Increasing brain palmitoylation reverses behavioral and pathological phenotype of Huntington disease mice

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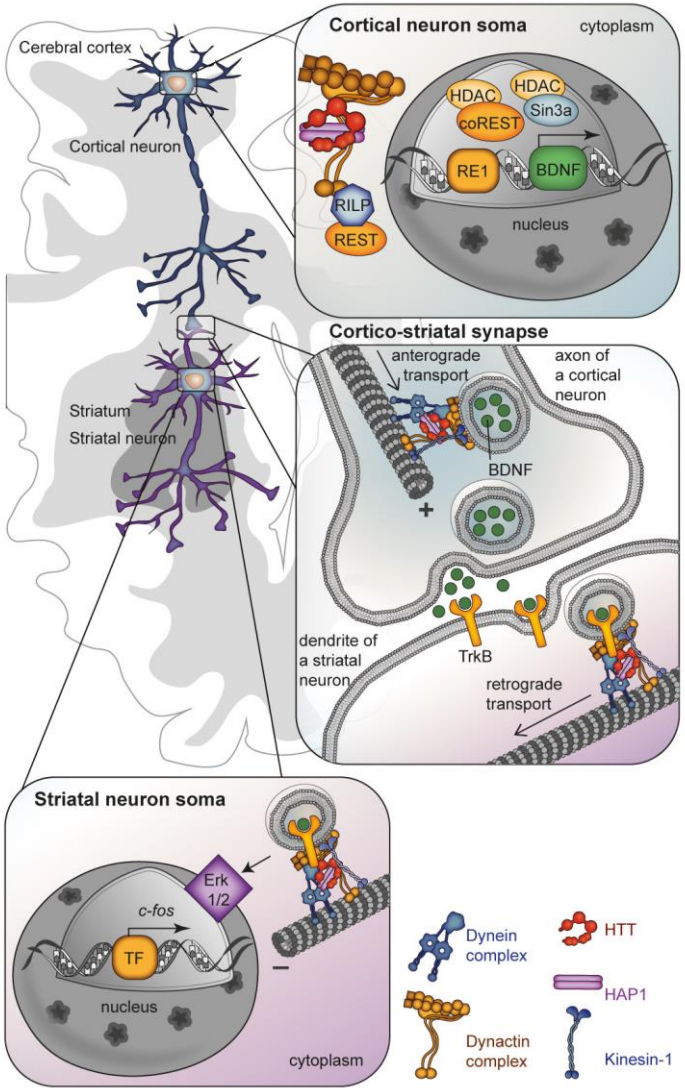
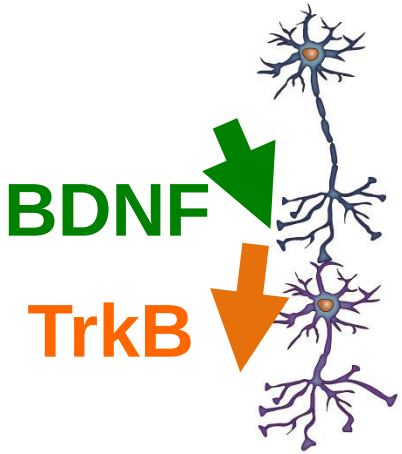
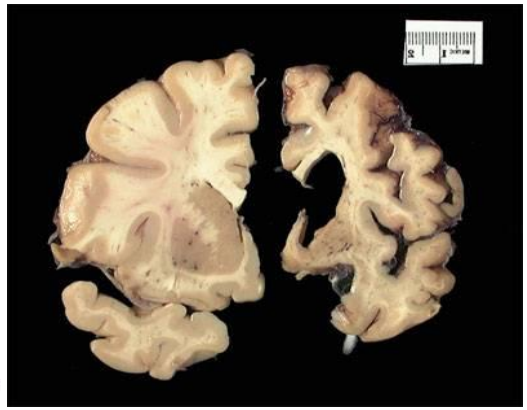
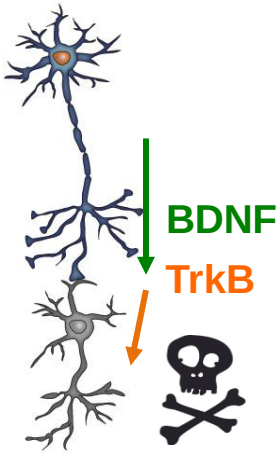
Grenoble excellence in neurodegeneration

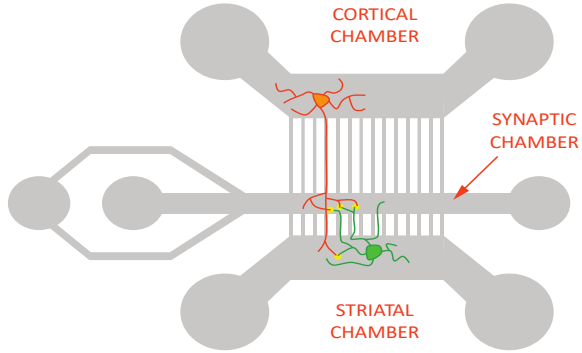
Huntington Disease and the corticostriatal circuit





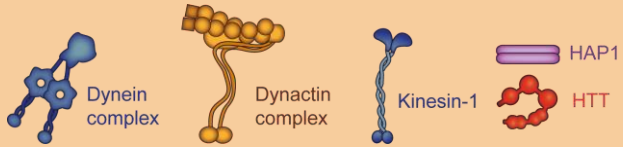




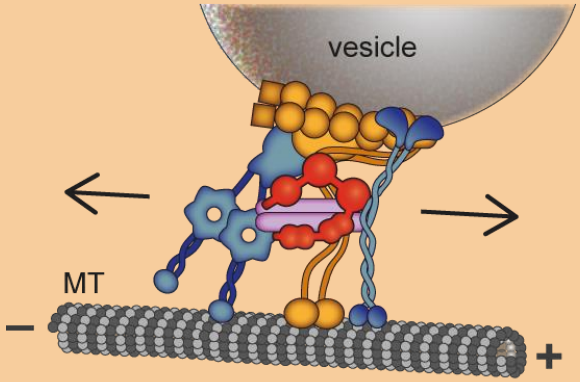


Reviewed in Saudou & Humbert Neuron 2016; see also Liot J Neurosci 2013; Plotkin, Neuron 2014, Brito, JCI, 2014, Zhao, PNAS, 2016,

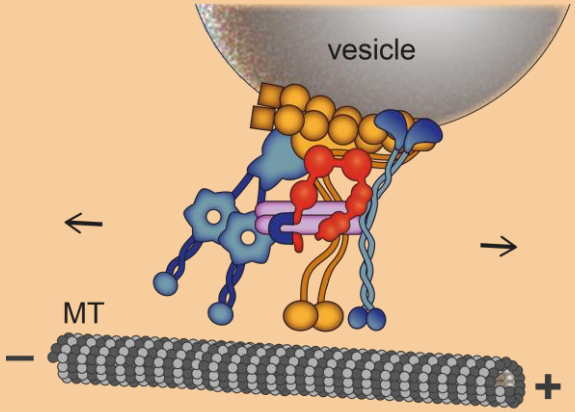
Vesicular transport along microtubules is facilitated by huntingtin and altered in disease



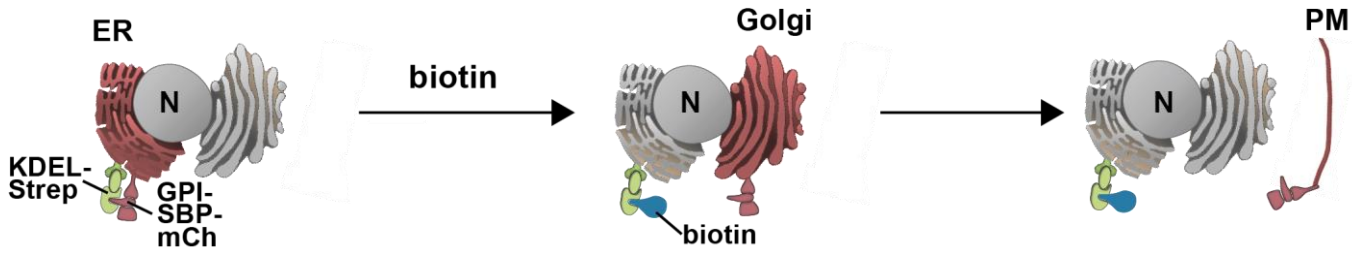
WT

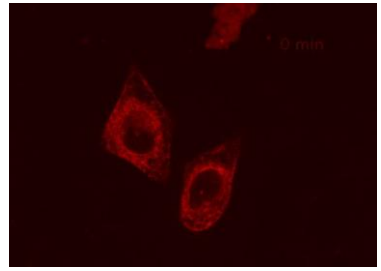


HD



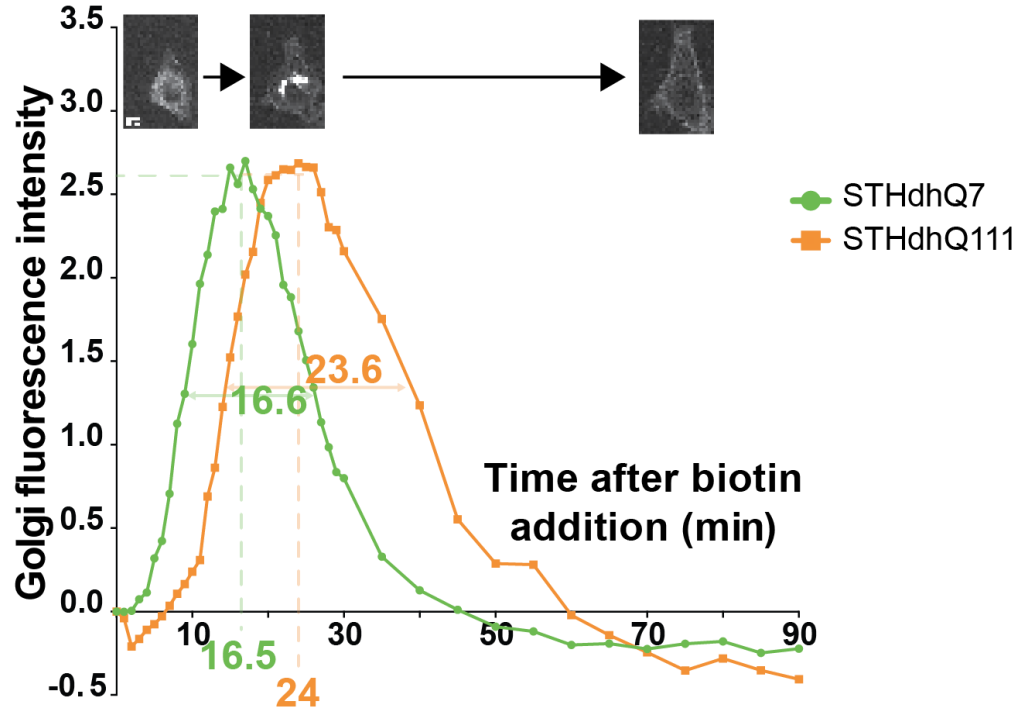
Gauthier, Cell 2004; McGuire JBC 2006;Caviston, PNAS 2007; Dompierre J Neurosci 2007;
Colin, EMBO J 2008; Zala HMG 2008; Pineda Mol Brain 2009; Pardo Mol Brain 2010





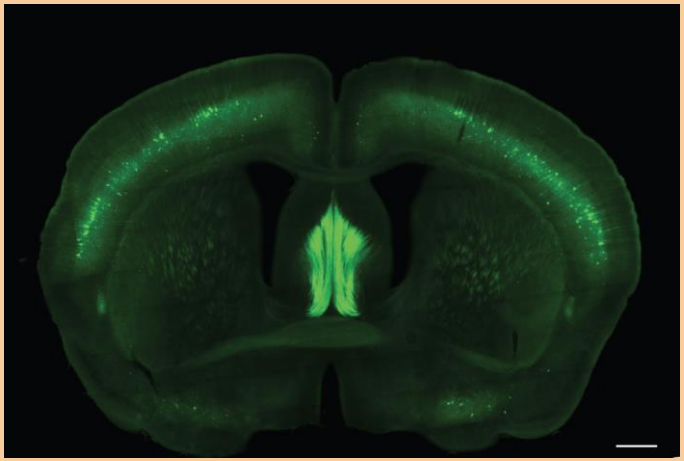
Strep-KDEL-SBP-mCherry-GPI
HeLa cells Biotin added at t0, acquisition every 30s during 90 min

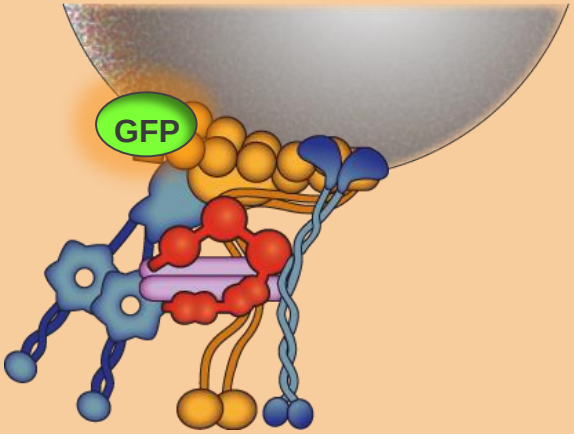
Boncompain G et al., Nature Communication, 2012

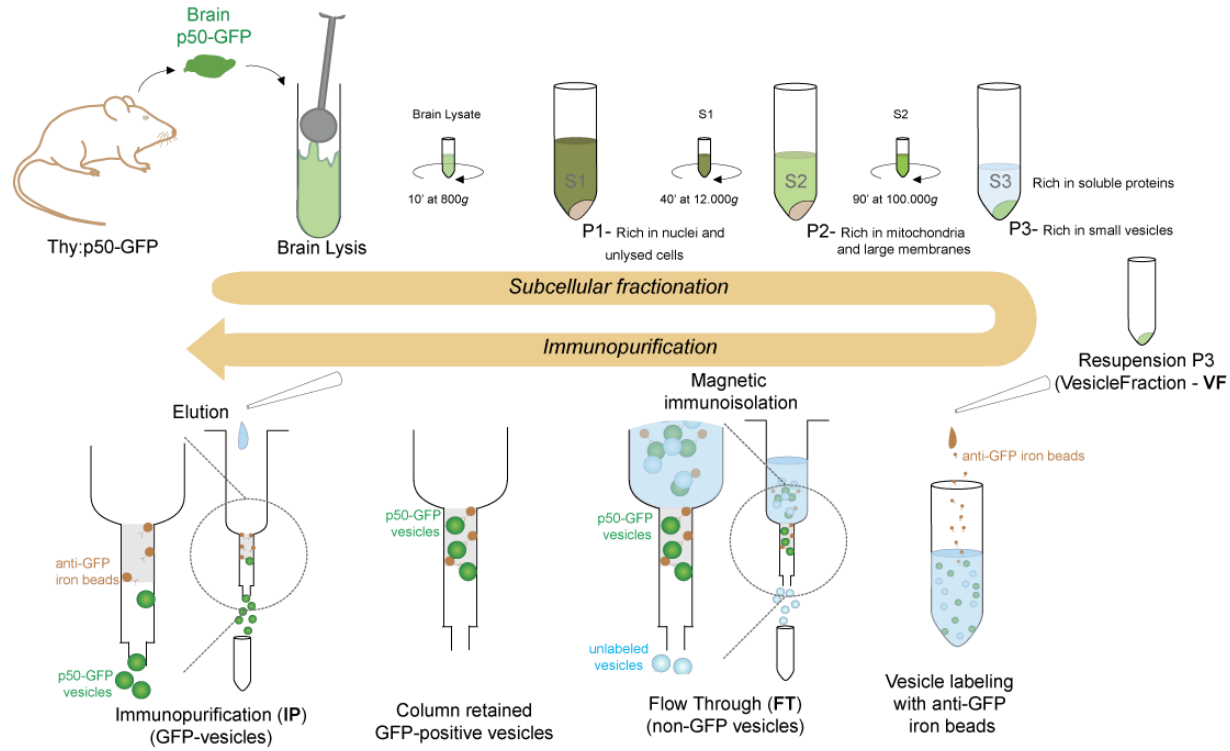


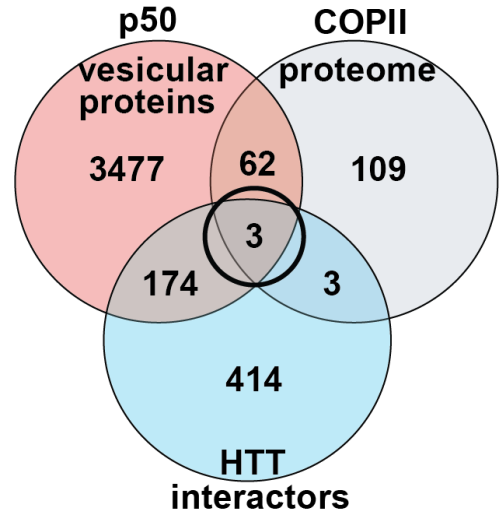
Identifying proteins transported in vesicles from corticostriatal projecting neurons

Thy1-p50-GFP mice





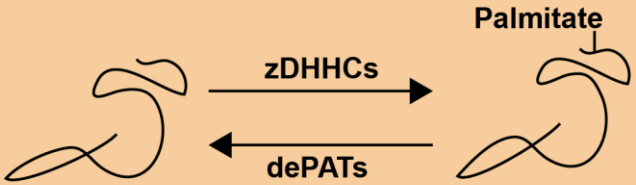




3 targets:

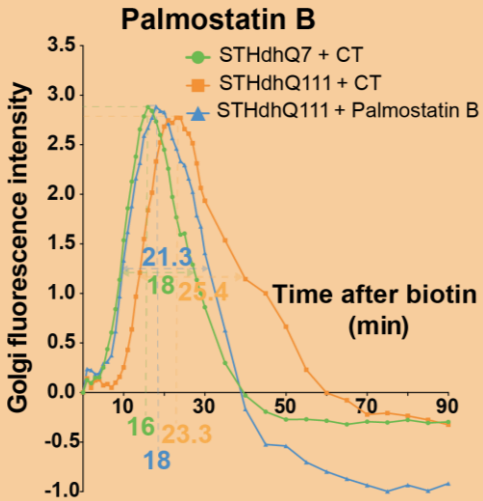
1) BASP1
2) VCP
3) **ZDHHC17/HIP14**

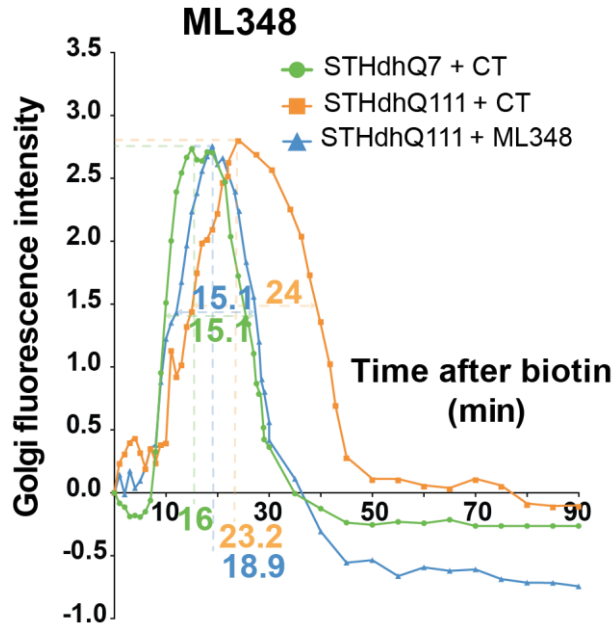
Increasing palmitoylation in cells restores ER to plasma membrane trafficking in HD

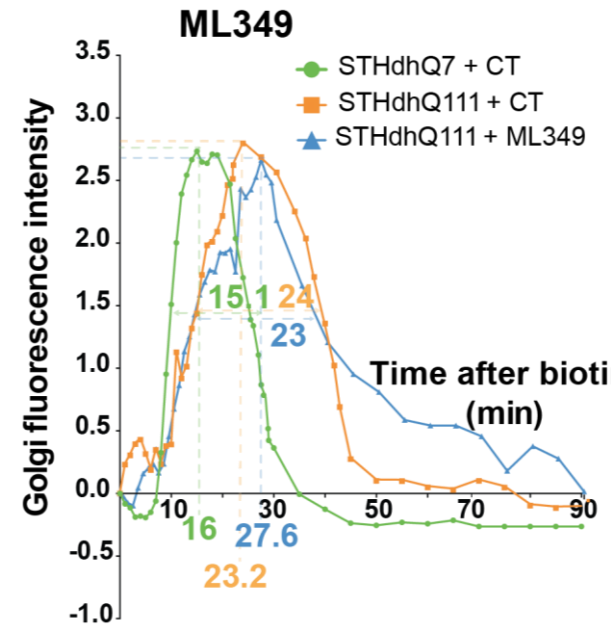


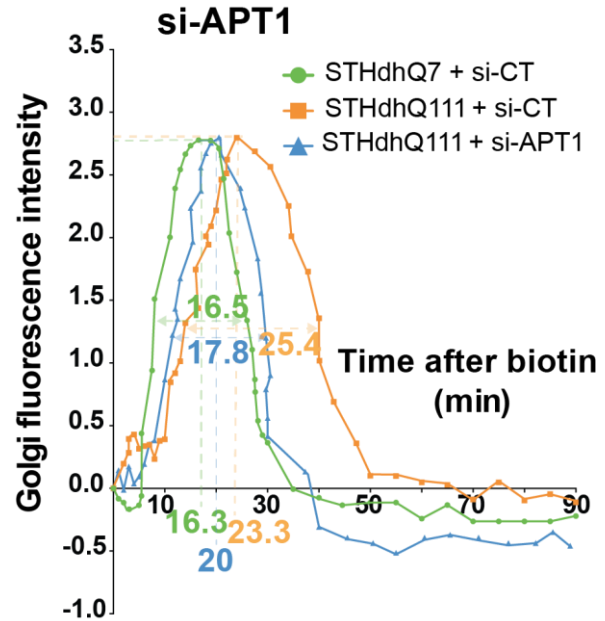
dePATs-Inhibitors

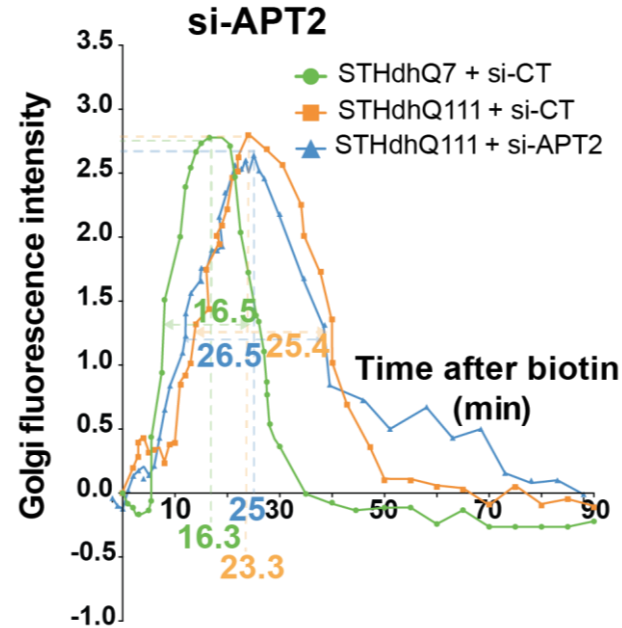
- Palmostatin B → APT1 ⊣ ML348
- Palmostatin B → APT2 ⊣ ML349



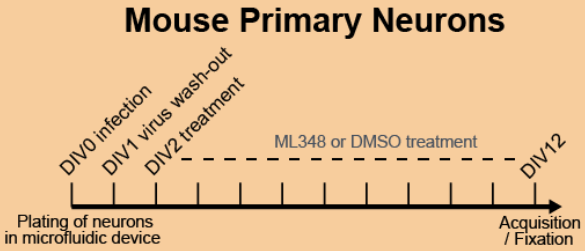


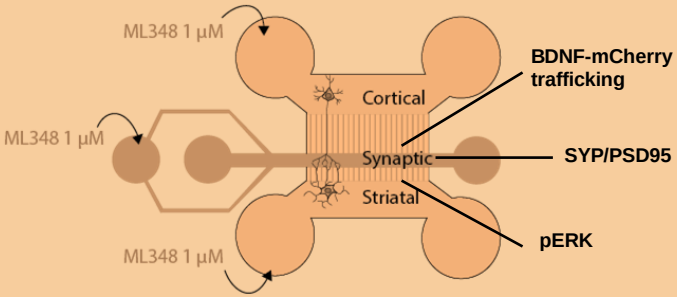




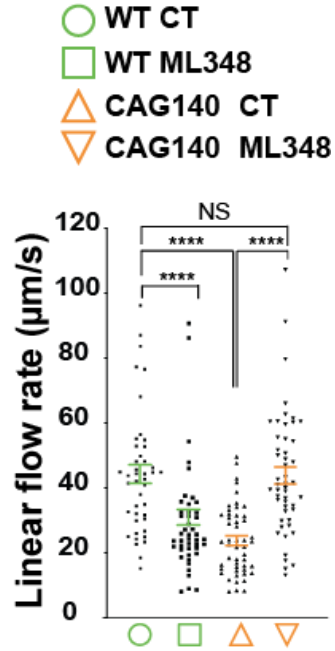


ML348 rescues BDNF transport and release, synaptic density and post-synaptic survival signals in HD corticostriatal circuit on-a-chip

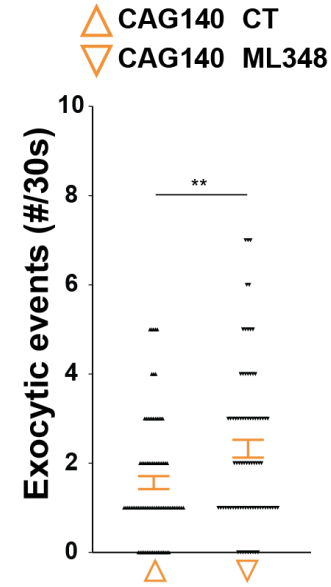




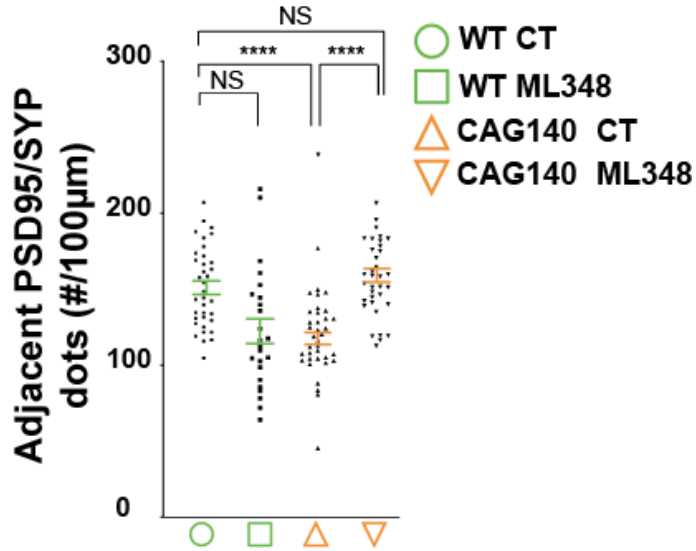
BDNF-mCherry transport



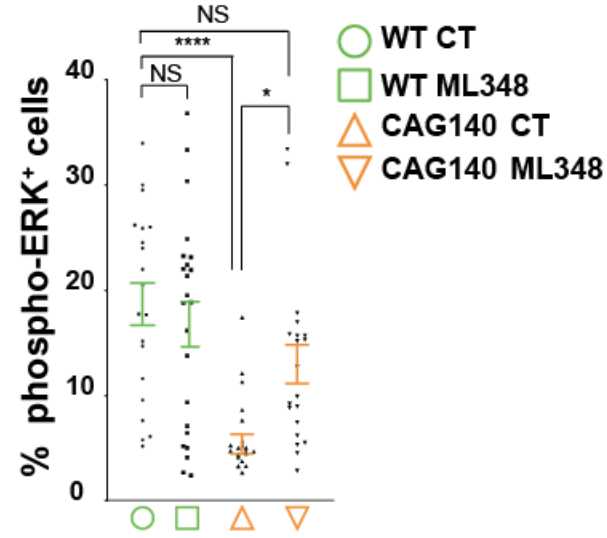
BDNF exocytosis



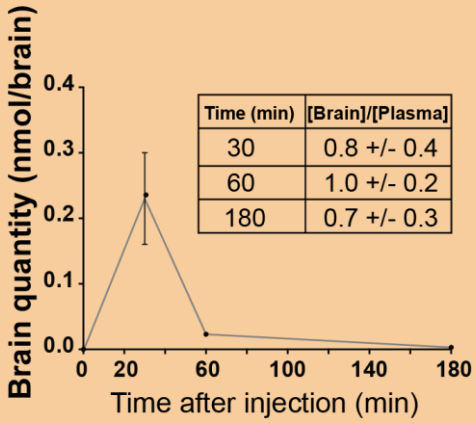
PSD95-SYP immunostaining



P-ERK immunostaining

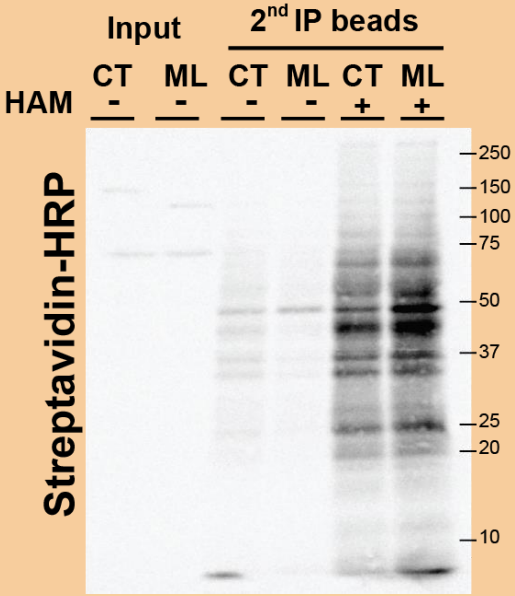


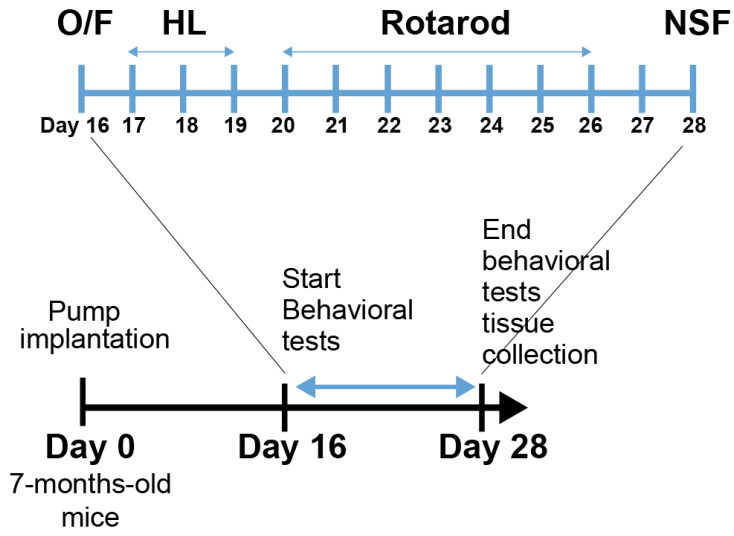
ML348 ameliorates behavior of HD mice



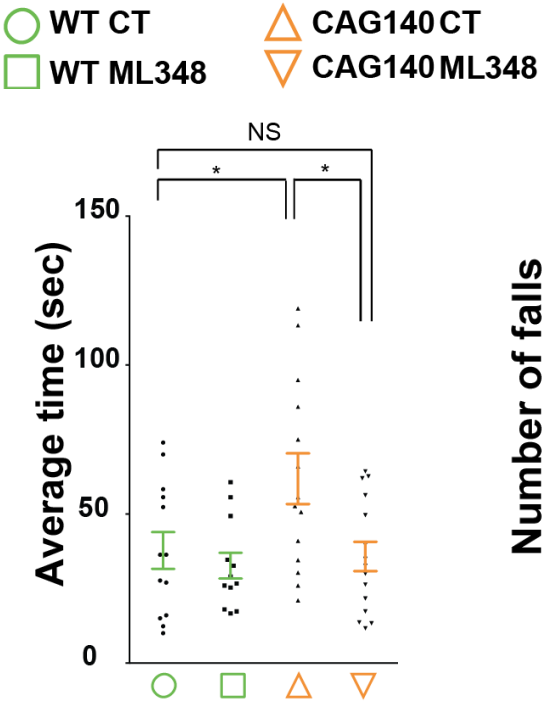
Time (min)	[Brain]/[Plasma]
30	0.8 +/- 0.4
60	1.0 +/- 0.2
180	0.7 +/- 0.3

Brain palmitoylation

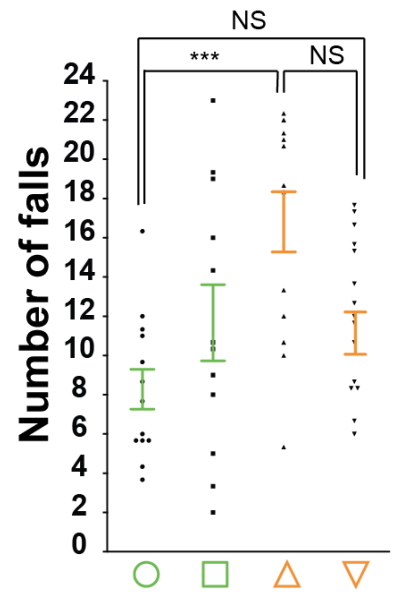




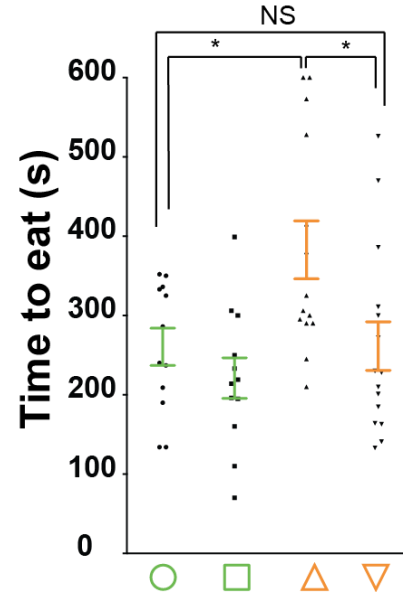
Horizontal ladder



Fixed rotarod (15 rpm)

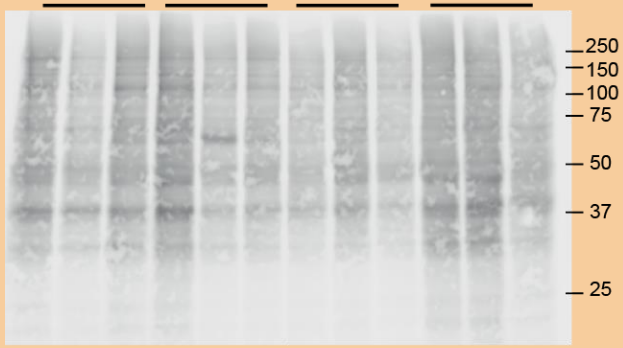


Novelty suppressed feeding

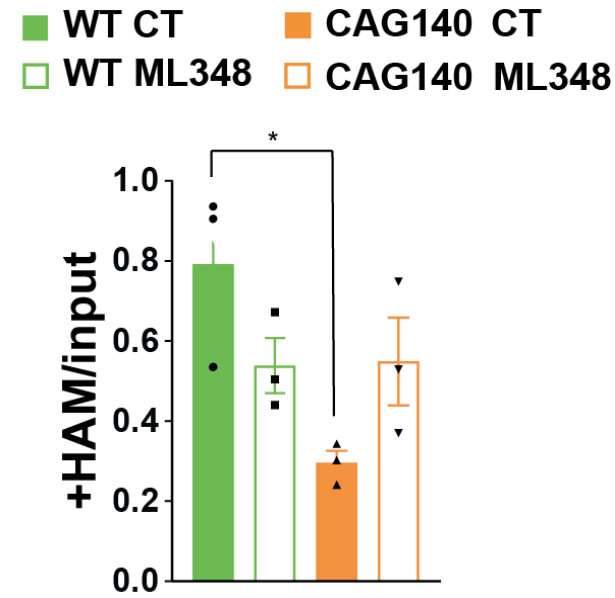


ML348 restores brain palmitoylation and reverses pathological phenotype of HD mice

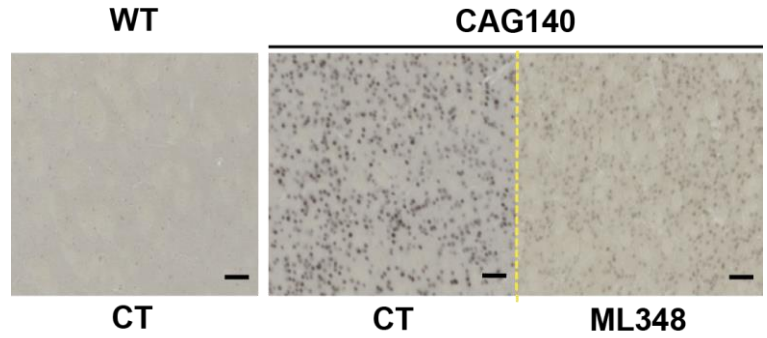
Brain palmitoylation

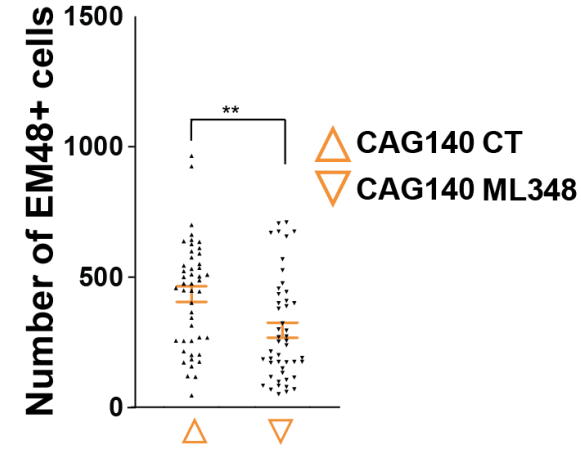


Brain palmitoylation

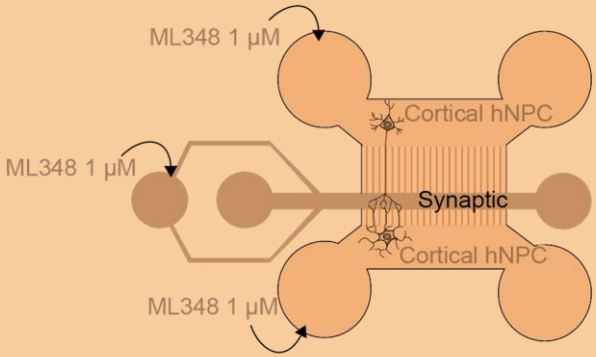


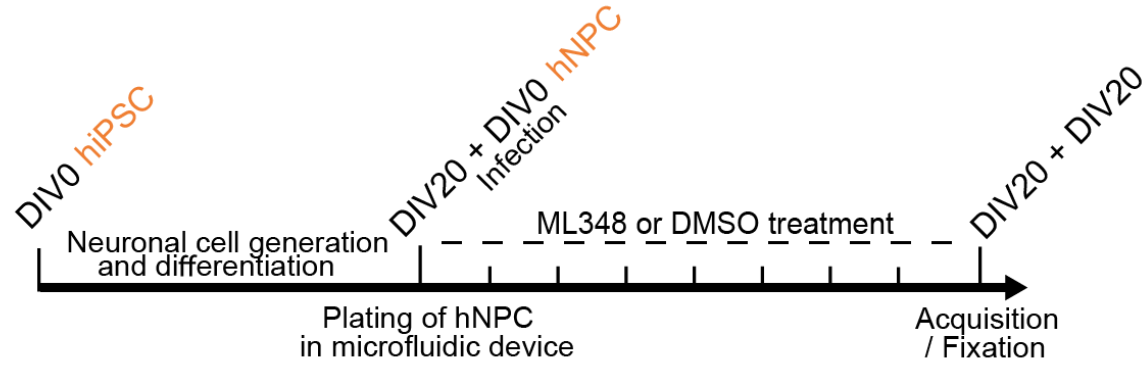
mHTT nuclear accumulation



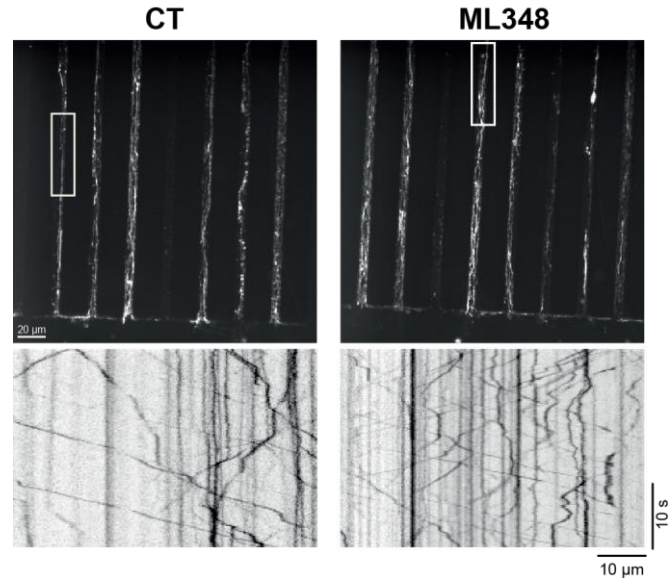


ML348 increases axonal transport in human HD patient iPSC derived cortical neurons

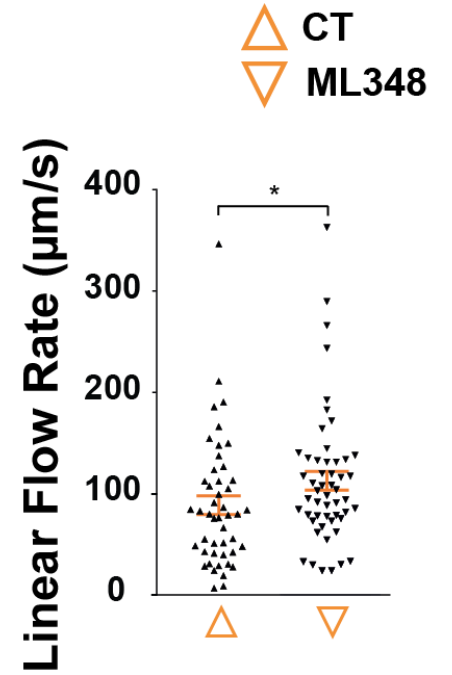




BDNF Axonal transport



BDNF-mCherry transport



Conclusion

- **The corticostriatal circuit is altered in HD**
- **Axonal transport delivers BDNF that is required for striatal survival**
- **The acyl-protein thioesterase APT1 regulates intracellular trafficking**
- **Increasing brain palmitoylation reverses behavioral and pathological phenotype of HD mice**
- **ML348 is of therapeutic interest for HD patients**

Virlogeux, Scaramuzzino et al., Science Advances, 2021