 points improvement in ADAS-Cog11 test, a statistically significant improvement from baseline and 3.3 points better than placebo treated patients at day 25.
* P<0.05

2. Improves WAIS Coding in AD patients

The WAIS coding test measures speed in movement and thinking. After 25 days 80mg ANVS401-treated PD patients showed a 6.6-point improvement in coding comparing with baseline (* P<0.05) and a 5.5-point improvement over placebo.

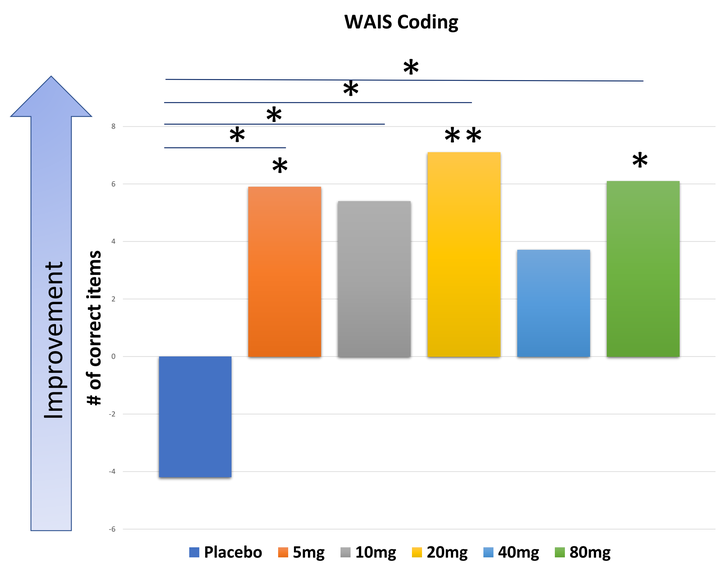


3. Improves total MDS-UPDRS, as well as part II, III and IV in PD patients



All doses of ANVS401 improved the MDS-UPDRS Part III with the most improvement at 10mg once per day.
*p<0.05

4. Improves WAIS Coding in PD patients



All doses of ANVS401 improved the WAIS coding test in speed of movement and coordination.
* p<0.05 **p<0.01

Conclusions

- ANVS401 is a translational inhibitor of neurotoxic aggregating proteins (TINAP).
- ANVS401 potentiates the binding of IRP1 to the atypical IREs in mRNAs of neurotoxic proteins.
- ANVS401 shows statistically significant improvements in Phase 2a clinical trials:
  - Cognition in AD patients
  - Motor function in PD patients
  - WAIS coding in AD and PD patients
- The successful completion of our Phase 2 clinical trials is providing validation of our approach in two diseases and allows us to move to Phase 3 trials in both diseases.

For more information, please Join our oral presentation on Friday 11/12 10:25am!