

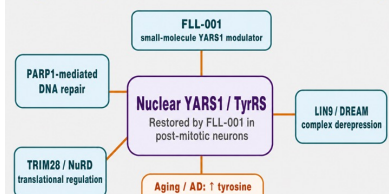
KEY TAKEAWAY

FLL-001 is a first-in-class TyrRS (YARS1) Chronomodulator with potent neuroprotective activity, on-target validation, favorable nonclinical safety, and complete oral bioavailability in mice.

INTRODUCTION

Tyrosyl-tRNA synthetase (TyrRS) has been nominated as a therapeutic target by the NIH Accelerating Medicines Partnership® Program for Alzheimer's Disease. TyrRS is an enzyme with a circadian cycle that includes non-canonical nuclear functions converging on three neuroprotective pathways: PARP1-mediated DNA repair, TRIM28/NuRD translational regulation, and LIN9/DREAM derepression. Elevated tyrosine in aging and Alzheimer's disease flattens TyrRS's circadian cycle, leading to impaired oxidative DNA damage repair and protein synthesis.

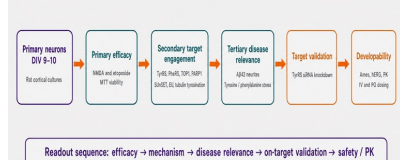
Figure 1. TyrRS triad and FLL-001 mechanism concept



METHODS

Primary rat cortical neurons (DIV 9-10) were evaluated in a tiered assay cascade. Primary assays measured neuroprotection against NMDA- and etoposide-induced toxicity. Secondary assays assessed target engagement by Western blot, protein synthesis, transcription, and tubulin tyrosination. Tertiary assays evaluated rescue of Aβ42-induced neurite degeneration. TyrRS dependency was tested by siRNA knockdown; safety and PK were also assessed.

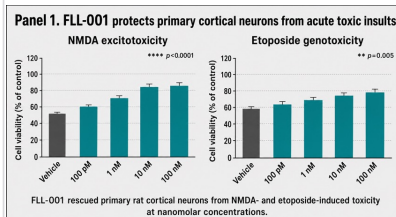
Figure 2. Tiered assay cascade used to evaluate FLL-001



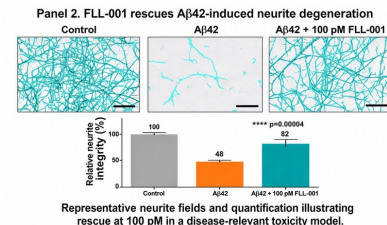
Readout sequence: efficacy → mechanism → disease relevance → on-target validation → safety / PK

RESULTS

FLL-001 protected rat cortical neurons against NMDA toxicity ($p < 0.0001$) and etoposide toxicity ($p = 0.005$) at nanomolar concentrations and rescued Aβ42-induced neurite degeneration at 100 pM ($p = 0.00004$).



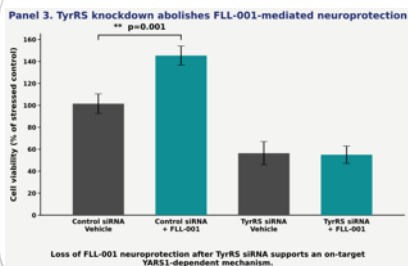
FLL-001 rescued primary rat cortical neurons from NMDA- and etoposide-induced toxicity at nanomolar concentrations.



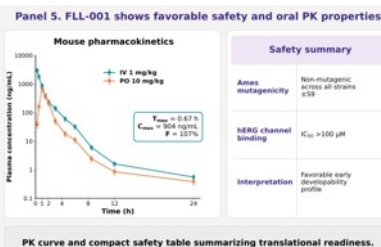
Representative neurite fields and quantification illustrating rescue at 100 pM in a disease-relevant toxicity model.

TARGET VALIDATION AND TRANSLATIONAL READINESS

TyrRS siRNA knockdown abolished neuroprotection ($p = 0.001$), confirming on-target activity. FLL-001 was non-mutagenic across all Ames strains, showed no hERG liability, and yielded rapid oral absorption, high exposure, and complete oral bioavailability in mice. FLL-001 is now in Pre-IND development for Alzheimer's Disease



Loss of FLL-001 neuroprotection after TyrRS siRNA supports an on-target YARS1-dependent mechanism.



PK curve and compact safety table summarizing translational readiness.

CONCLUSIONS

- FLL-001 showed neuroprotection against excitotoxic, genotoxic, and Aβ42-mediated injury.
- FLL-001 engages YARS1/TyrRS circadian biology and its downstream neuroprotective program.
- On-target validation and favorable early safety/PK support IND-enabling development.
- If therapeutically validated for the treatment of AD, FLL-001 adds the reconstitution of a higher-order maintenance program to therapeutic approaches focusing on clearance of toxic metabolic byproducts.

REFERENCES

- Sajish M, Schimmel P. Nature. 2015.
- Coquelet A, et al. FEBS Journal. 2025.
- AAIC 2026 abstract #13223.

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