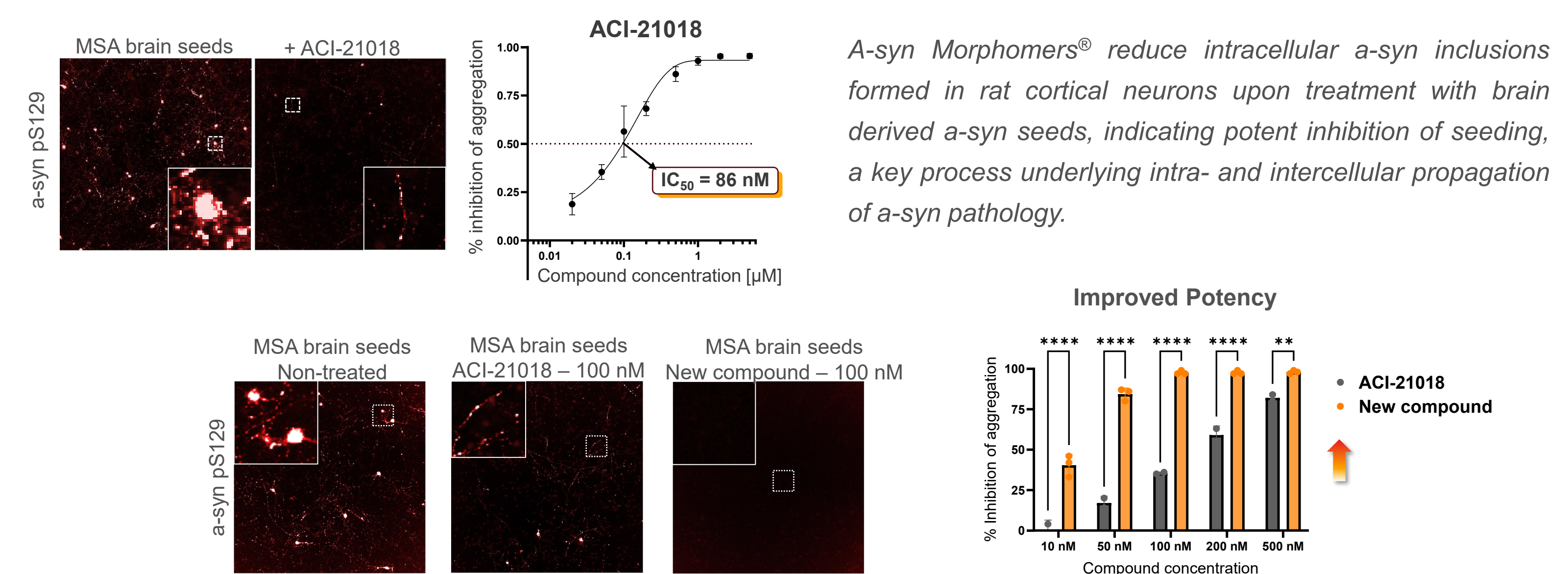


Development of an aggregation inhibitor targeting alpha-synuclein pathology

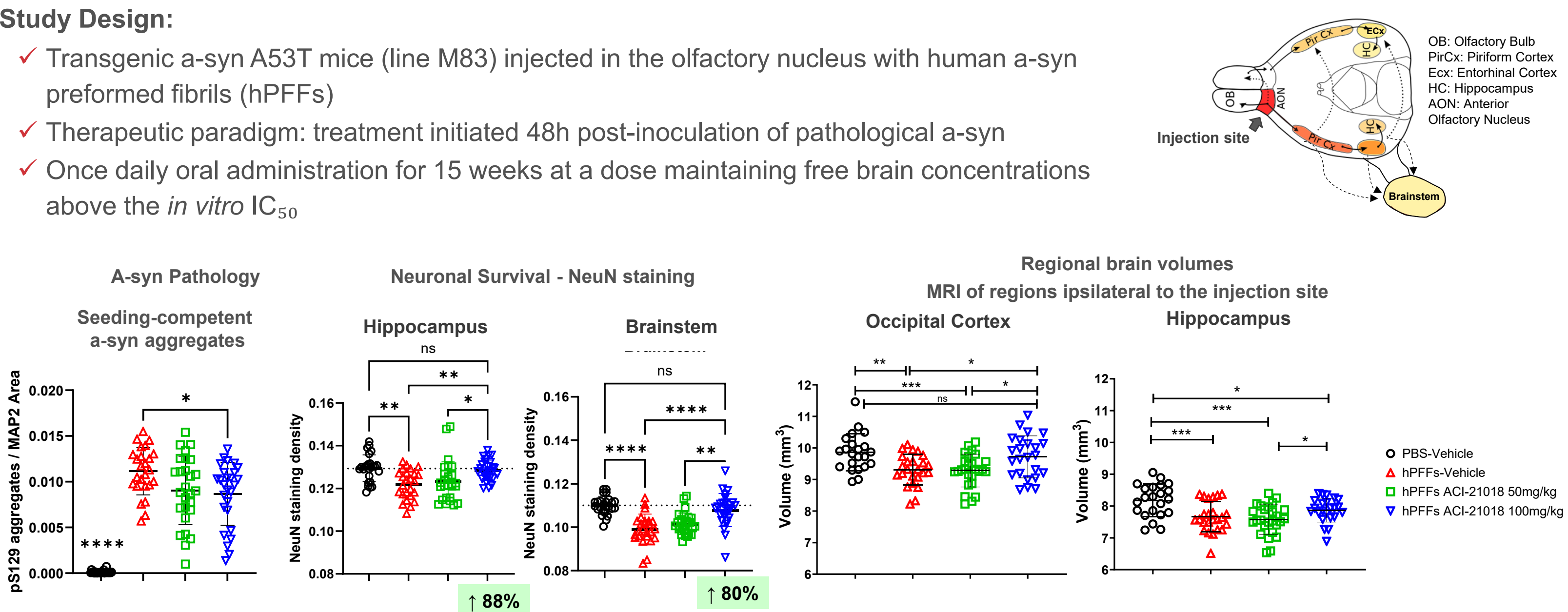
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 AC Immune SA, EPFL Innovation Park, Building B, 1015 Lausanne, Switzerland

- 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

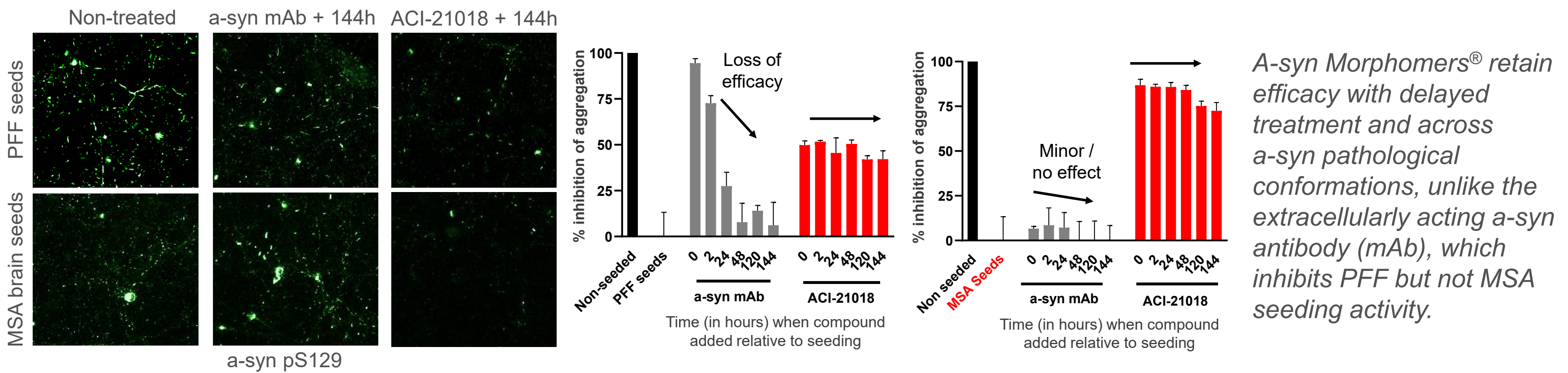


A-syn pathology reduction and neuroprotective effects *in vivo*

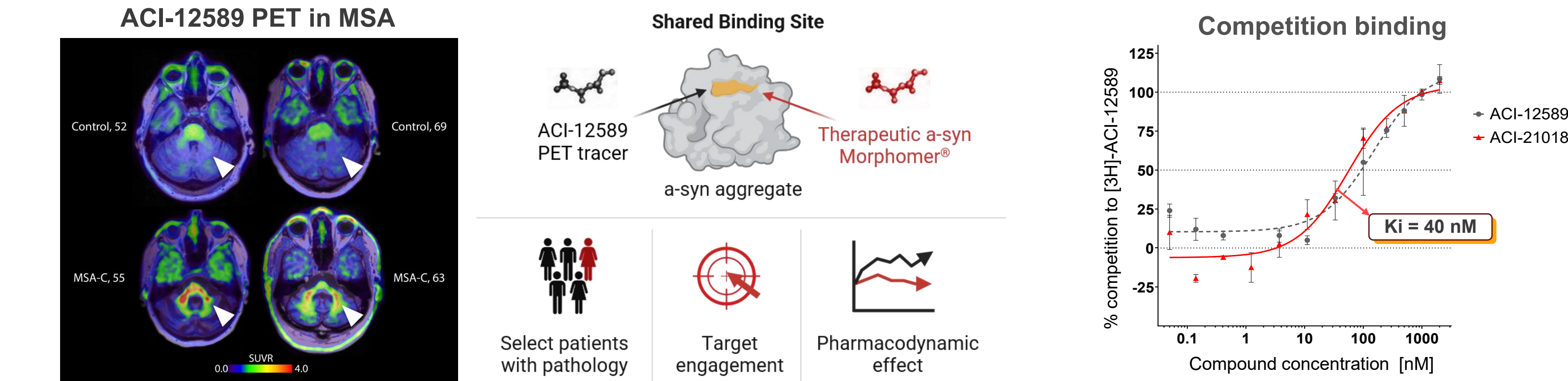


- ACI-21018 treatment led to:
- ✓ significant reduction of pathological a-syn species
 - ✓ Near-complete rescue of neuronal loss in regions proximal and distal to disease initiation
 - ✓ Rescue of brain atrophy, with MRI volumes nearing healthy levels, supporting disease-modifying potential and translational relevance

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

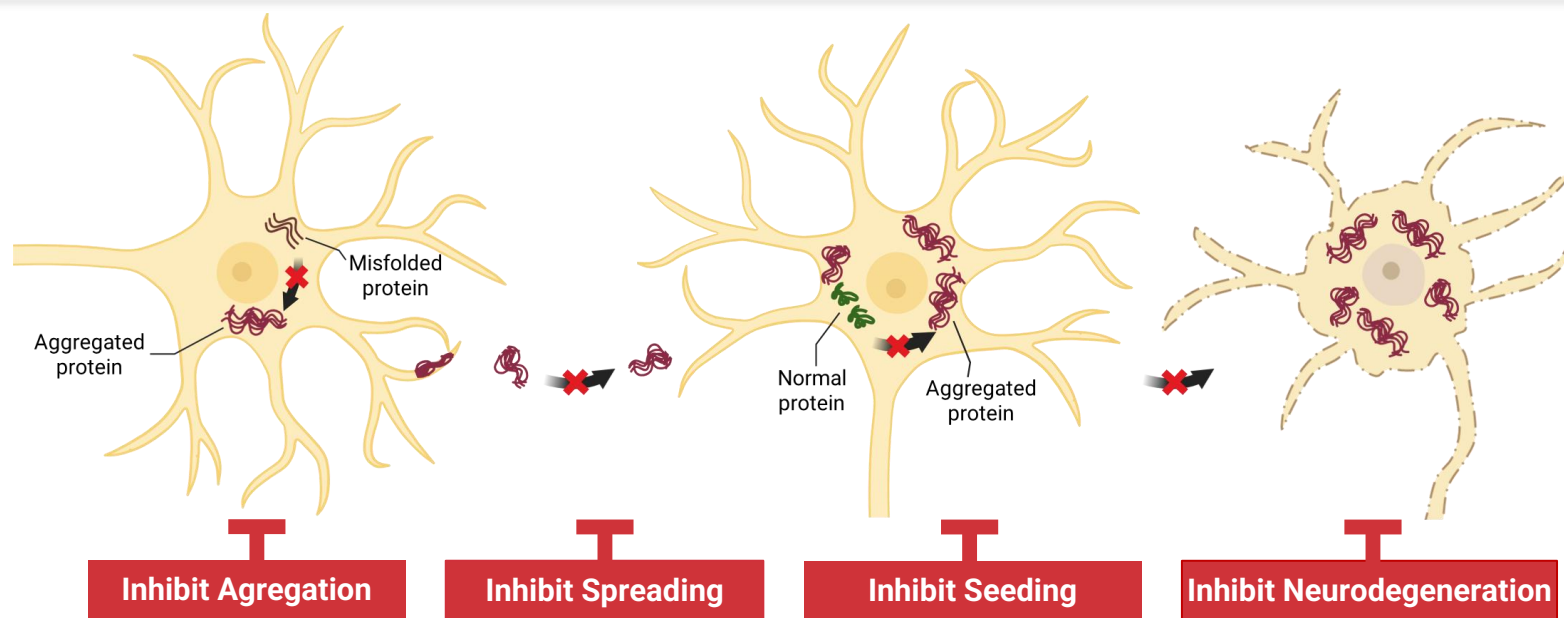


Therapeutic-diagnostic synergy with the a-syn PET tracer ACI-12589



- 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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