Development of an aggregation inhibitor targeting alpha-synuclein pathology

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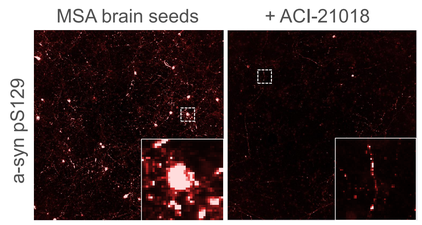
Background:

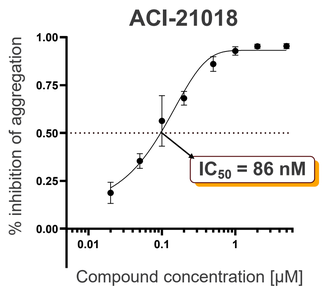
- Alpha-synuclein (a-syn) aggregation is a key pathological driver of several neurodegenerative disorders and a common co-pathology in Alzheimer's disease where it is associated with exacerbated cognitive decline
- We aim to discover cell-permeable, orally bioavailable and brain penetrant small molecules that inhibit aggregation and intracellular accumulation of pathological a-syn

Results:

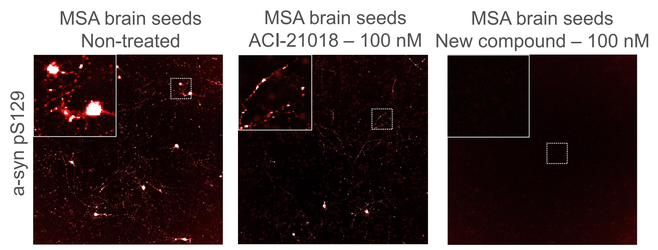
- Identified CNS-penetrant, a-syn aggregation inhibitors with nanomolar potency for inhibiting intracellular a-syn aggregate accumulation
- Robust effects observed even in post-seeding treatment paradigms thanks to intracellular targeting
- Reduced seeding-competent a-syn pathology in the Tg hPFF mouse model with significant neuroprotective effects supporting disease-modifying potential
- Shared binding site with PET tracer ACI-12589 supports translational biomarker and clinical development strategies

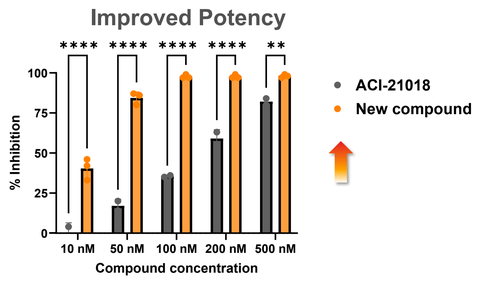
Halting intracellular a-syn aggregation with nM potency





A-syn Morphomers® reduce intracellular a-syn inclusions formed in rat cortical neurons upon treatment with brain derived a-syn seeds, indicating potent inhibition of seeding, a key process underlying intra- and intercellular propagation of a-syn pathology.





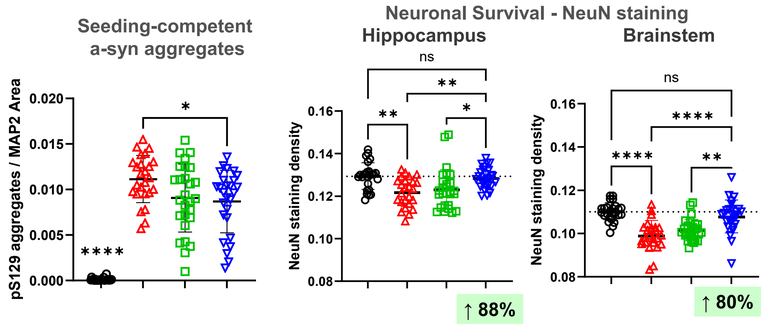
A-syn pathology reduction and neuroprotective effects *in vivo*

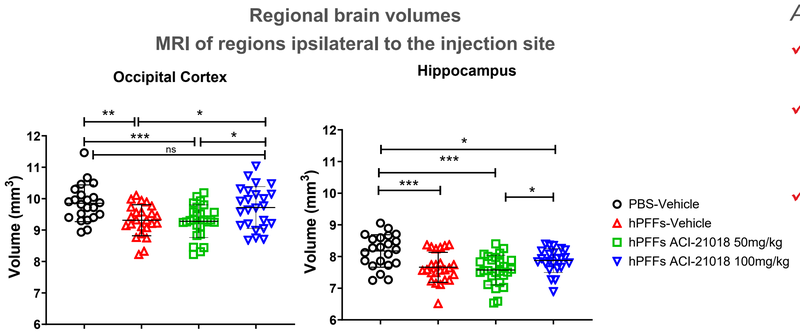
Study Design:

✓Transgenic a-syn A53T mice (line M83) injected in the olfactory nucleus with human a-syn preformed fibrils (hPFFs)

✓Therapeutic paradigm: treatment initiated 48h post-inoculation of pathological a-syn

✓Once daily oral administration for 15 weeks at a dose maintaining free brain concentrations above the *in vitro* IC_{50}

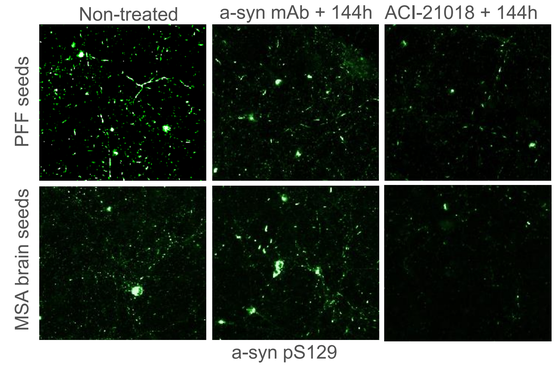


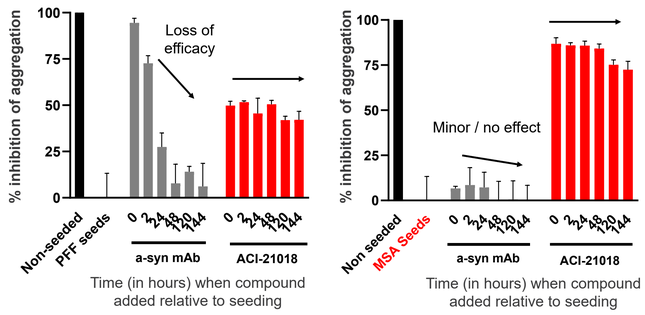


ACI-21018 treatment led to:

- ✓ *significant reduction of pathological a-syn species*
- ✓ *Near-complete rescue of neuronal loss in regions proximal and distal to disease initiation*
- ✓ *Rescue of brain atrophy, with MRI volumes nearing healthy levels, supporting disease-modifying potential and translational relevance*

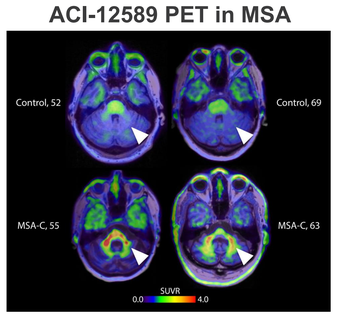
A-syn Morphomer® efficacy retained when treatment begins post-seeding

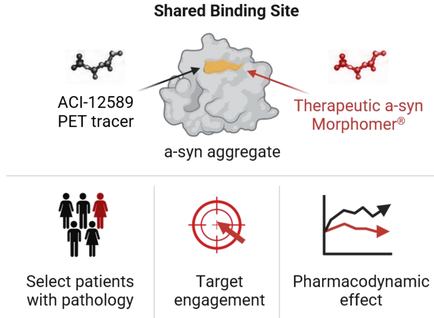


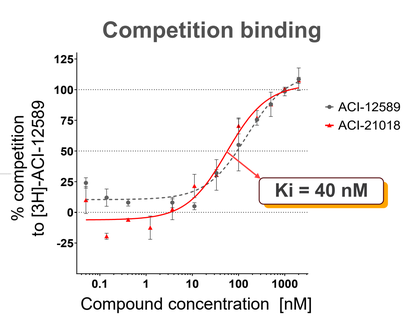


A-syn Morphomers® retain efficacy with delayed treatment and across a-syn pathological conformations, unlike the extracellularly acting a-syn antibody (mAb), which inhibits PFF but not MSA seeding activity.

Therapeutic-diagnostic synergy with the a-syn PET tracer ACI-12589



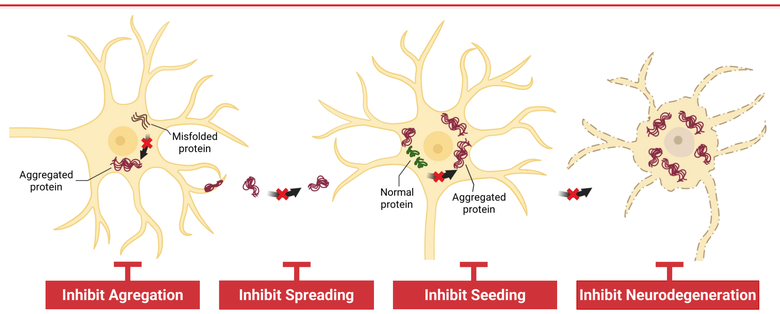




Conclusions

- Discovery of highly potent, brain-penetrant a-syn aggregation inhibitors
- Blockade of intracellular aggregation and intercellular propagation of a-syn pathology to slow disease progression
- Neuroprotective effects *in vivo* support disease-modifying potential of a-syn Morphomers®
- Therapeutic-diagnostic synergy enables optimal translation and accelerated development

A-syn Morphomers® halt pathology at multiple points



Acknowledgements

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