Understanding the Impact of Disaggregases Through Unbiased Proteomics

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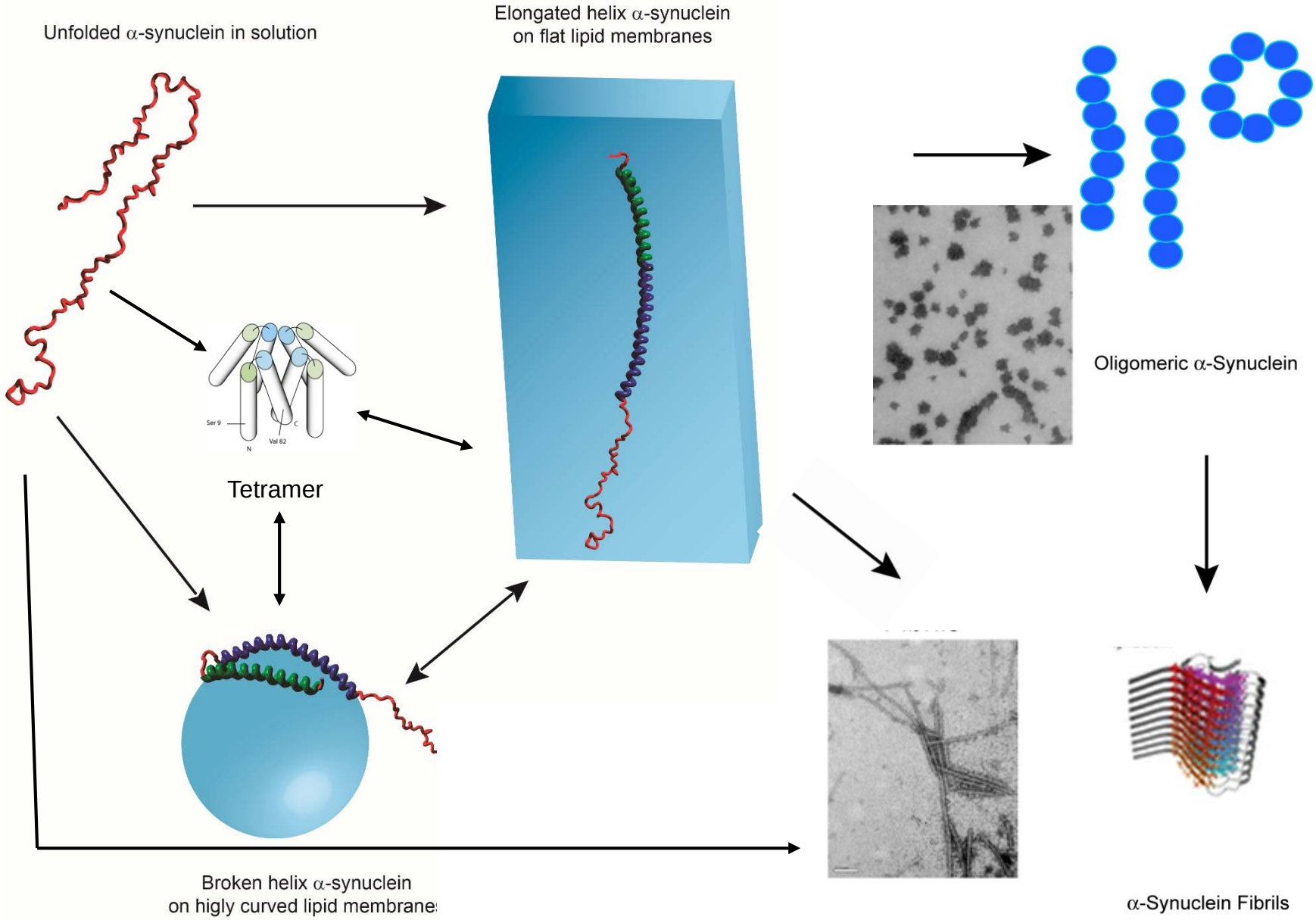
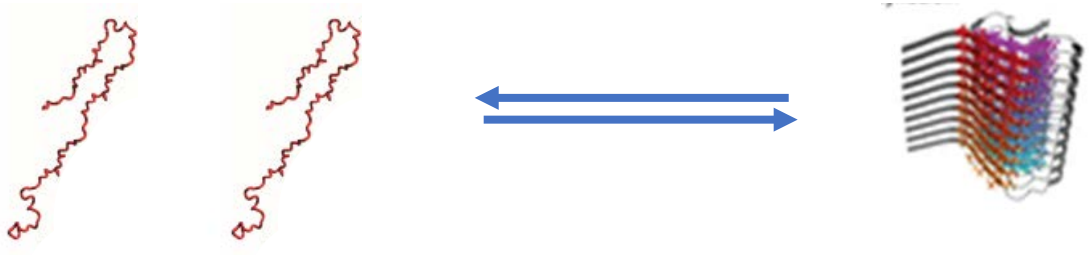
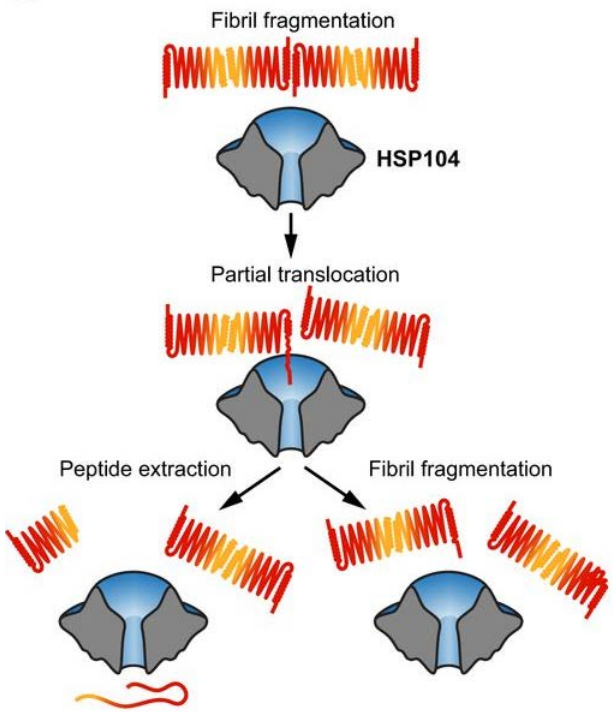
Protein aggregation is a common feature of neurodegenerative disease



Can protein aggregation be reversed?

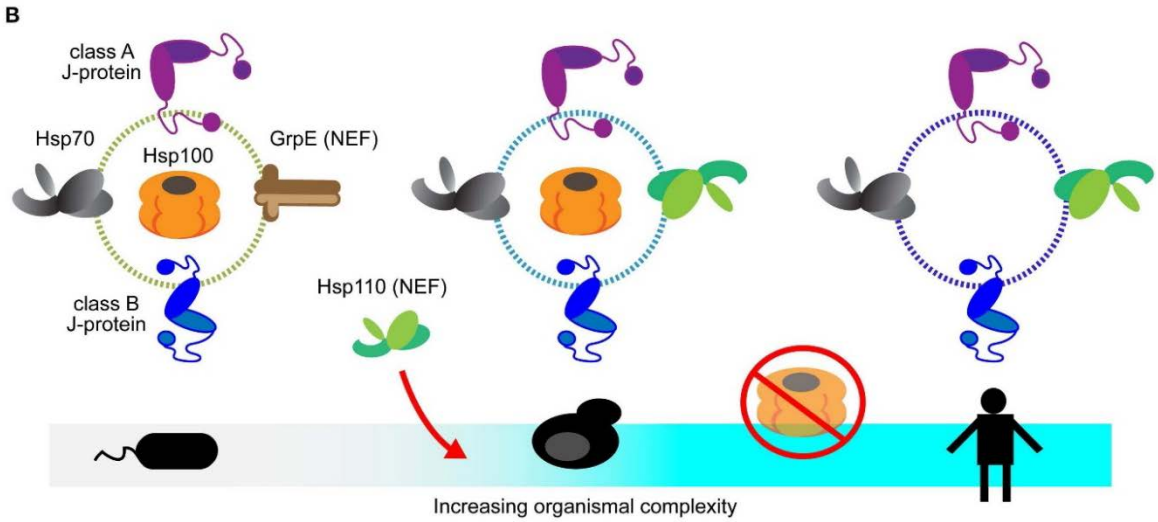


Hsp104 is a disaggregase in lower organisms



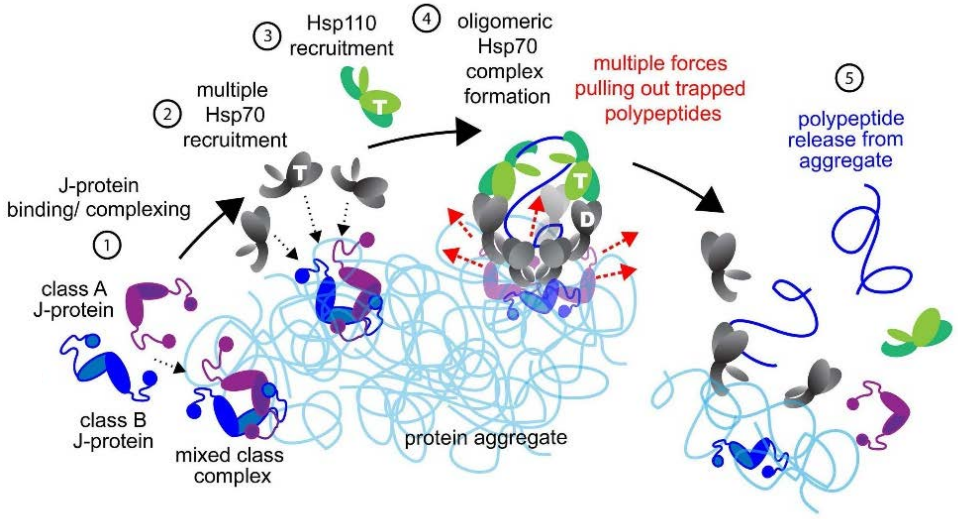
A

	cytosolic/ nuclear Hsp100	Hsp70	J-protein	NEF
E. coli	1	3	6	1
S. cerevisiae	1	11	22	8
H. sapiens	0	12	54	19



Nillegoda & Bukau, FMB, 2016

Mammalian disaggregase was identified recently



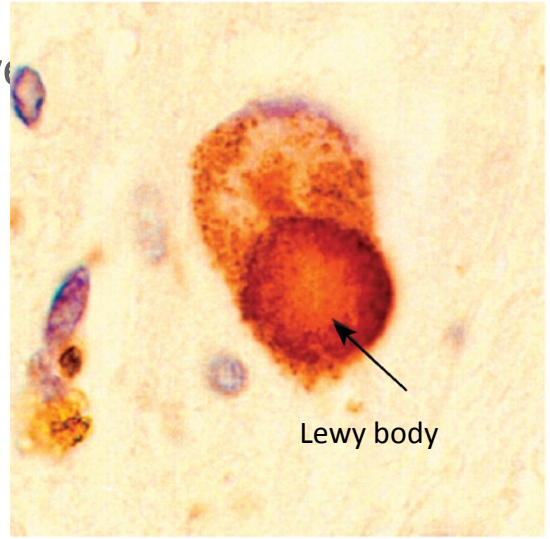
Hsp70:DNAJ:Hsp110=1.0:0.5:0.1

Nillegoda & Bukau, FMB, 2016

α-Synuclein and Neurodegenerative Disorders

- Five independent mutations cause familial Parkinson's disease
  A30P, A53T, E46K, G51D, H50Q (PARK 1 locus)
- A case of duplication & triplication of wild type α-synuclein gene
  (PARK 4 locus)
- Top GWAS hit for all PD- both familial and sporadic
- α-synuclein is the major component of Lewy Bodies
- Many other neurodegenerative diseases have
  synuclein lesions: Synucleinopathies

Alzheimer's disease, Lewy Body variant
Dementia with Lewy Bodies
Multiple System Atrophy



α–Synuclein disaggregase was identified recently

Molecular Cell
Article

Human Hsp70 Disaggregase Reverses Parkinson's-Linked α-Synuclein Amyloid Fibrils

Xuechao Gao,[1,2] Marta Carroni,[3] Carmen Nussbaum-Krammer,[1,2] Axel Mogk,[1,2] Nadinath B. Nillegoda,[1,2] Anna Szlachcic,[1,2] D. Lys Guilbride,[4] Helen R. Saibil,[3] Matthias P. Mayer,[4] and Bernd Bukau[1,2,*]
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[2]German Cancer Research Center (DKFZ), DKFZ-ZMBH Alliance, Im Neuenheimer Feld 282, 69120 Heidelberg, Germany
[3]Department of Crystallography, Institute for Structural and Molecular Biology, Birkbeck College, Malet Street, London WC1E 7HX, U
[4]ZMBH, DKFZ-ZMBH Alliance, Im Neuenheimer Feld 282, 69120 Heidelberg, Germany
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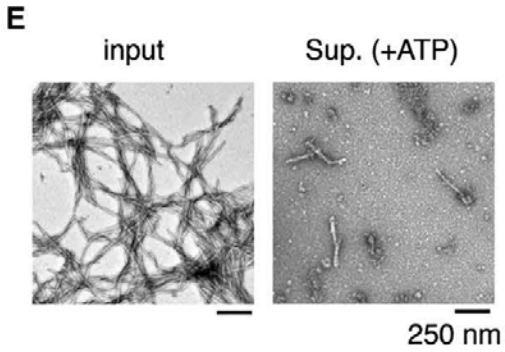
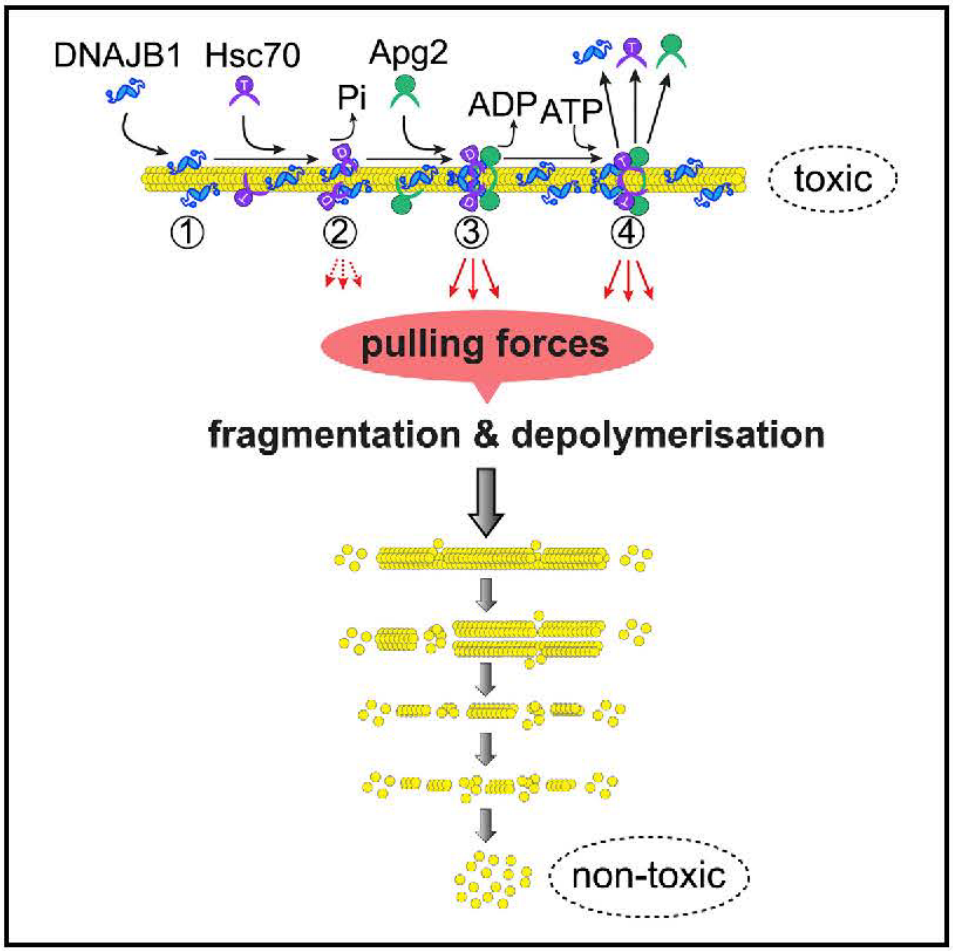
http://dx.doi.org/10.1016/j.molcel.2015.07.012



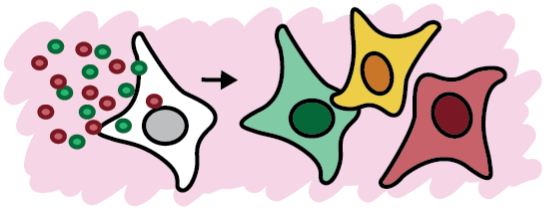


Hsc70:DNAJB1:Hsp110 (Apg2) =1.0:0.5:0.1

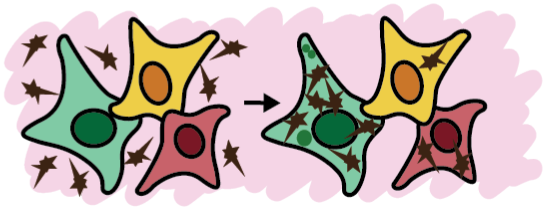
Gao et al, Mol. Cell 2015

α–Synuclein seeding assay

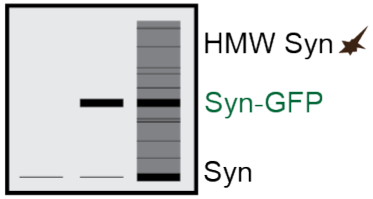
1. Transfect HEK293T Cells with Hsp110 and α-Synuclein-GFP



2. Add α-Synuclein Seeds to HEK293T Media and Allow for Internalization

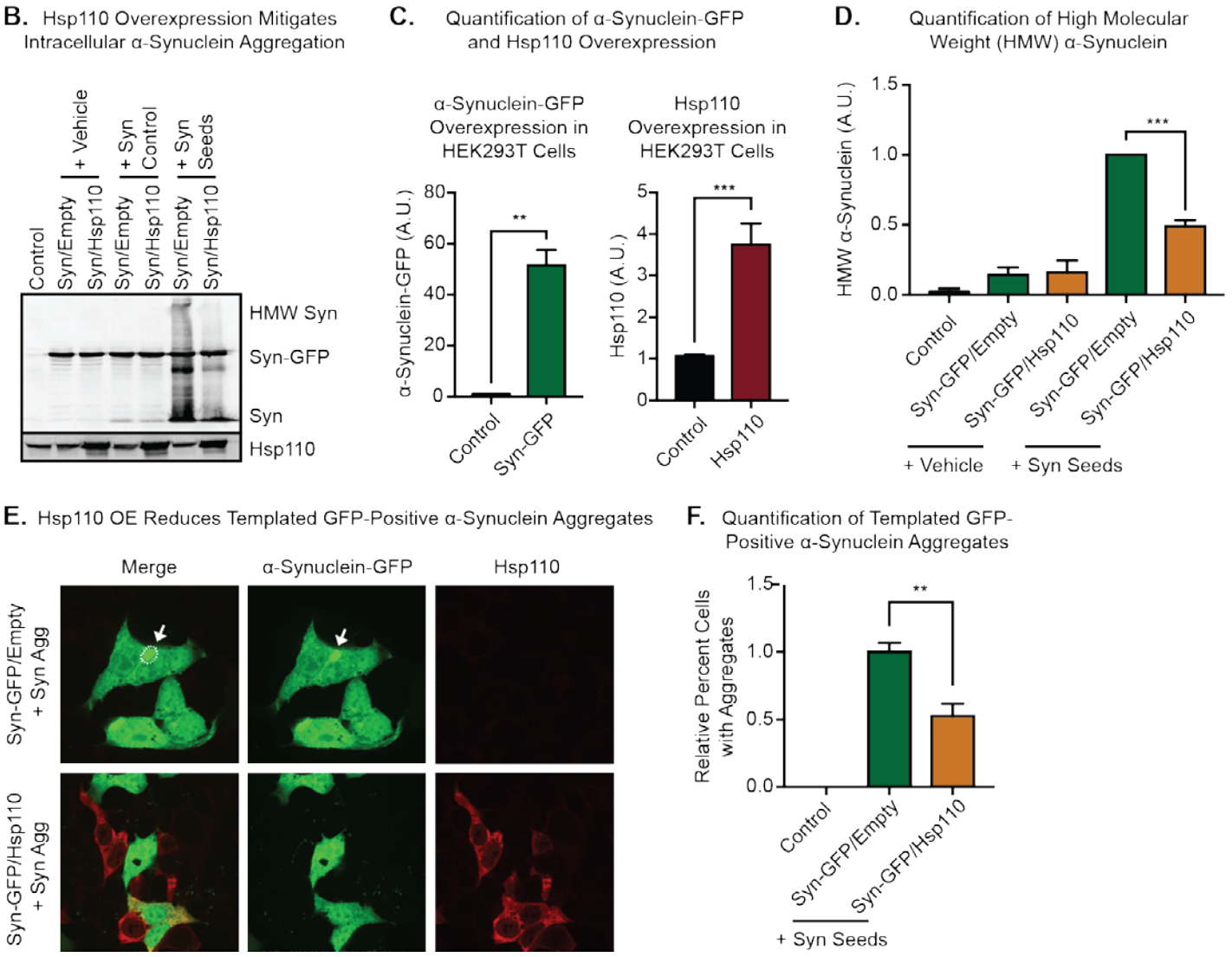


3. Assess Internal α-Synuclein Aggregation by Western Blot



4. Image Templated GFP-α-Synuclein Aggregates

Hsp110 ameliorates α-synuclein aggregation in cells



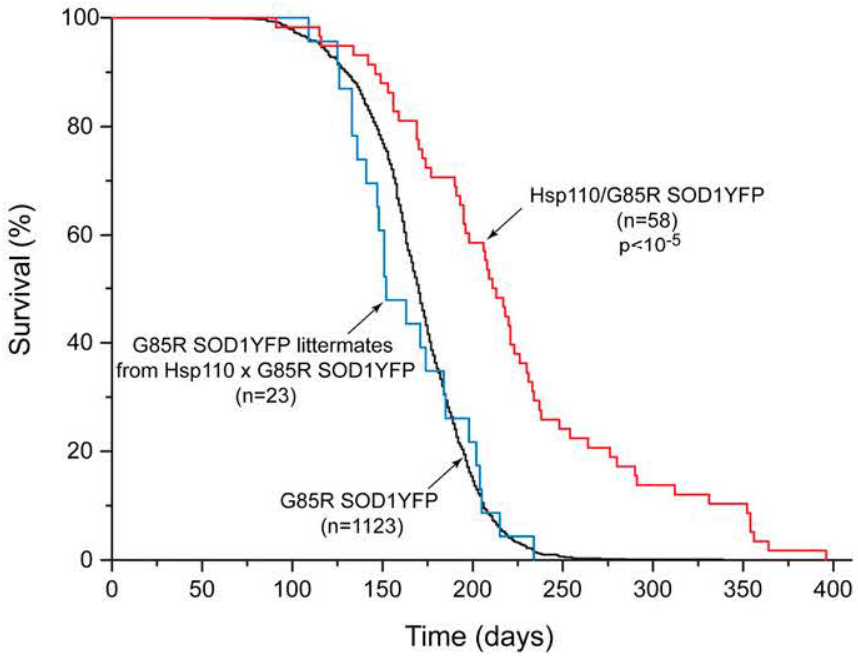
Transgenic Hsp110 expression is beneficial in ALS mice

PNAS

Extended survival of misfolded G85R SOD1-linked ALS mice by transgenic expression of chaperone Hsp110

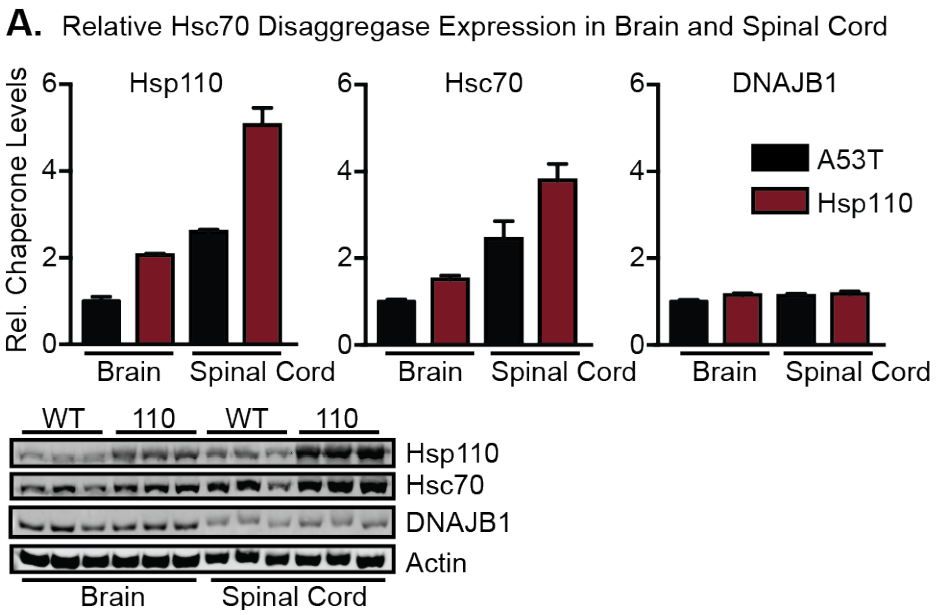
Maria Nagy[a,b], Wayne A. Fenton[b], Di Li[a,b], Krystyna Furtak[a,b], and Arthur L. Horwich[a,b,1]

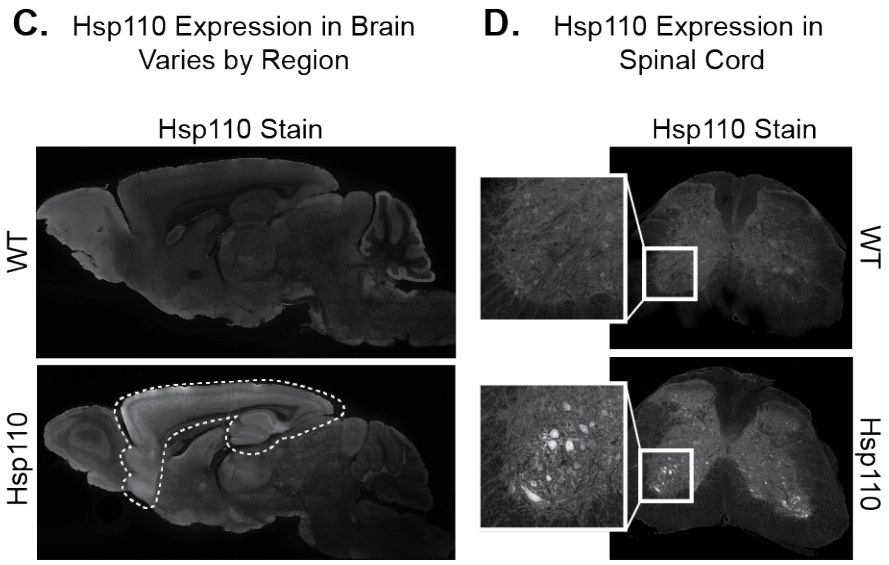
[a]Howard Hughes Medical Institute, Yale School of Medicine, New Haven, CT 06510; and [b]Department of Genetics, Yale School of Medicine, New Haven, CT 06510



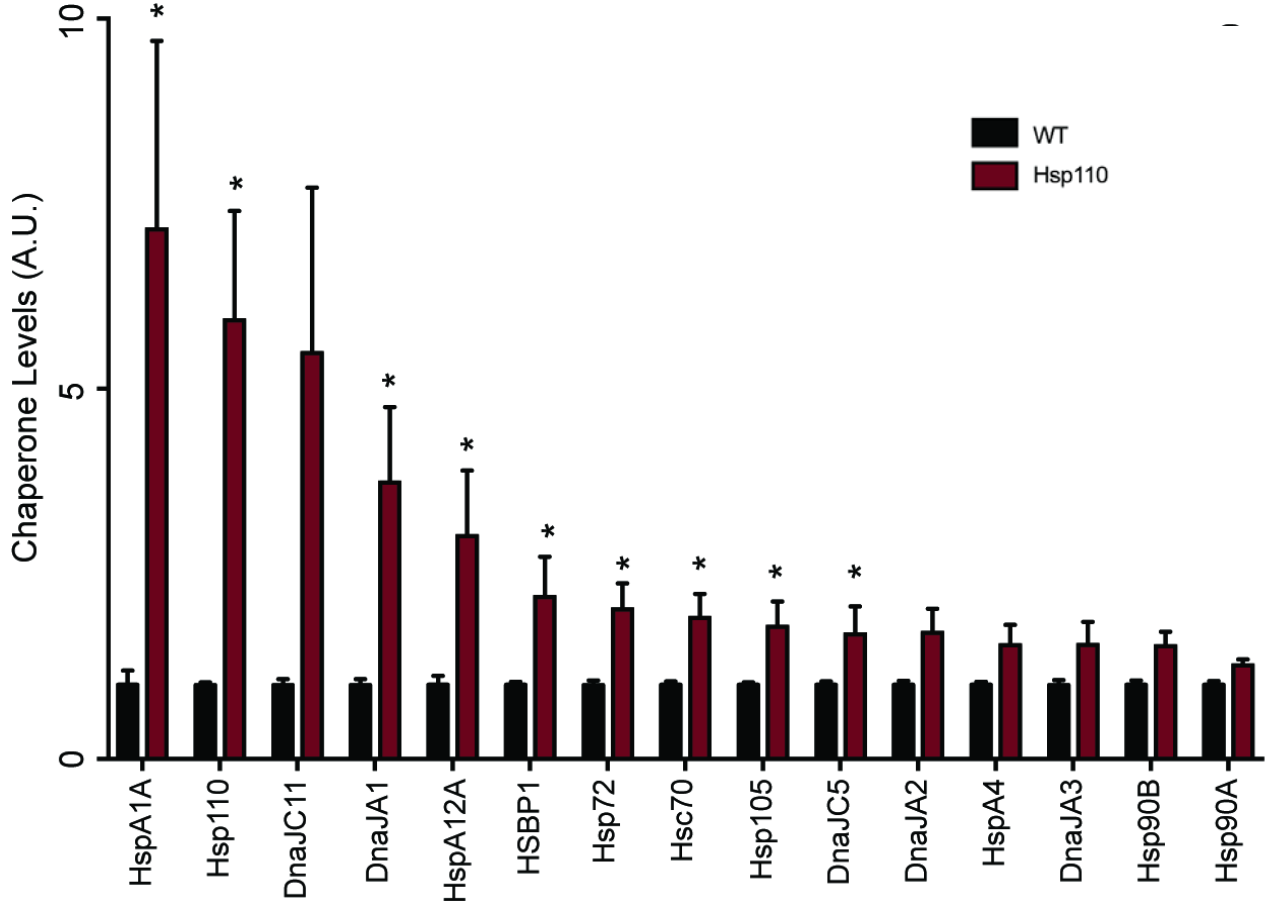
Nagy et al PNAS 2016

Broad Hsp110 expression in transgenic

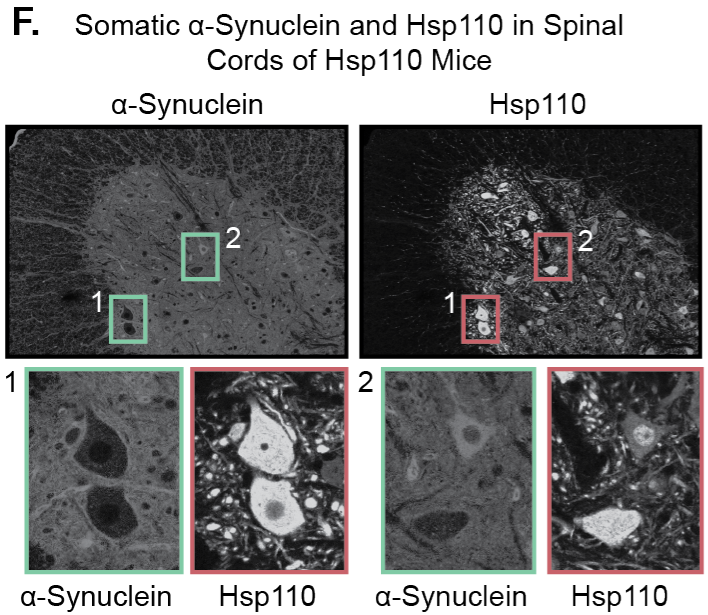


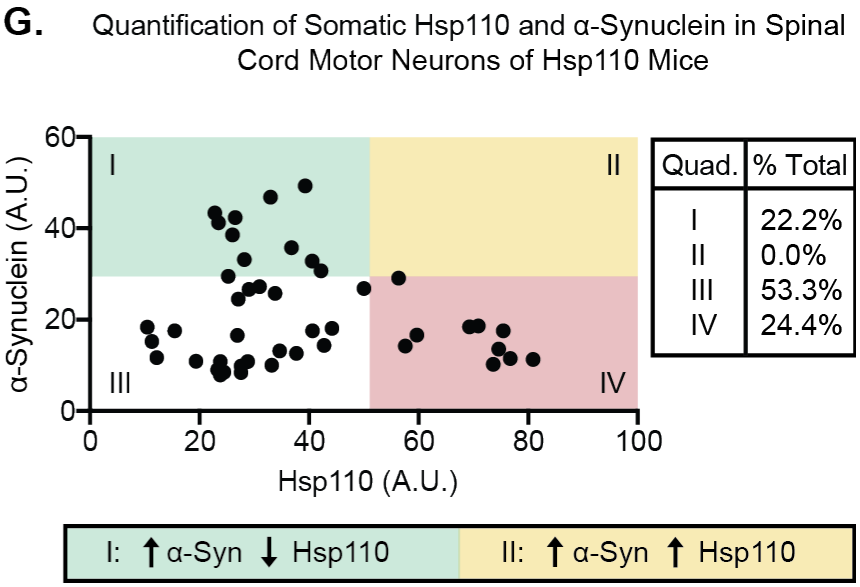


Hsp110 tg show higher synaptic chaperone capacity

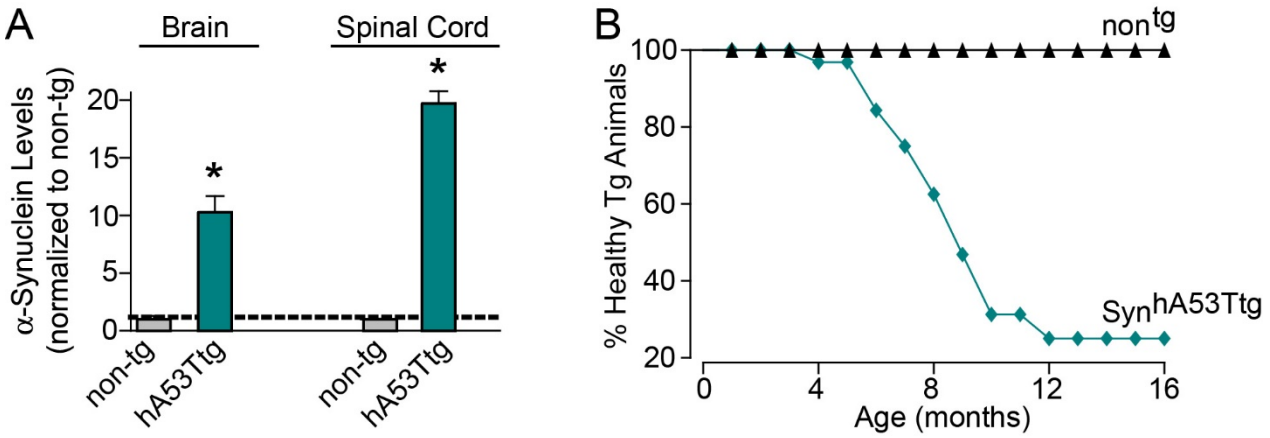


Hsp110 expression decreases somatic α-synuclein

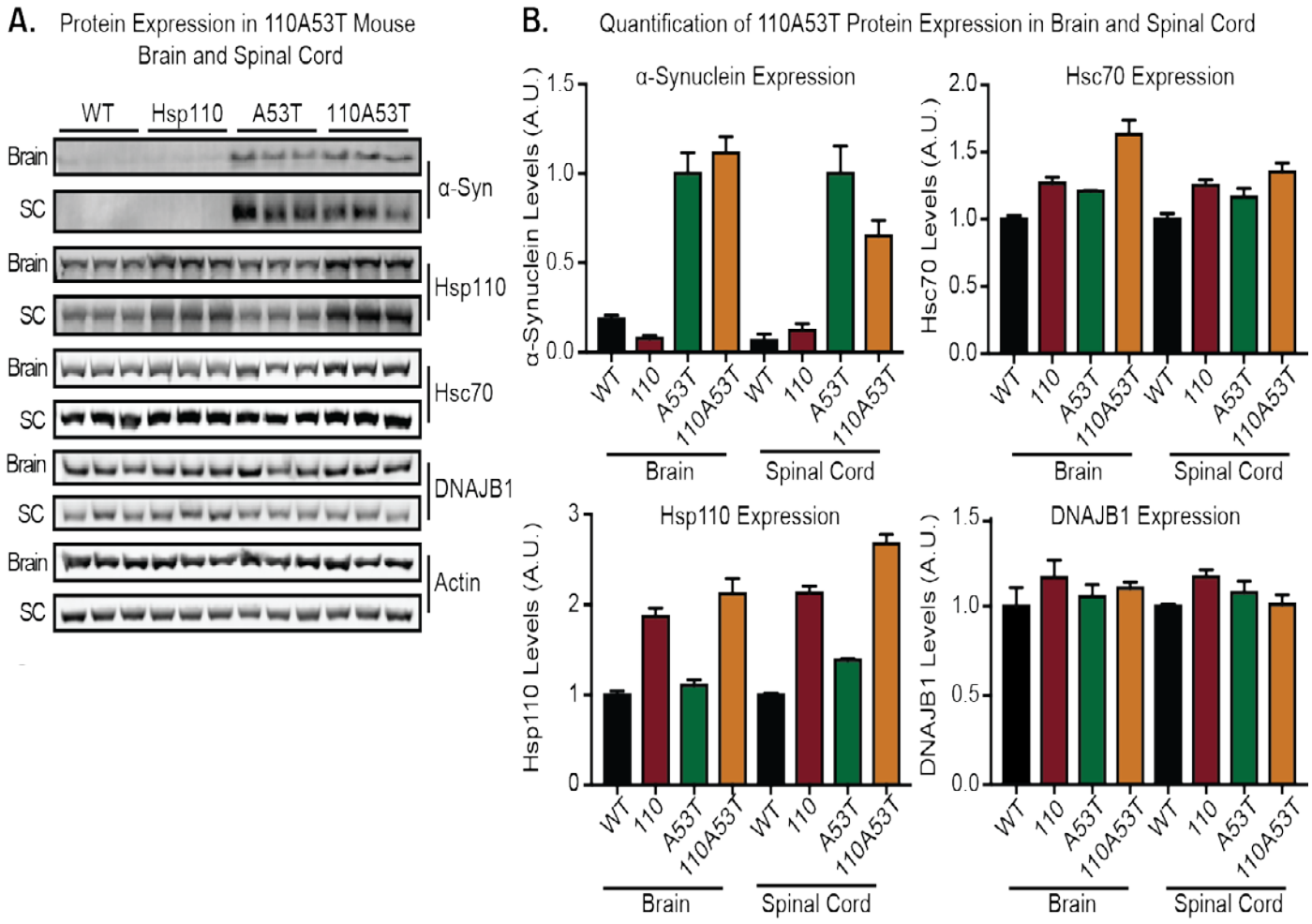




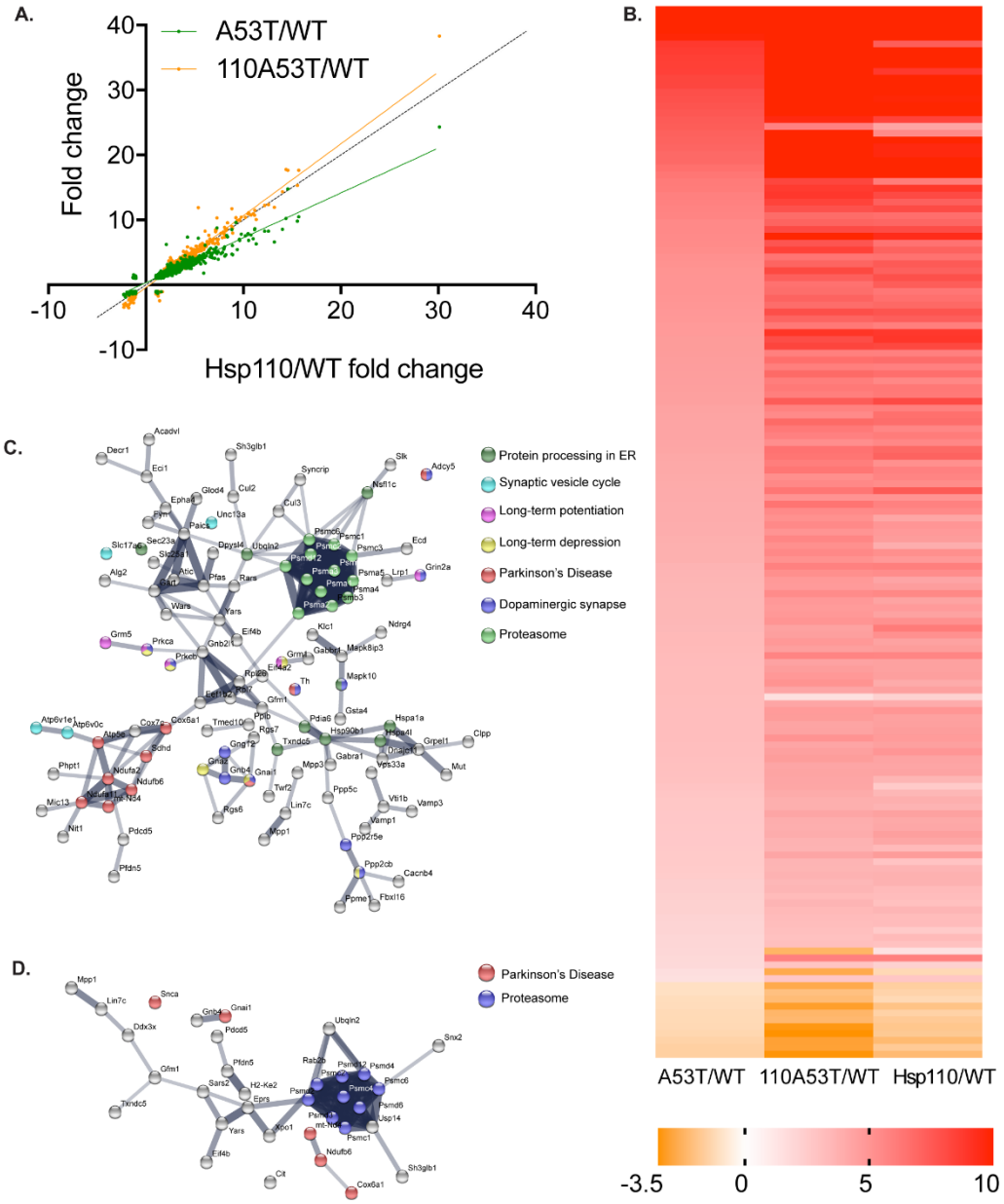
A53T α-Synuclein transgenic: Mouse model of PD



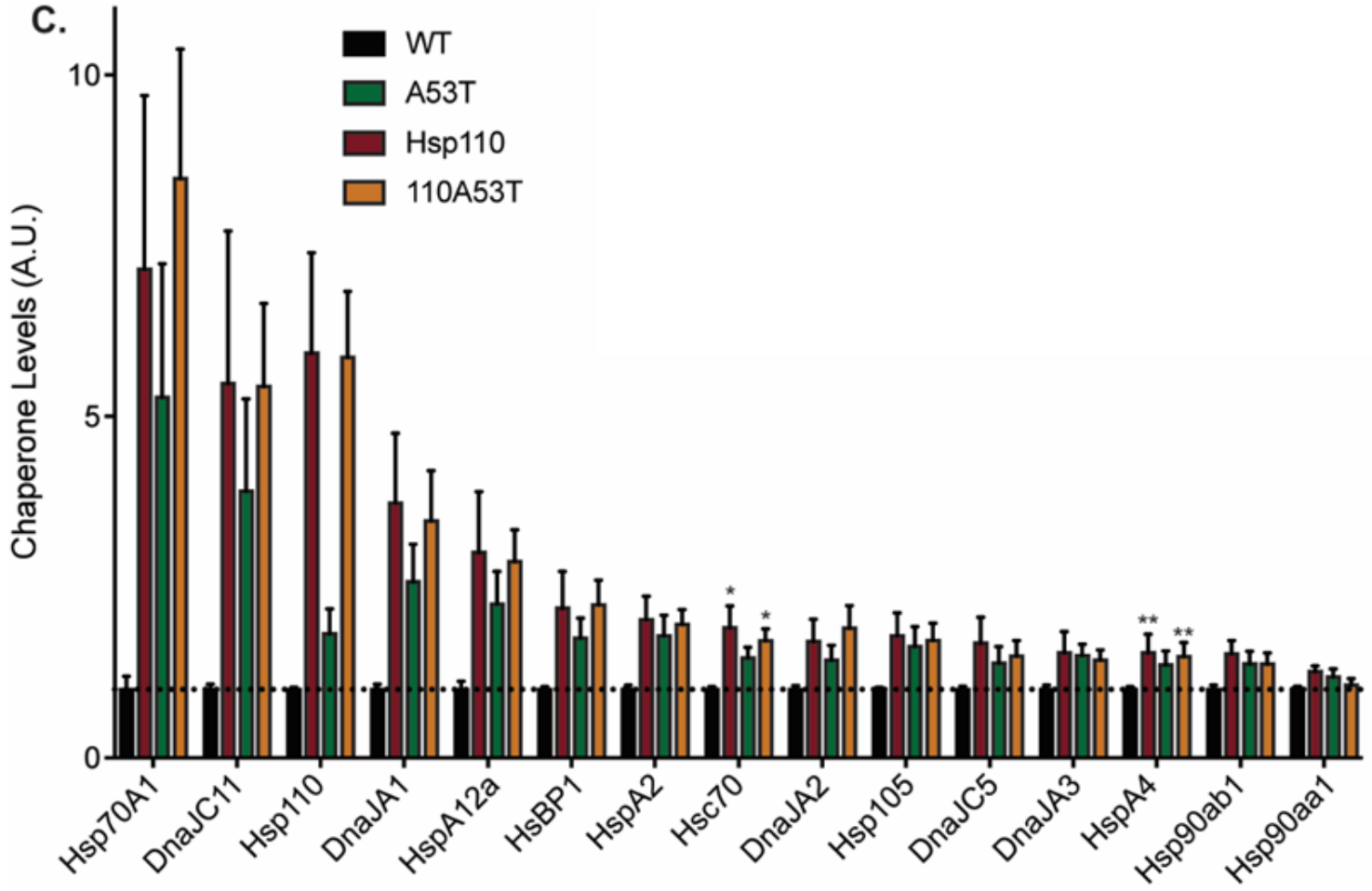
Hsp110 expression enhances chaperone capacity



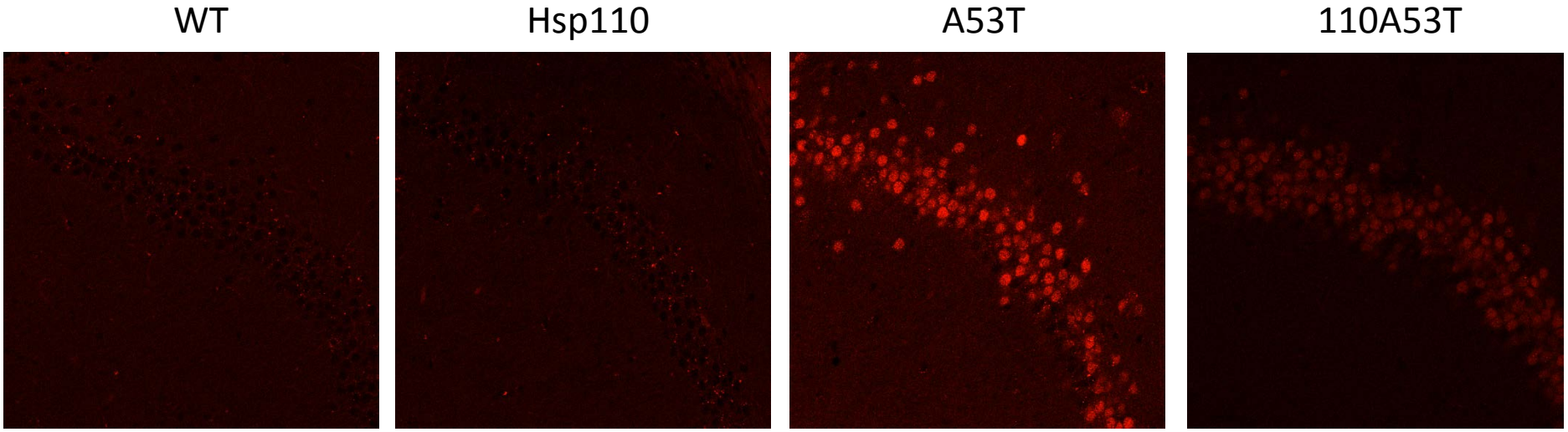
Synaptic Proteomics: 110A53T ameliorates effects of A53T



Hsp110 tg show higher synaptic chaperone capacity



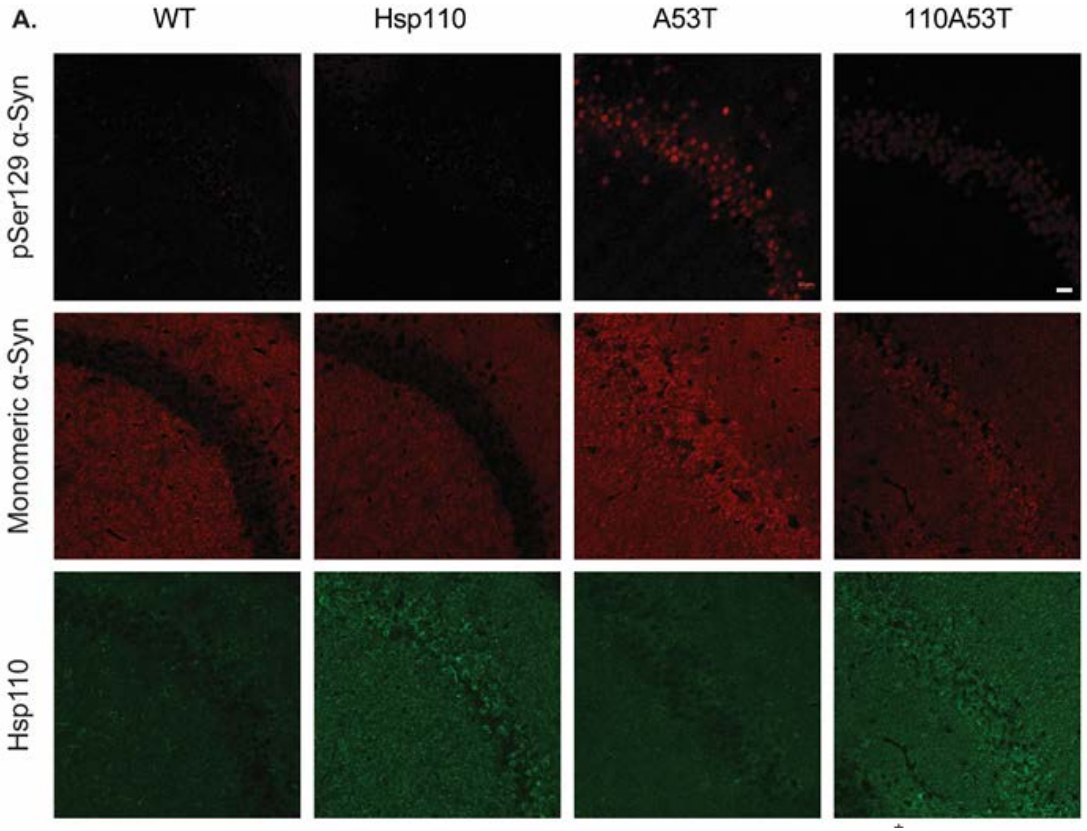
Hsp110/Syn tg have decreased Ser129 pathology in brain

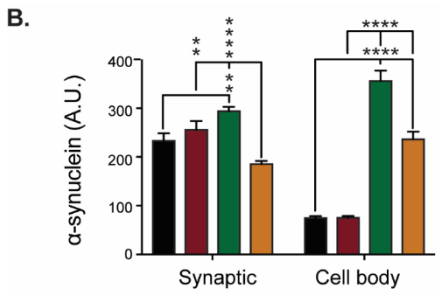


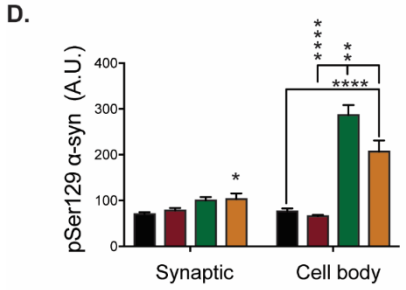
Ser129-phospho-α-synuclein
Staining in 6 month littermate cohorts

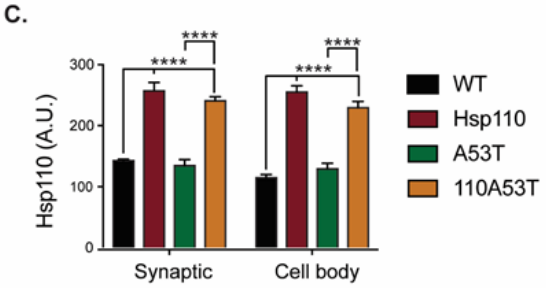
Maria Nagy

110A53T show decreased α–synuclein pathology

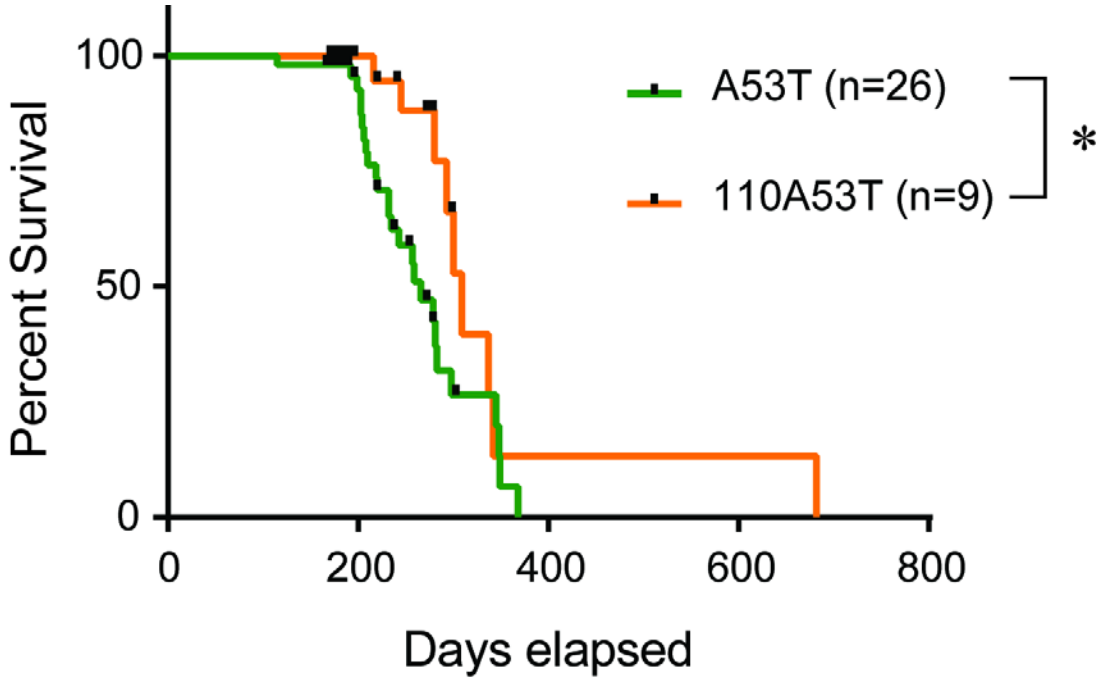








Hsp110 tg increase survival of α-synuclein transgenic



α-Synuclein PFF in vivo assay

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Science 16 November 2012:
Vol. 338 no. 6109 pp. 949-953
DOI: 10.1126/science.1227157
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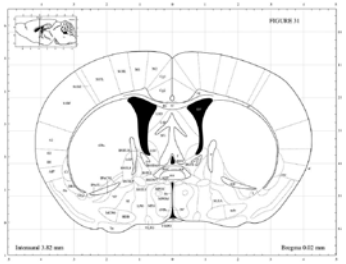
REPORT

Pathological α-Synuclein Transmission Initiates Parkinson-like Neurodegeneration in Nontransgenic Mice

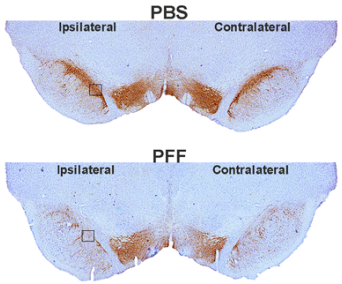
Kelvin C. Luk, Victoria Kehm, Jenna Carroll, Bin Zhang, Patrick O'Brien, John Q. Trojanowski, Virginia M.-Y. Lee*

Inject PFF in striatum

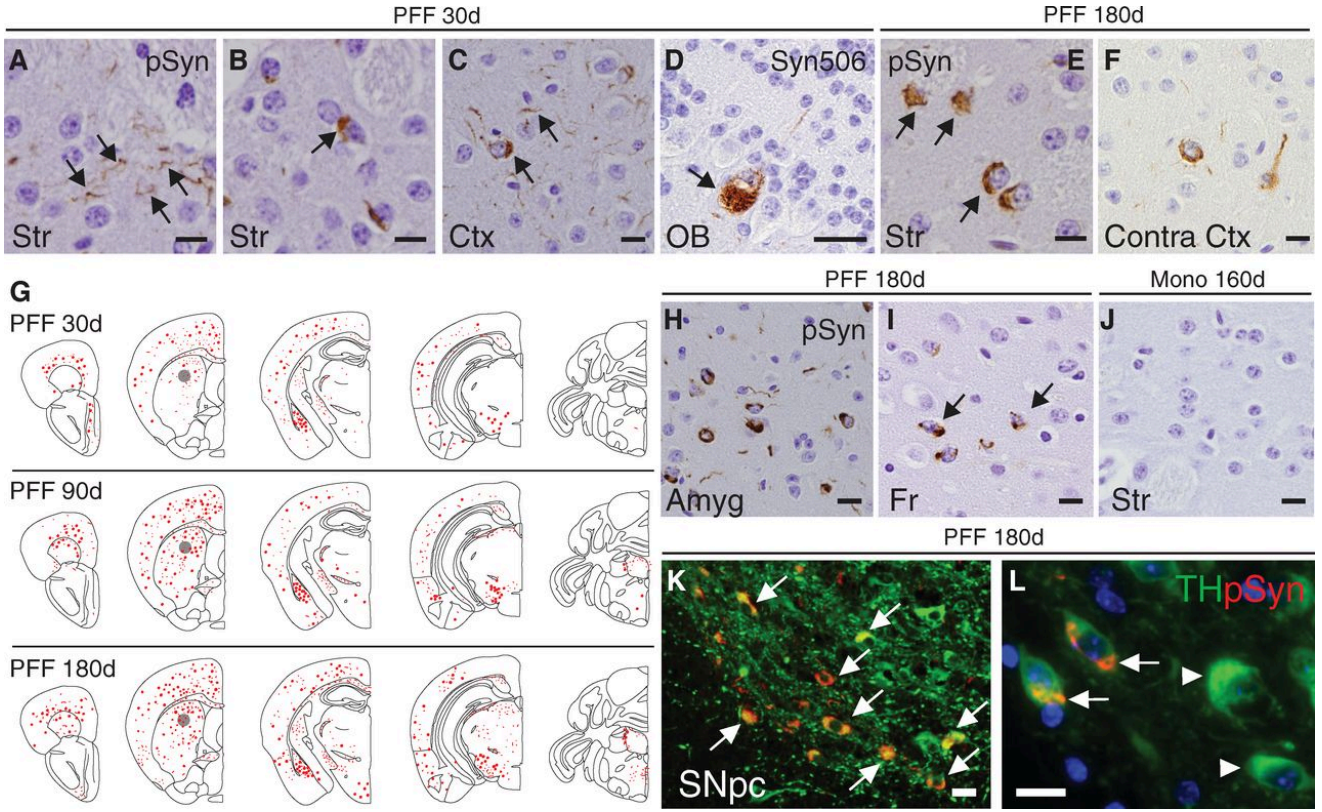


time

Stain for TH and pα-syn in nigra

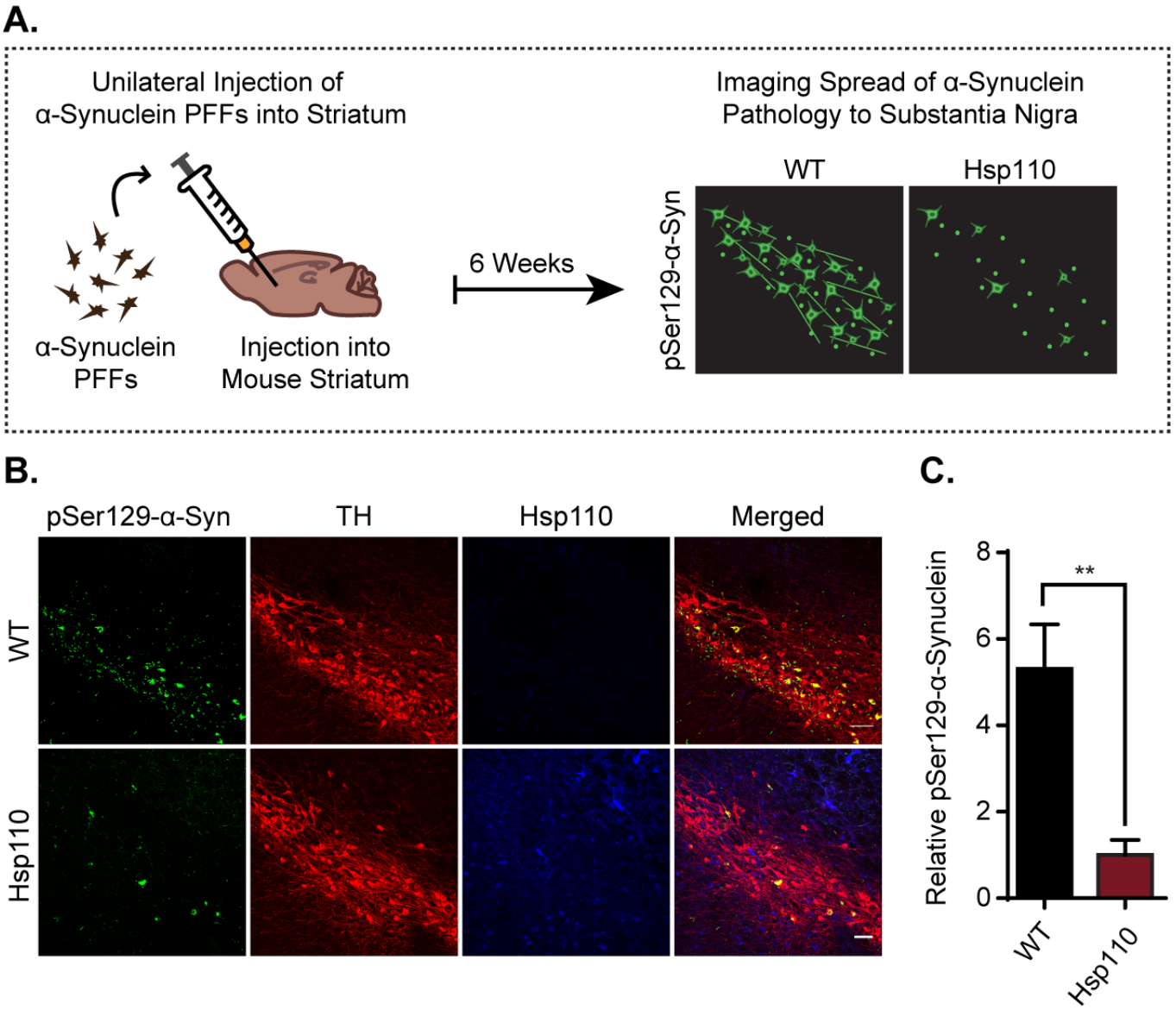


α- Synuclein Propagates in a Prion-Like Manner



Luk et al. (2012) Science 338: 949.

Hsp110 tg show decreased α-synuclein propagation



Conclusions

Hsp110 overexpression is a good strategy to tackle protein aggregation

Unbiased proteomics show increased chaperone capacity in Hsp110 transgenic

Hsp110 is effective in two models of α-synucleinopathies

Acknowledgements

Yumi Taguchi
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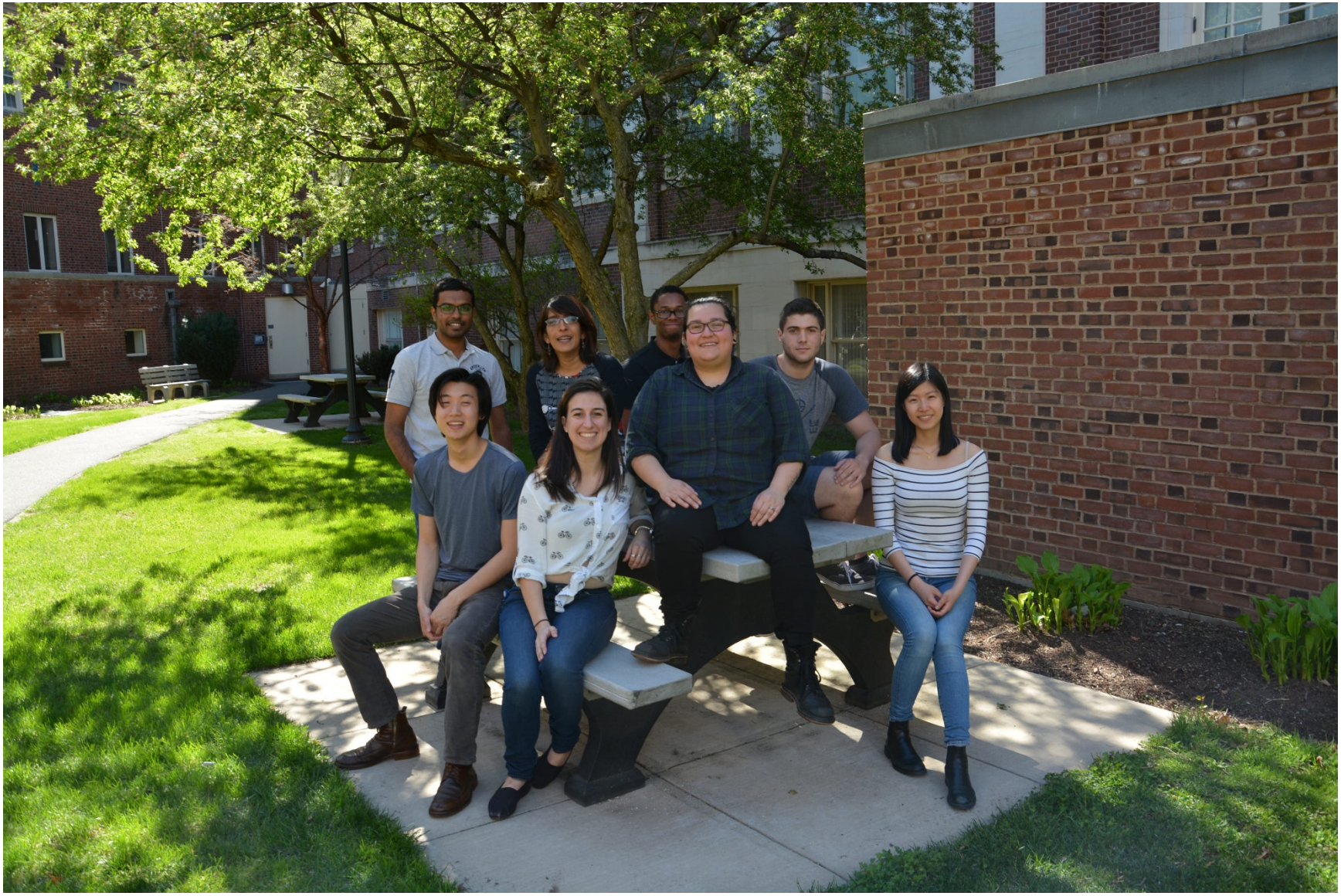
Wayne Fenton
Maria Nagy

Tukiet Lam (NIDA Neuroproteomics Center)

Laura Volpicelli-Daly (UAB)
Drake Thrasher



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NIDA Neuroproteomic Center