

Removing protein build up in your brain cells

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- Why does tau build up in your neurons (brain cells) in aging and diseases?
- What is autophagy (from Greek words auto phagos, translation “self eating”) and why is it an important in removing garbage in cells?
- How do we regulate autophagy and use it as a treatment?
- What is the outcome of preclinical testing for possible therapeutics to treat FTD and tauopathies like PSP and CBD

Acknowledgements

FUNDING

CurePSP

ADDF – AFTD

Tau Consortium

National Health Institute

Merck and Co

Alzheimer's Association, USA

American Health Assistance Foundation

Weston Brain Institute

Ceracuity

Tauopathies – Learning Biology From Many Diseases

Progressive Supranuclear Palsy

Corticobasal Degeneration

Pick disease / complex

FTD/FTLD (Frontotemporal dementia and parkinsonism linked to chromosome 17,
Frontotemporal lobar degeneration)

Alzheimer's disease

TBI/CTE

Argyrophilic grain disease

Tangle-predominant dementia

Lytico-Bodig disease (Parkinson-dementia complex of Guam)

Dementia pugilistica (chronic traumatic encephalopathy)

Subacute sclerosing panencephalitis

lead encephalopathy

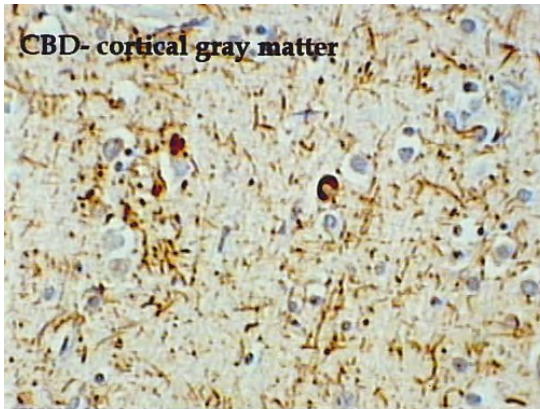
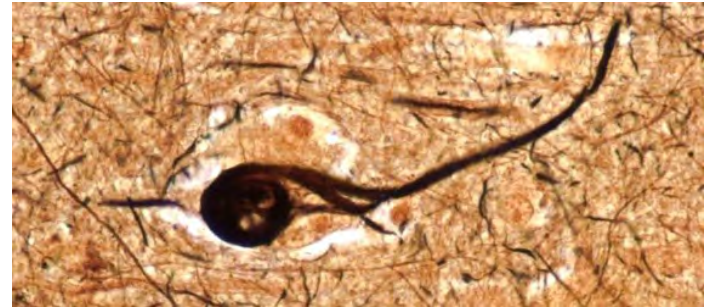
tuberous sclerosis

Hallervorden-Spatz disease

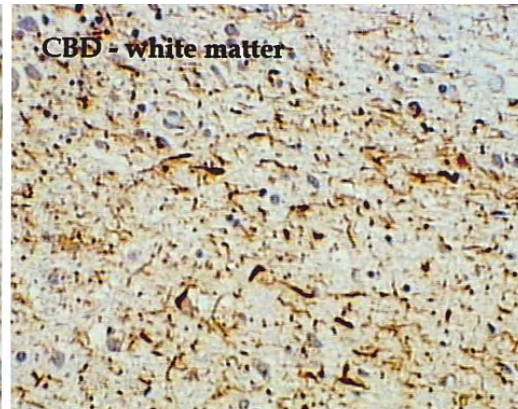
Lipofuscinosis

Ganglioglioma, gangliocytoma and Meningioangiomatosis

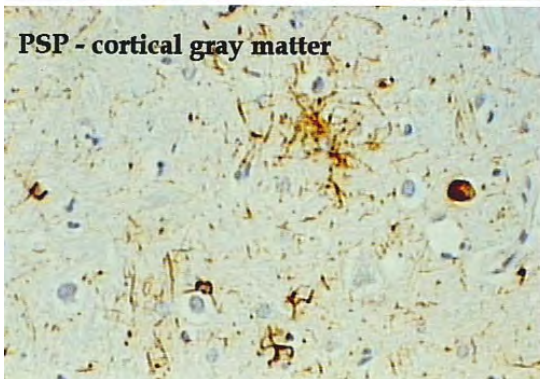
Neurofibrillary tangles (Alzheimer disease)



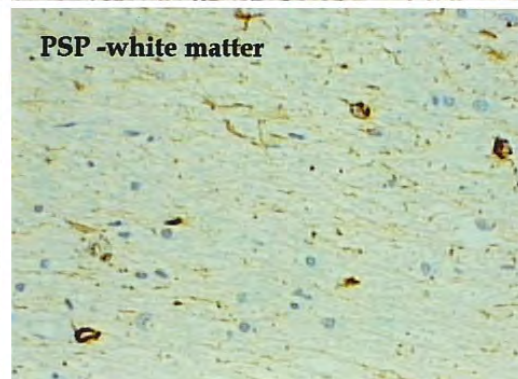
CBD- cortical gray matter



CBD - white matter



PSP - cortical gray matter



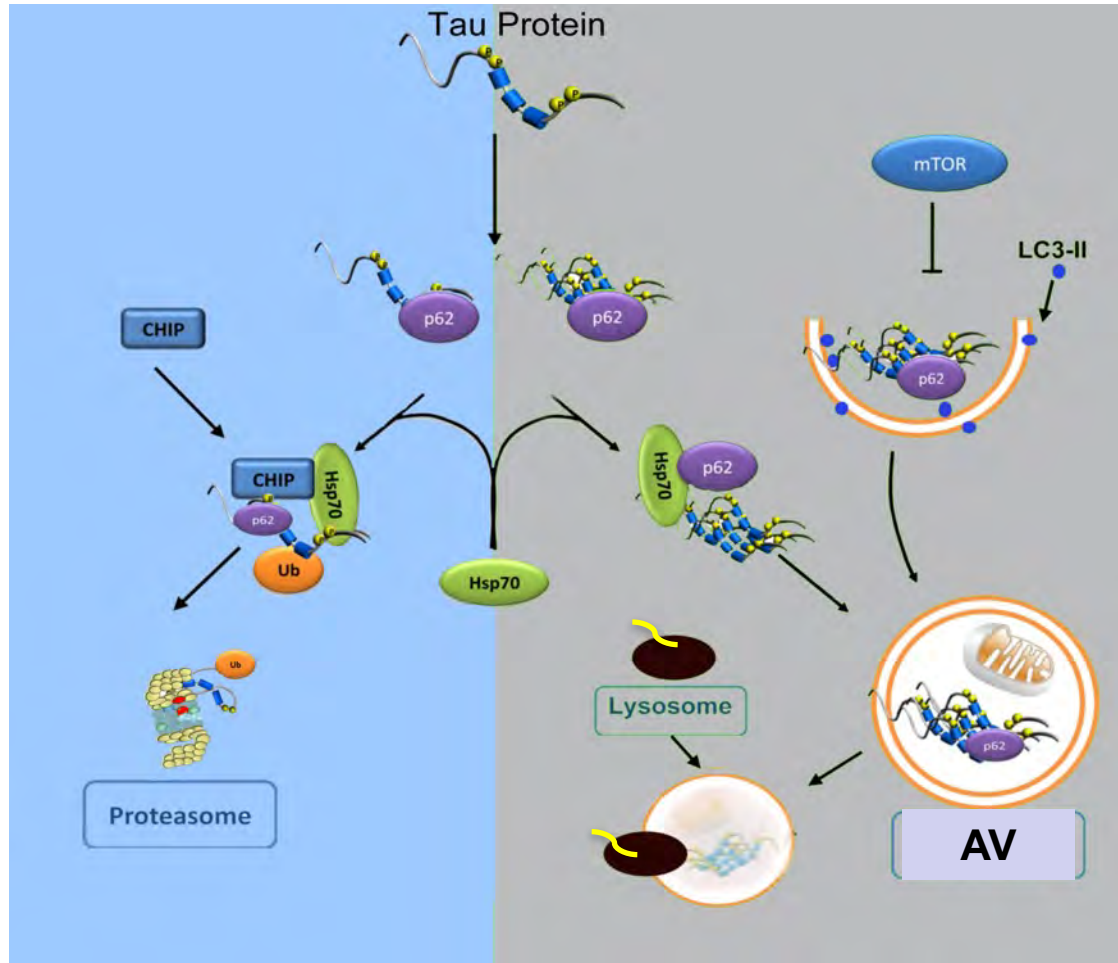
PSP -white matter

Dickson, *Neurol* (1999) 246
[Suppl 2]: II/6–II/15

Protein Clearance

Proteasomal

Autophagic-Lysosomal



Proteasome – remove unfolded soluble proteins

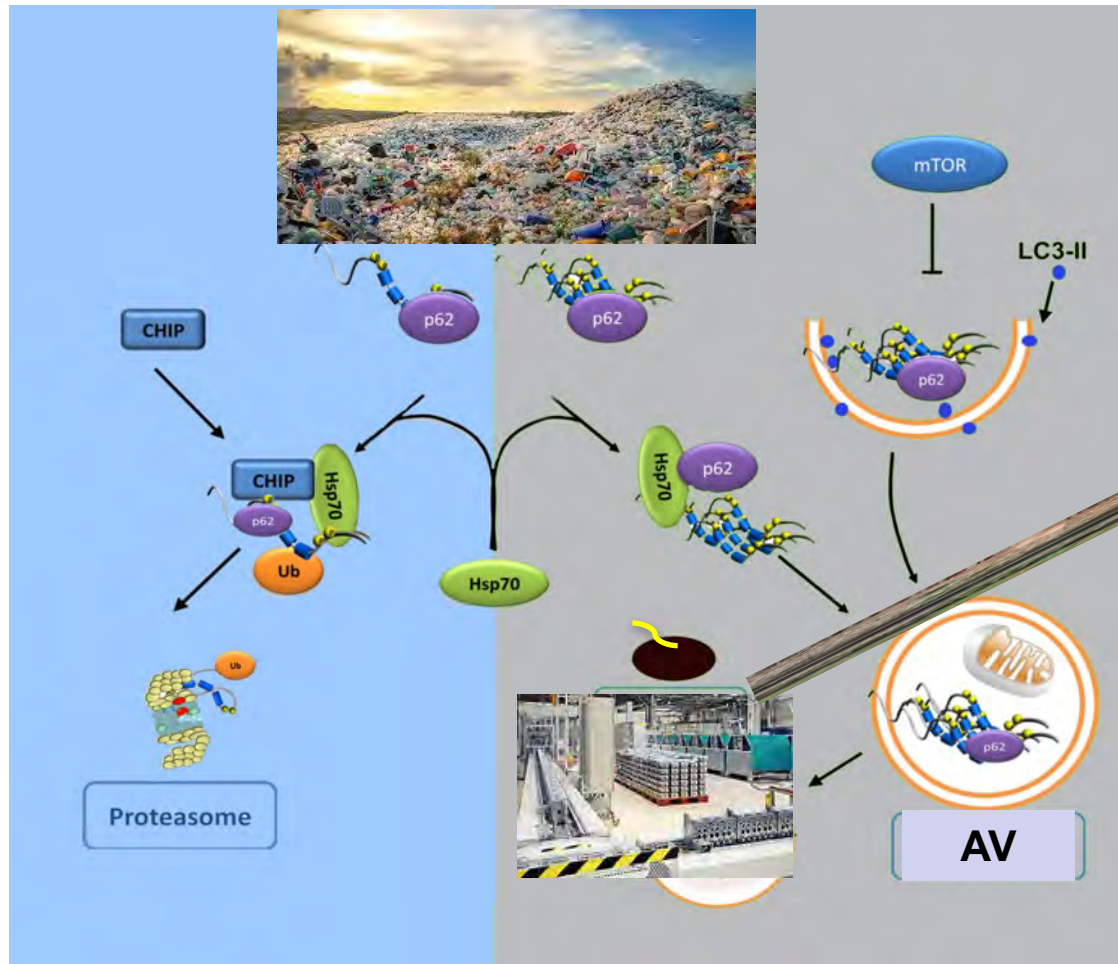
Autophagy – remove aggregates following autophagic induction

Lysosome – degrade most proteins – lysosomal acidification

Protein Clearance

Proteasomal

Autophagic-Lysosomal

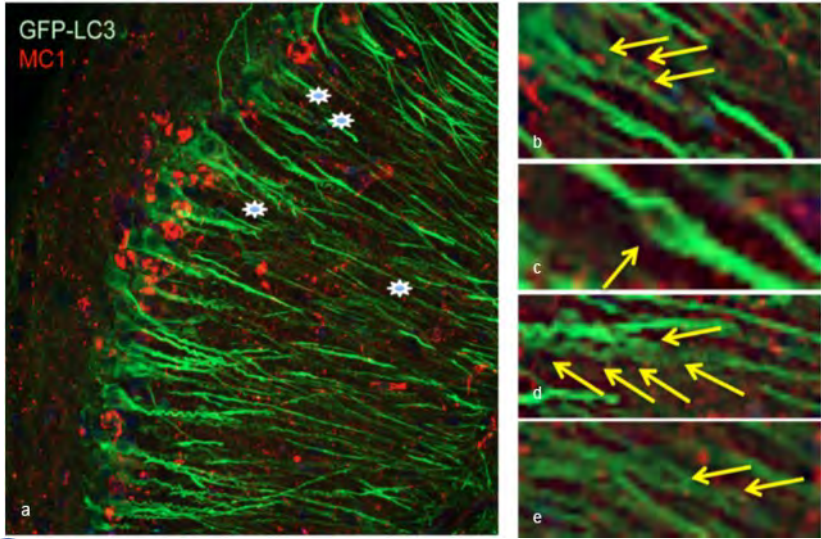
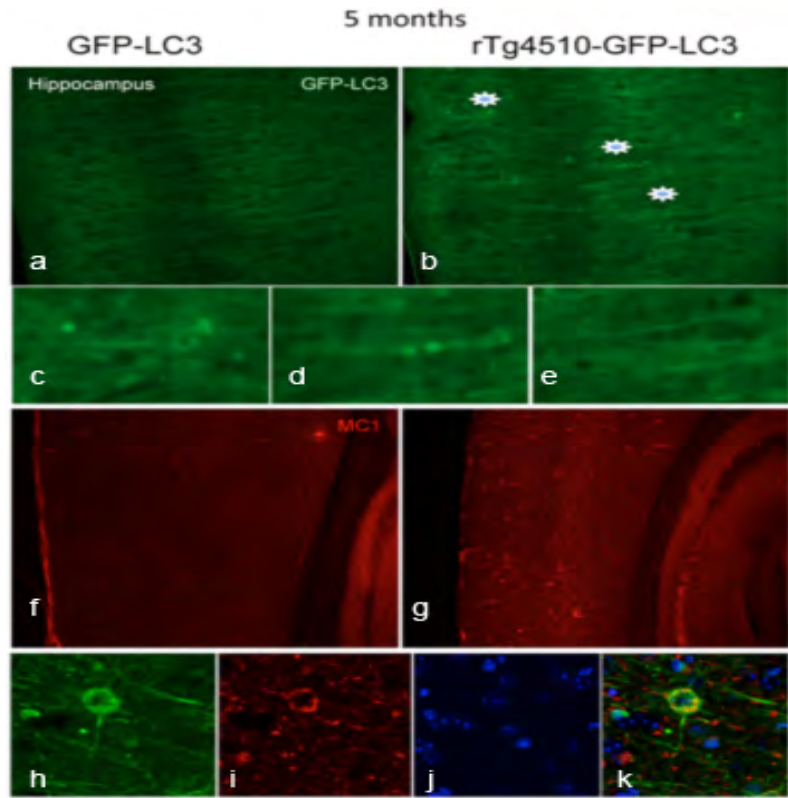
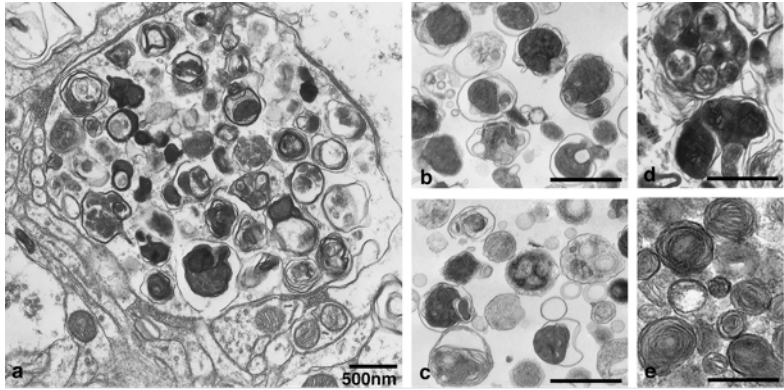
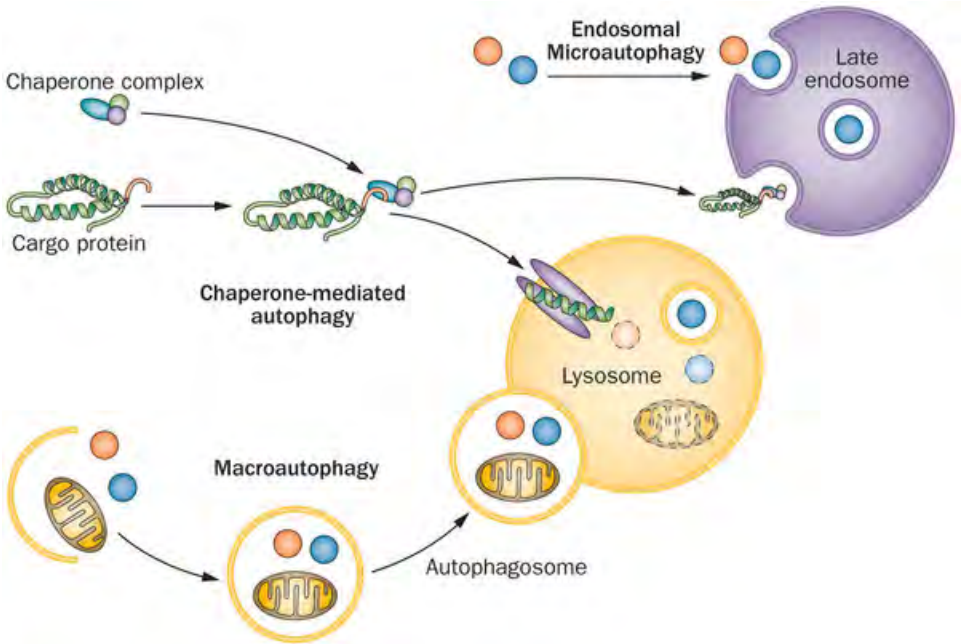


Proteasome – remove unfolded soluble proteins

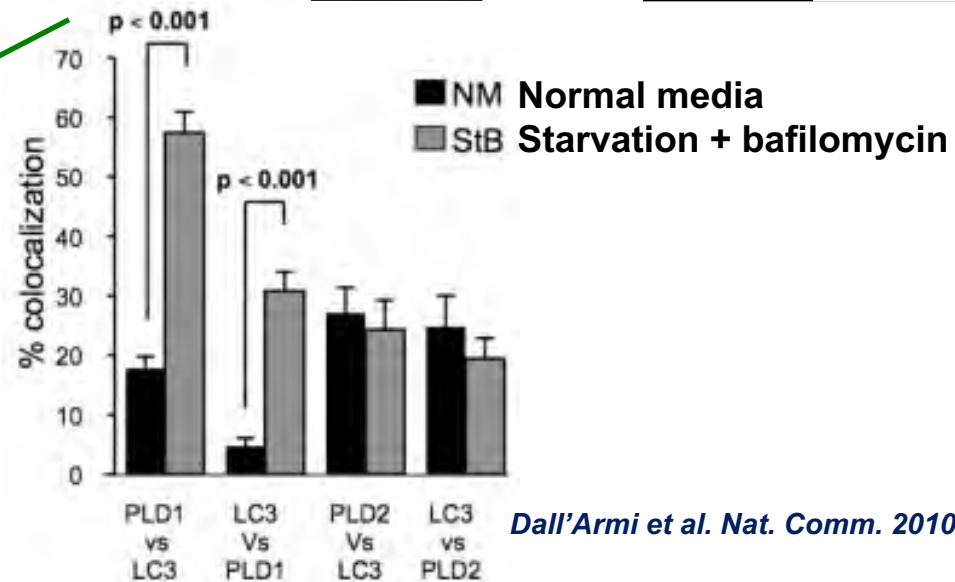
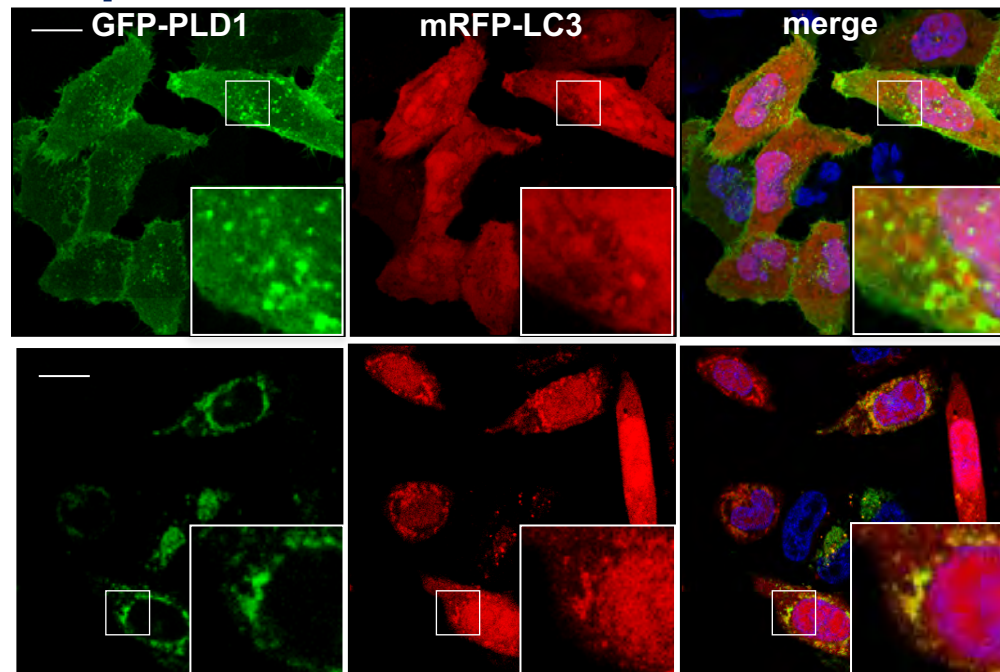
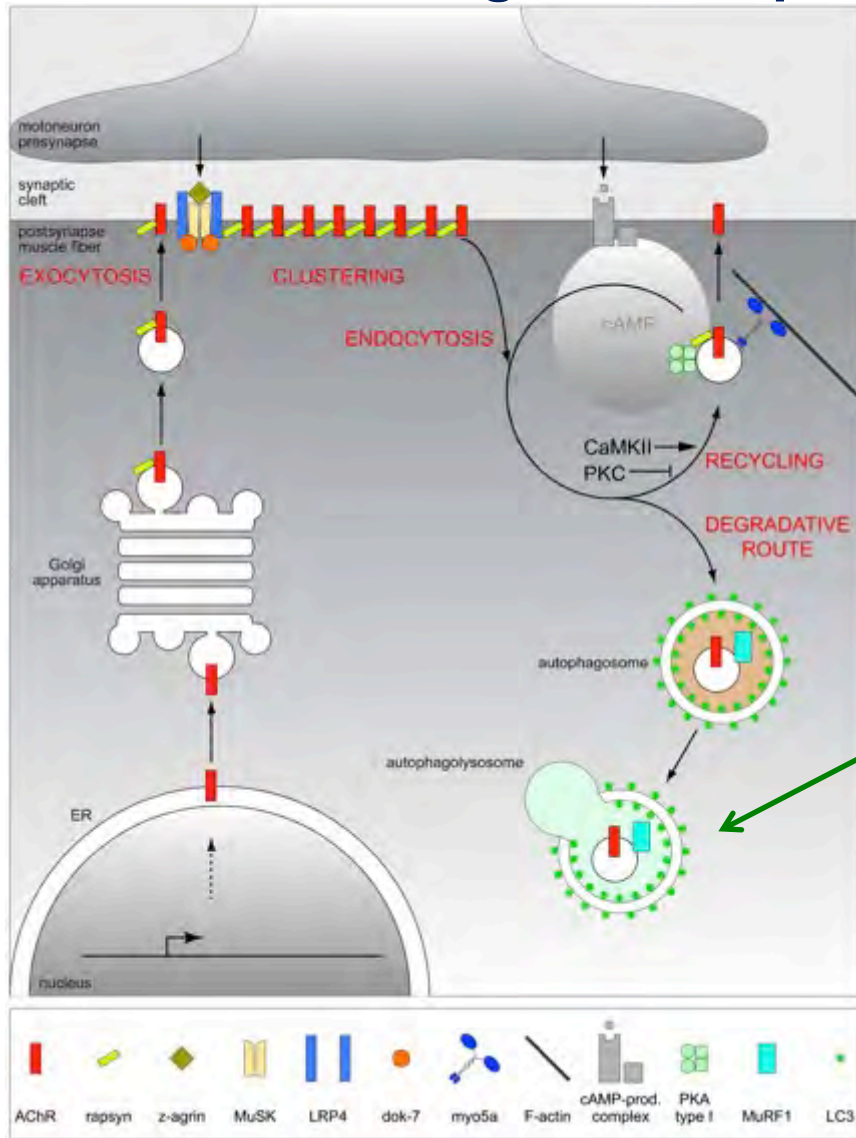
Autophagy – remove aggregates following autophagic induction

Lysosome – degrade most proteins – lysosomal acidification

Autophagy – the Good and Bad



Strategies to help clear proteins in brain cells



Dall'Armi et al. Nat. Comm. 2010

Next steps:

Does it work in models of disease?

Can we improve the drug to enter brain and last longer?