Network analysis to identify new targets and mechanism(s) of neurodegeneration

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Meta Gene Expression in Sporadic PD

GPEX Consortium

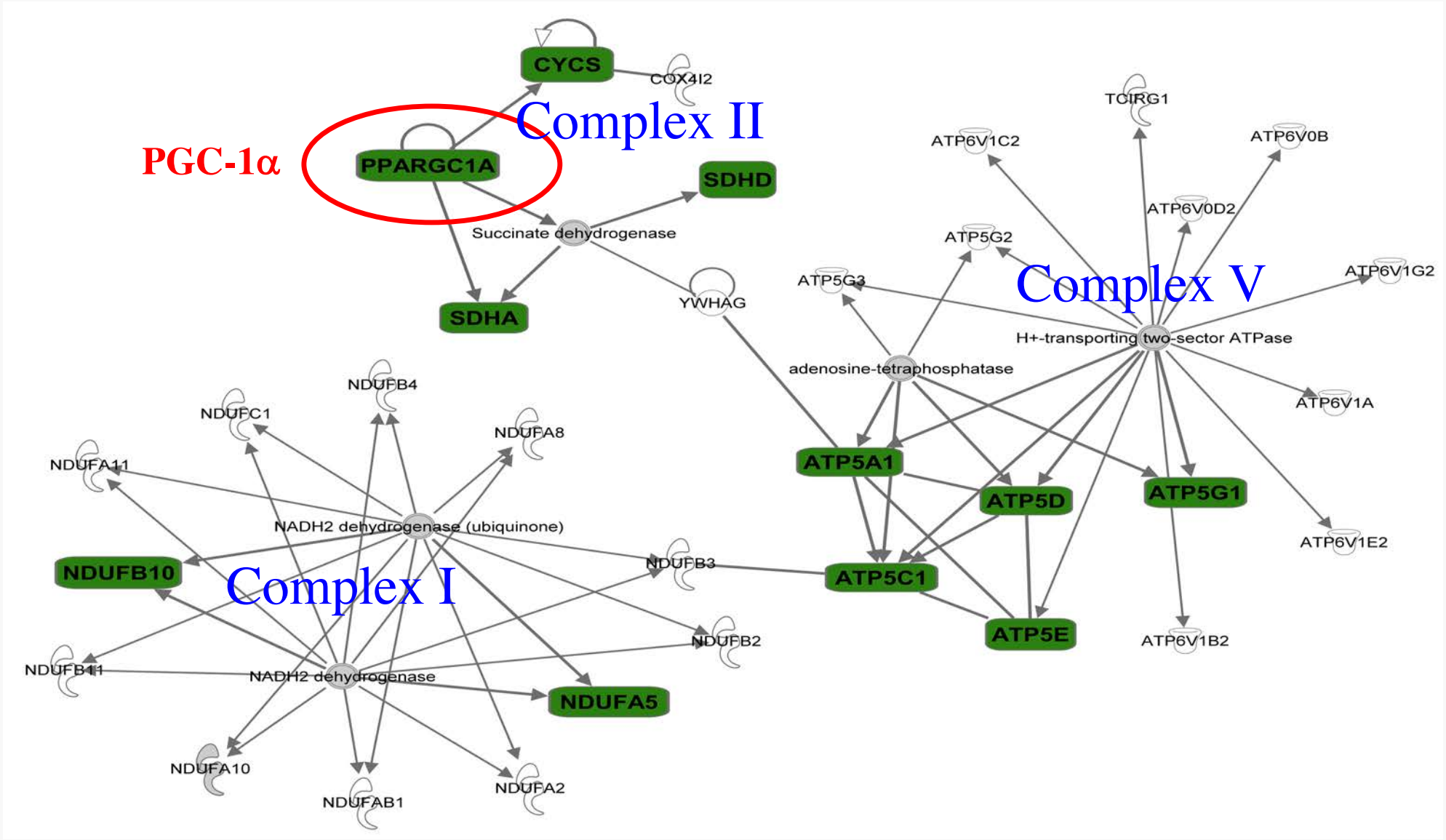
			Stage I (SN & DA)		Stage II (Braak PD stages 1-3)		Stage III (non-SN)		All data			All SN data		
Gene set	N Genes	Annotation	sNES	*P* value	sNES	*P* value	sNES	*P* value	N	sNES	*P* value	N	sNES	*P* value
Electron Transport Chain	95	Broad	-1.583	$<1x10^{-8}$	-1.496	$1.46x10^{-2}$	-1.420	$1.0x10^{-5}$	410	-1.519	$<1x10^{-8}$	218	-1.580	$<1x10^{-8}$
MAP00190 Oxidative phosphorylation	46	GenMAPP	-1.572	$<1x10^{-8}$	-1.716	$4.70x10^{-2}$	-1.132	$2.26x10^{-3}$	410	-1.388	$<1x10^{-8}$	218	-1.586	$2.66x10^{-7}$
MAP00620 Pyruvate metabolism	31	GenMAPP	-1.529	$3.36x10^{-8}$	-1.844	$2.37x10^{-2}$	-1.062	$4.64x10^{-3}$	410	-1.332	$<1x10^{-8}$	218	-1.541	$5.32x10^{-7}$
VOXPHOS	87	BioCarta	-1.527	$1.34x10^{-7}$	-1.451	$2.28x10^{-2}$	-1.389	$1.0x10^{-5}$	410	-1.471	$<1x10^{-8}$	218	-1.524	$7.92x10^{-8}$
Mitochondr	447	Broad	-1.464	$6.76x10^{-7}$	-1.761	$1.43x10^{-2}$	-1.247	$4.50x10^{-4}$	410	-1.376	$3.11x10^{-8}$	218	-1.479	$5.54x10^{-7}$
Krebs-TCA Cycle	29	BioCarta	-1.447	$3.38x10^{-7}$	-1.633	$3.02x10^{-2}$	-1.184	$1.34x10^{-3}$	410	-1.359	$6.22x10^{-8}$	218	-1.462	$8.71x10^{-7}$
Human mitoDB 6 2002	428	Broad	-1.427	$3.38x10^{-7}$	-1.750	$1.23x10^{-2}$	-1.271	$4.51x10^{-4}$	410	-1.373	$<1x10^{-8}$	218	-1.445	$5.32x10^{-7}$
GO 0005739	170	GO	-1.369	$3.72x10^{-6}$	-1.758	$2.04x10^{-2}$	-1.230	$3.91x10^{-4}$	410	-1.322	$<1x10^{-8}$	218	-1.391	$3.19x10^{-6}$
PGC	425	Broad	-1.366	$6.75x10^{-6}$	-1.576	$4.96x10^{-2}$	-0.884	$1.46x10^{-2}$	410	-1.165	$1.27x10^{-5}$	218	-1.379	$2.93x10^{-6}$
ChREBP Pathway	20	Broad	-1.280	$3.34x10^{-5}$	-2.100	$1.19x10^{-2}$	-0.799	$2.93x10^{-2}$	410	-1.127	$1.58\ x10^{-5}$	218	-1.341	$6.92x10^{-6}$
Urea cycle Pathway	7	KEGG	-1.262	$6.77x10^{-5}$	-1.671	$1.46x10^{-2}$	-0.575	$1.05x10^{-1}$	410	-0.994	0.00002212	218	-1.294	$7.94x10^{-5}$
MAP00252 Alanine and aspartate metabolism	21	GenMAPP	-1.165	$3.39x10^{-5}$	-1.831	$1.80x10^{-2}$	-0.482	$1.80x10^{-1}$	410	-0.908	0.00015813	218	-1.213	0.00013384

PGC-1α and the electron transport chain were downregulated

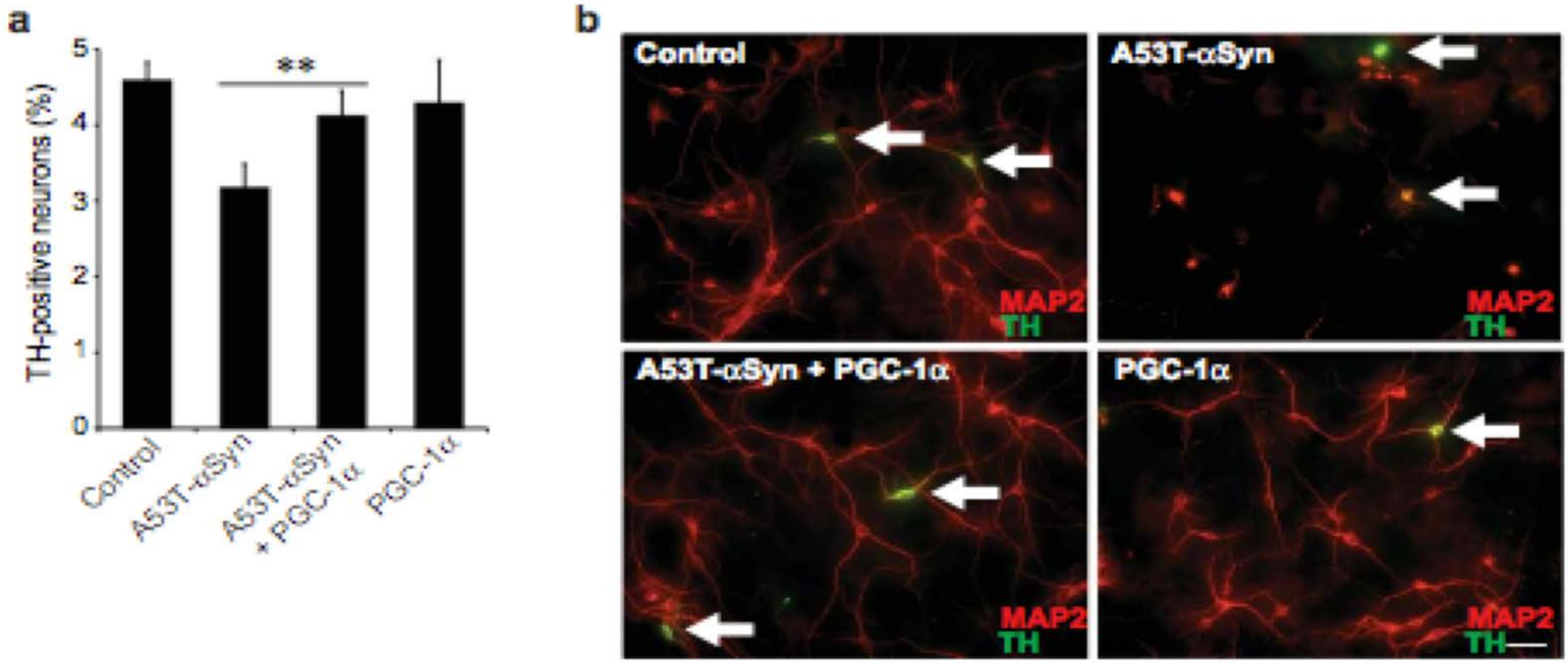
Zheng, B., et al, *Sci Trans Med*, 2010

Meta Gene Expression Analysis Network

(From the data of Zheng, B., et al, *Science Translational Medicine*, 2010)



PGC-1α Blocks α-Synuclein Toxicity in Dopaminergic Neurons



Sci Transl Med. 2010 Oct 6; 2(52): 52ra73

Screen of FDA Approved Drugs: Seeking PGC-1α modulators

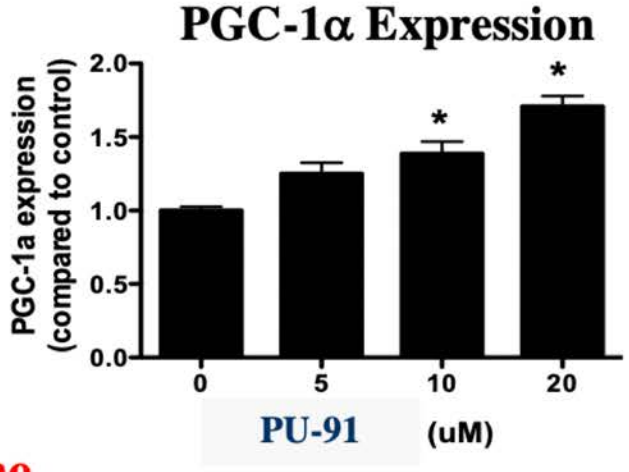
- Screened several thousand FDA approved molecules in a retinal cell line
- 14 identified
- 14 corroborated as PGC-1α modulators in MN9D cells
- One selected for further study, compound PU-91

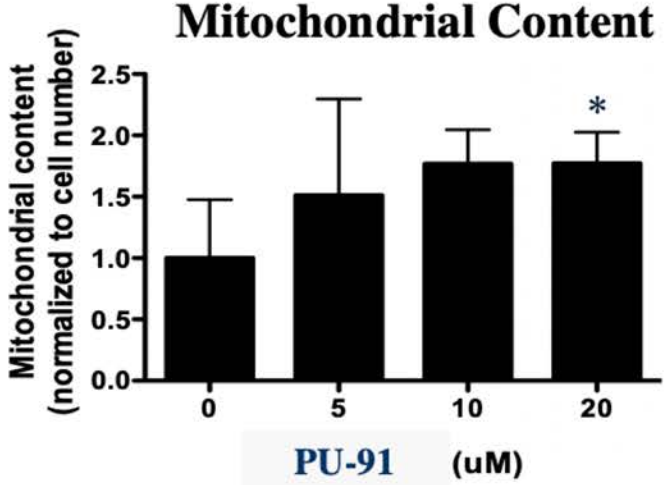
PU-91 Induces PGC-1α in Dopaminergic cells & Promotes Neuroprotection

PU-91

MN9D

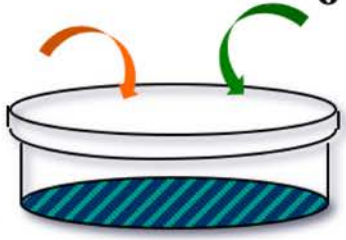
Dopaminergic cell line



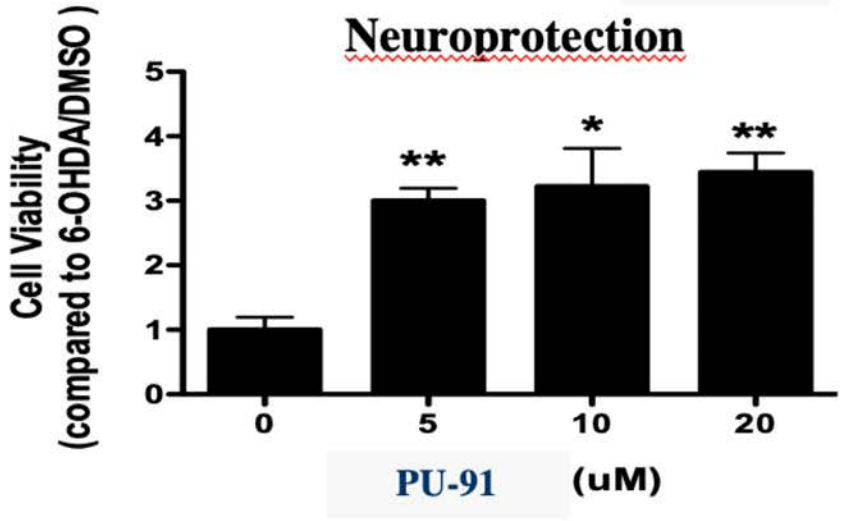


PU-91

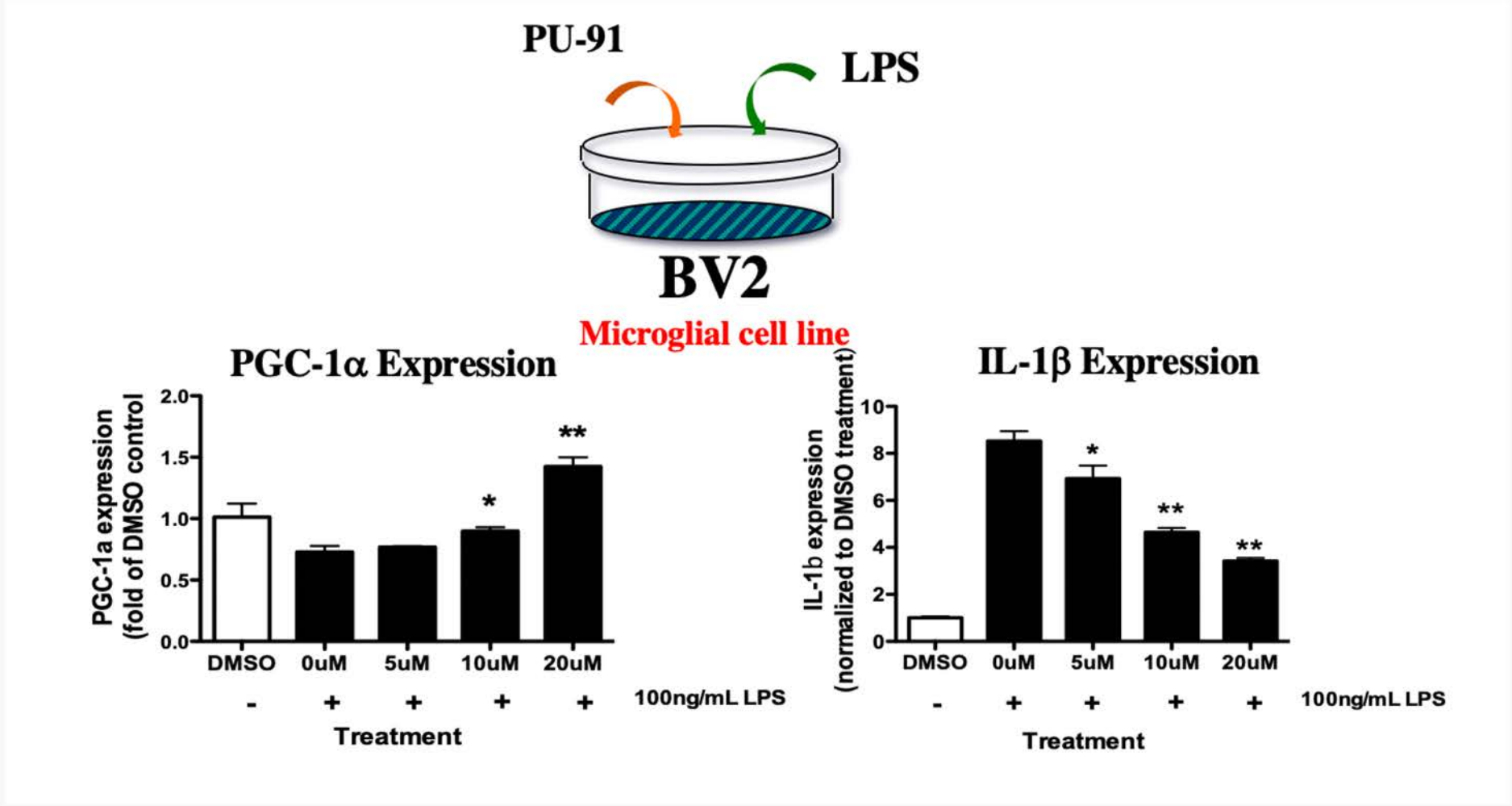
6-OHDA



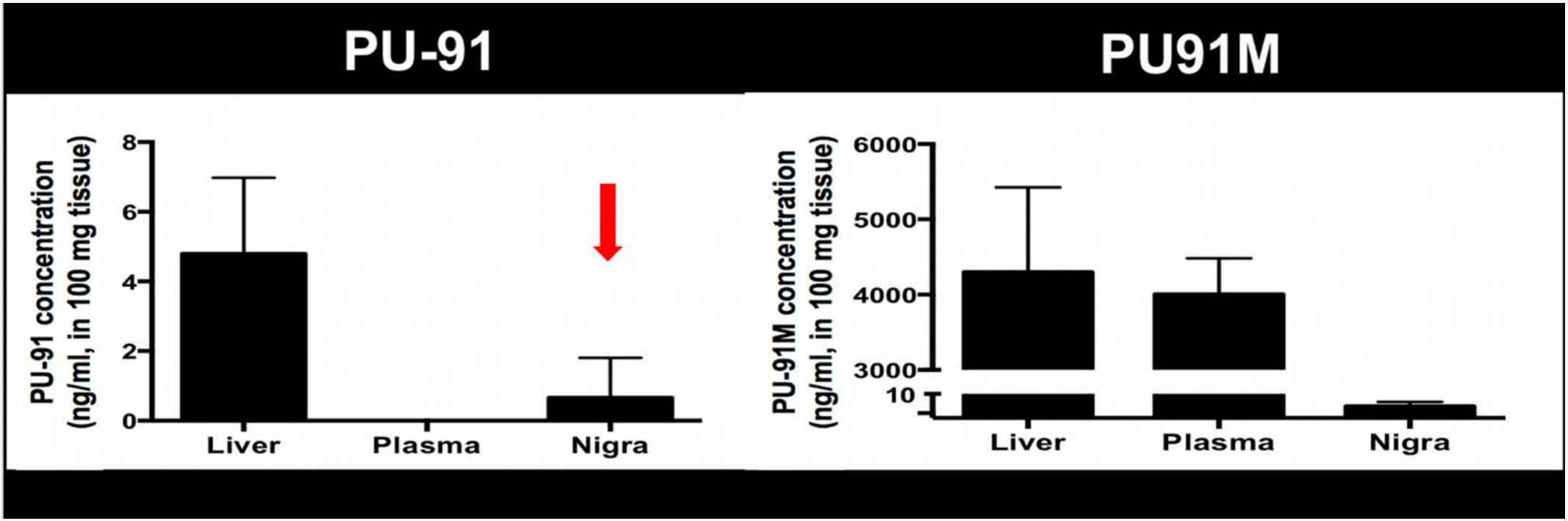
MN9D



PU-91 Induces PGC-1α in Microglial Cells and Promotes an Anti-inflammatory Effect

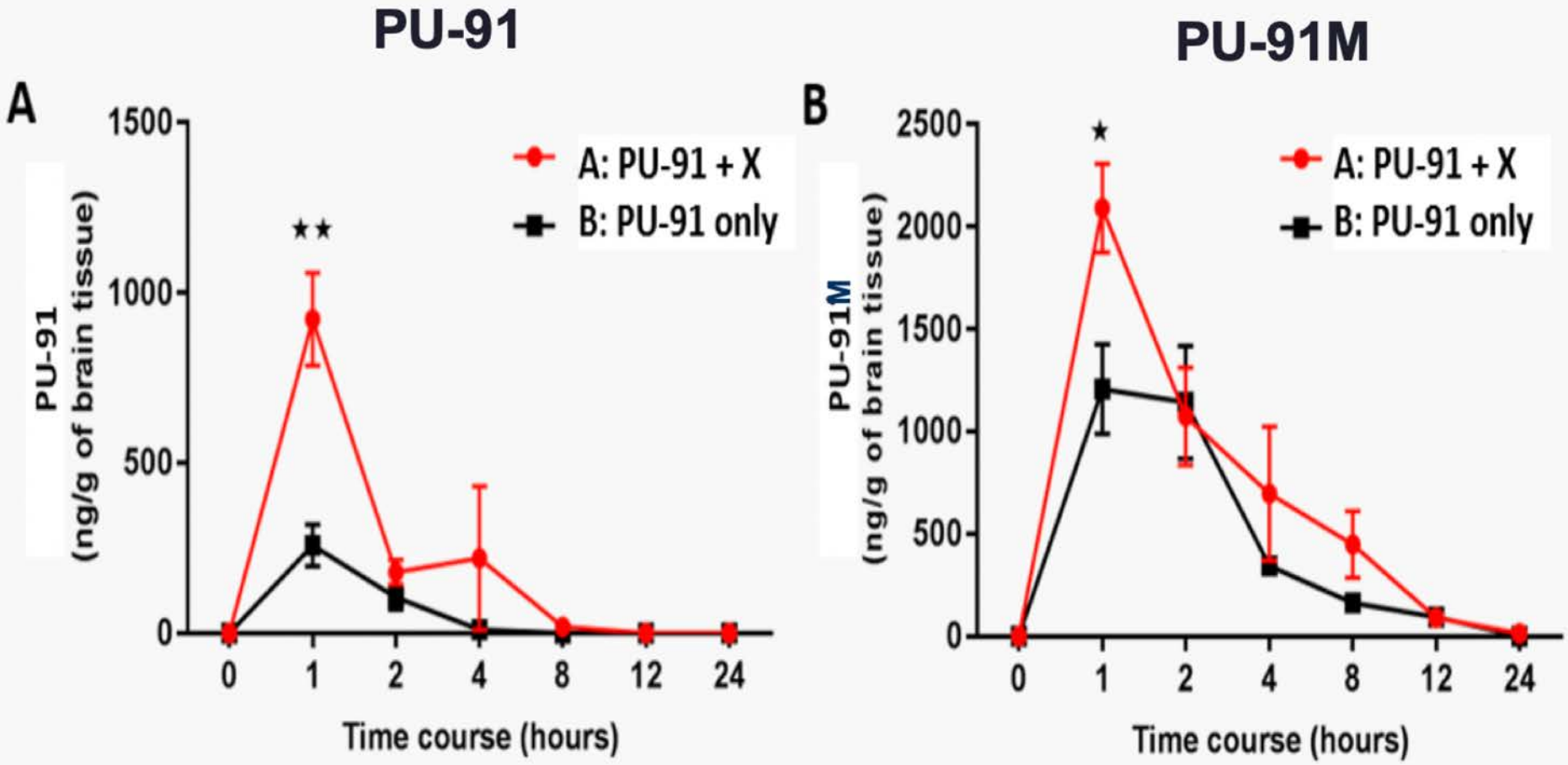


PU-91 is Metabolized after Oral Delivery



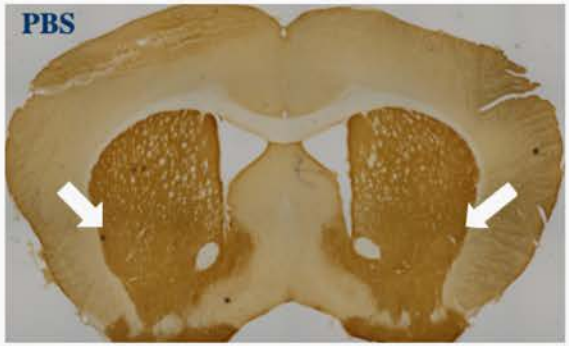
Mice administered PU-91 by gavage and sampled at 2 hours

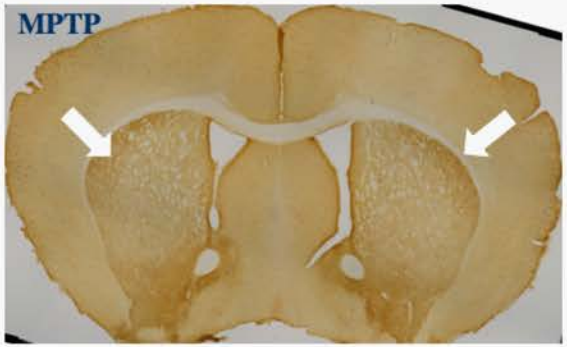
Co-Administration of PU-91 + X Improves Brain Levels

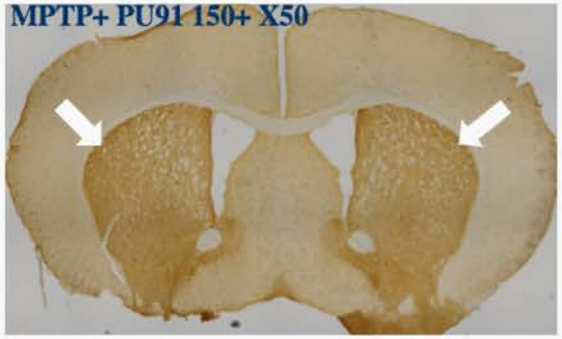


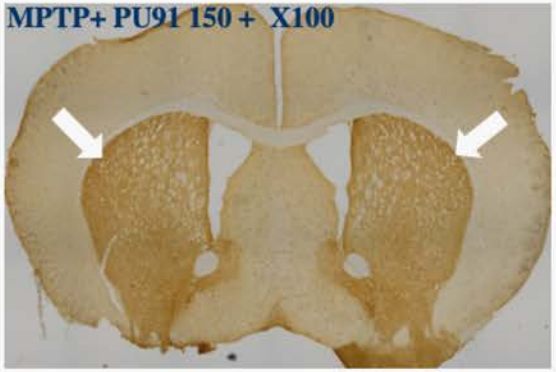
Is PU-91 +/- Comp X protective in PD models?

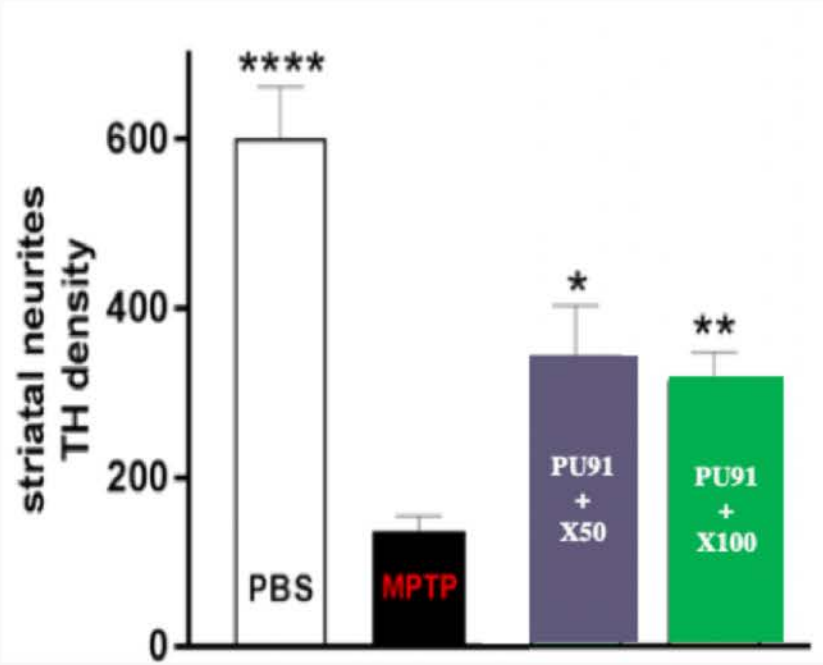
Co-administration PU-91 and Cmpd X Sustains TH Terminals in Striatum











Co-administration PU-91 and Cmpd X Preserves TH Neurons Substantia Nigra