UNIVERSITY OF CAMBRIDGE

Modifiers of Amyloid-beta Toxicity in Alzheimer's Disease

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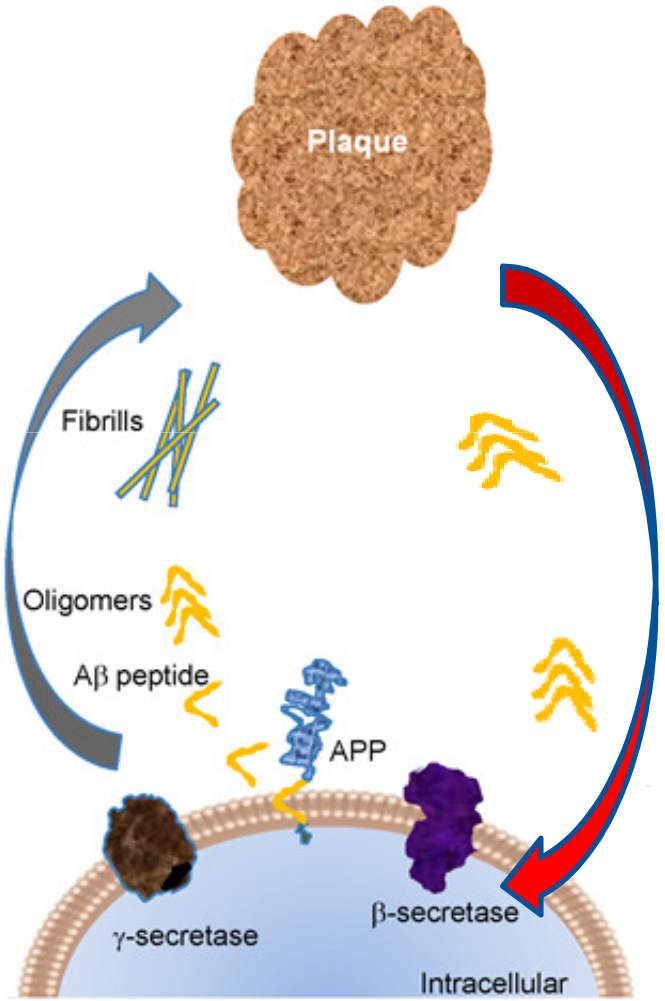
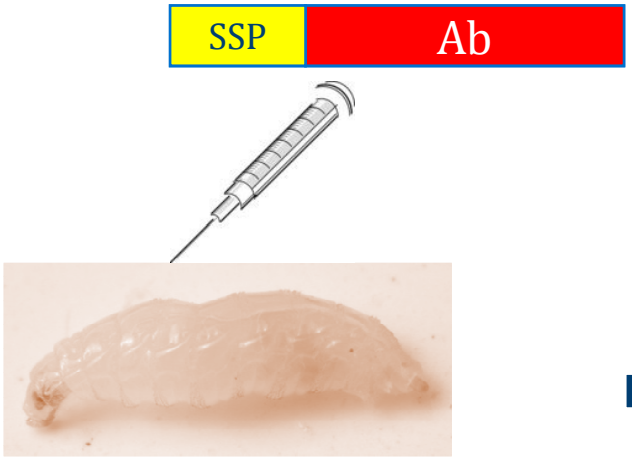
Department of Genetics

Alzheimer's disease and Dementia, 2014

Is there an interaction between two pools of Aβ?



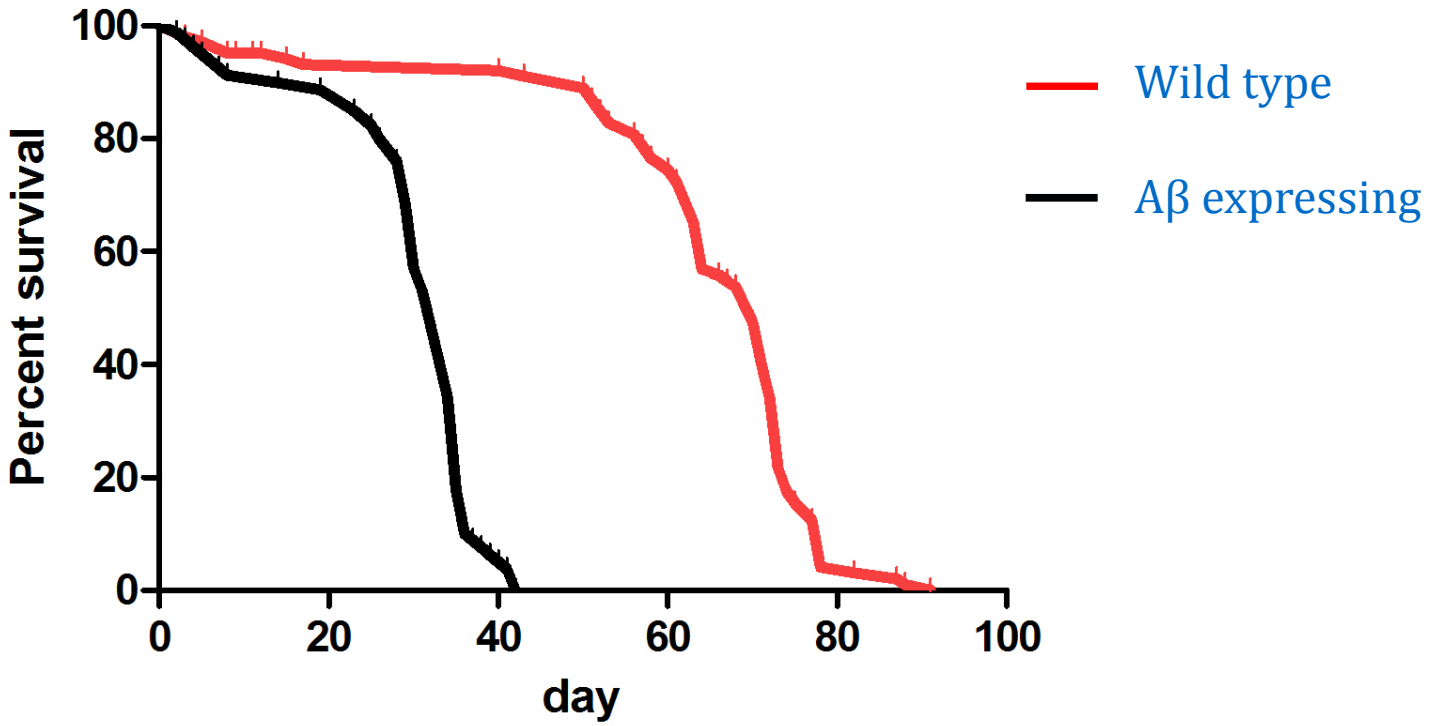
We secrete Aβ peptides from the neurons of fly brain and study toxicity



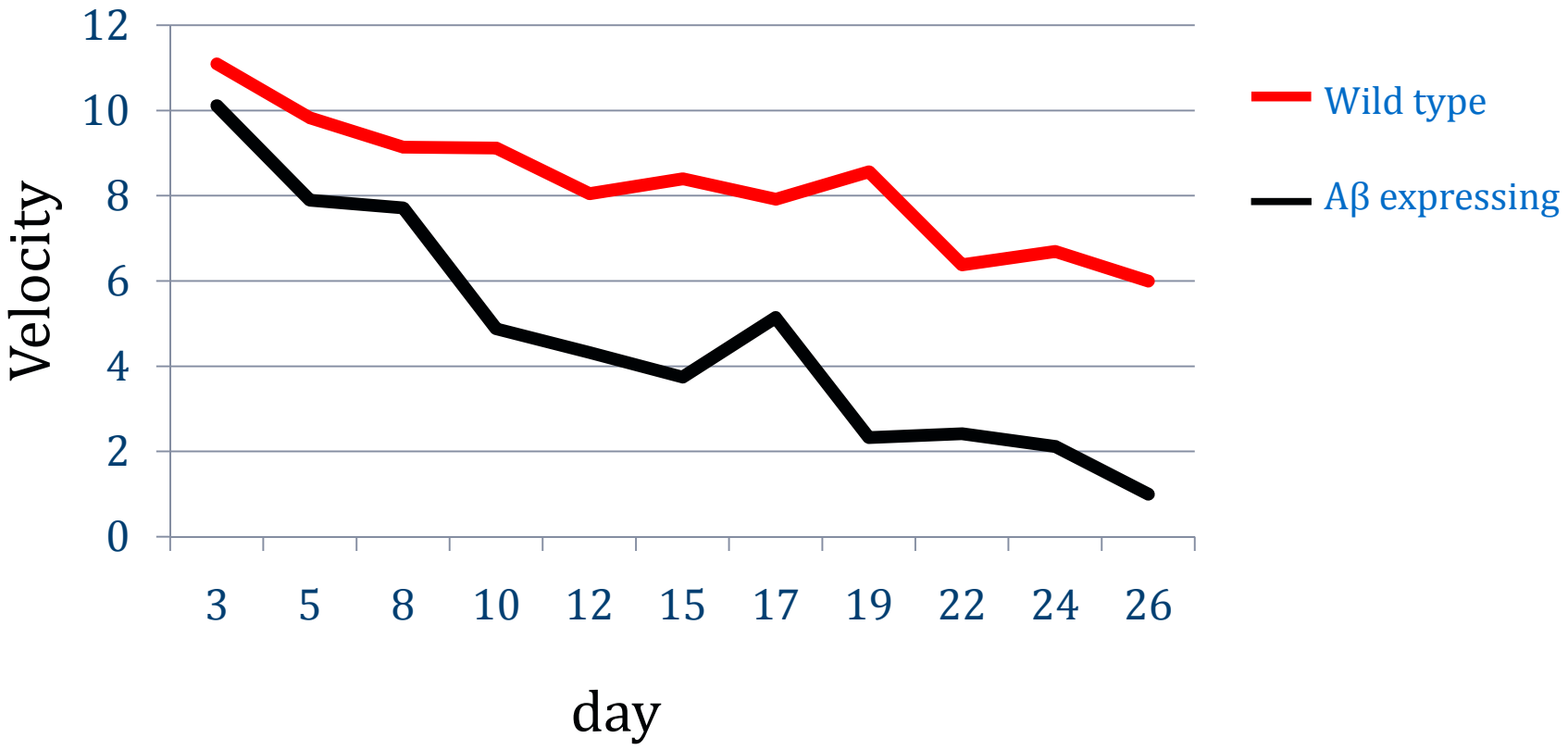
Crowther et al, 2005

Secreted Aβ is toxic in Drosophila

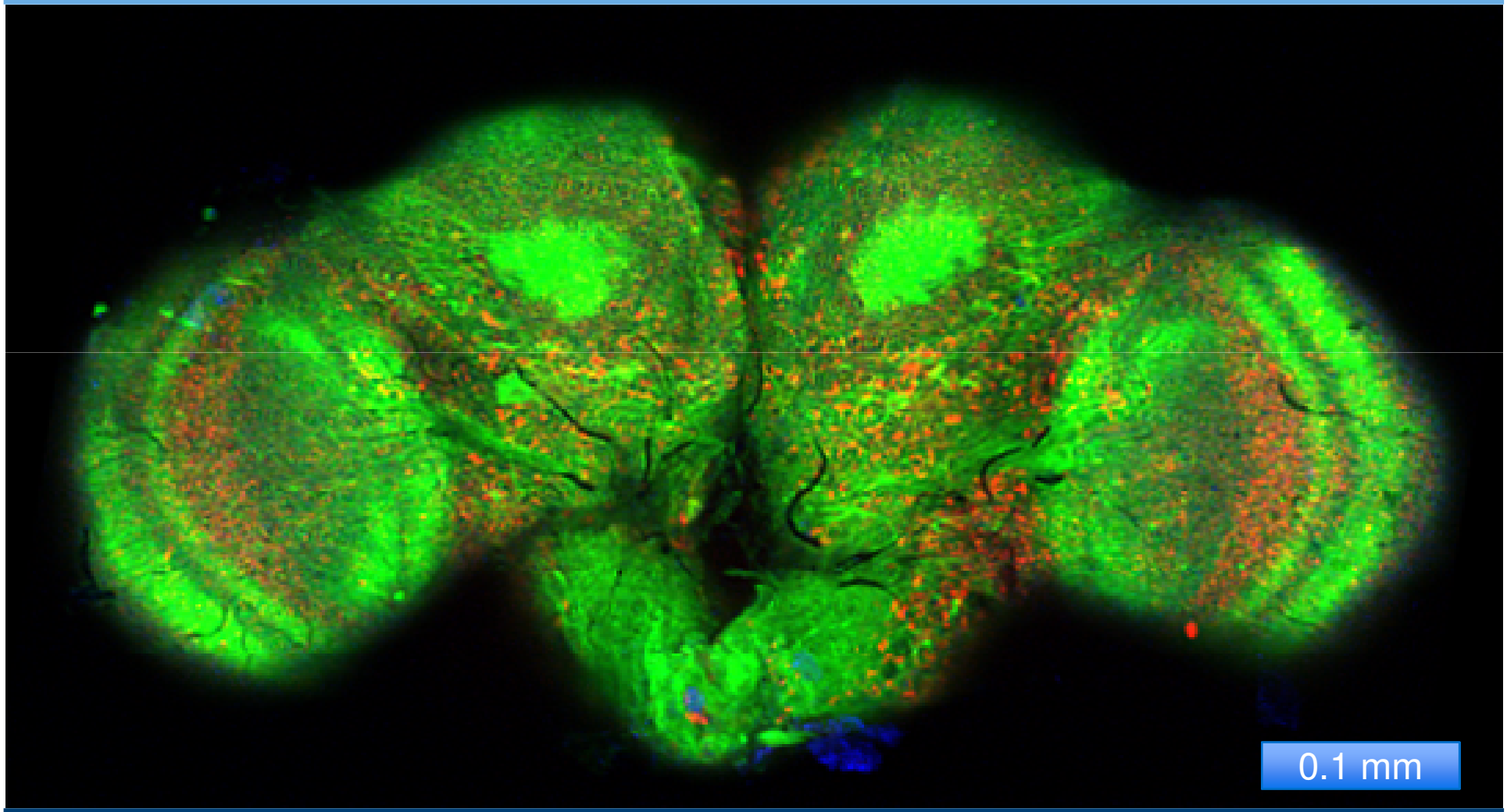
Reduced Longevity



Locomotor deficit

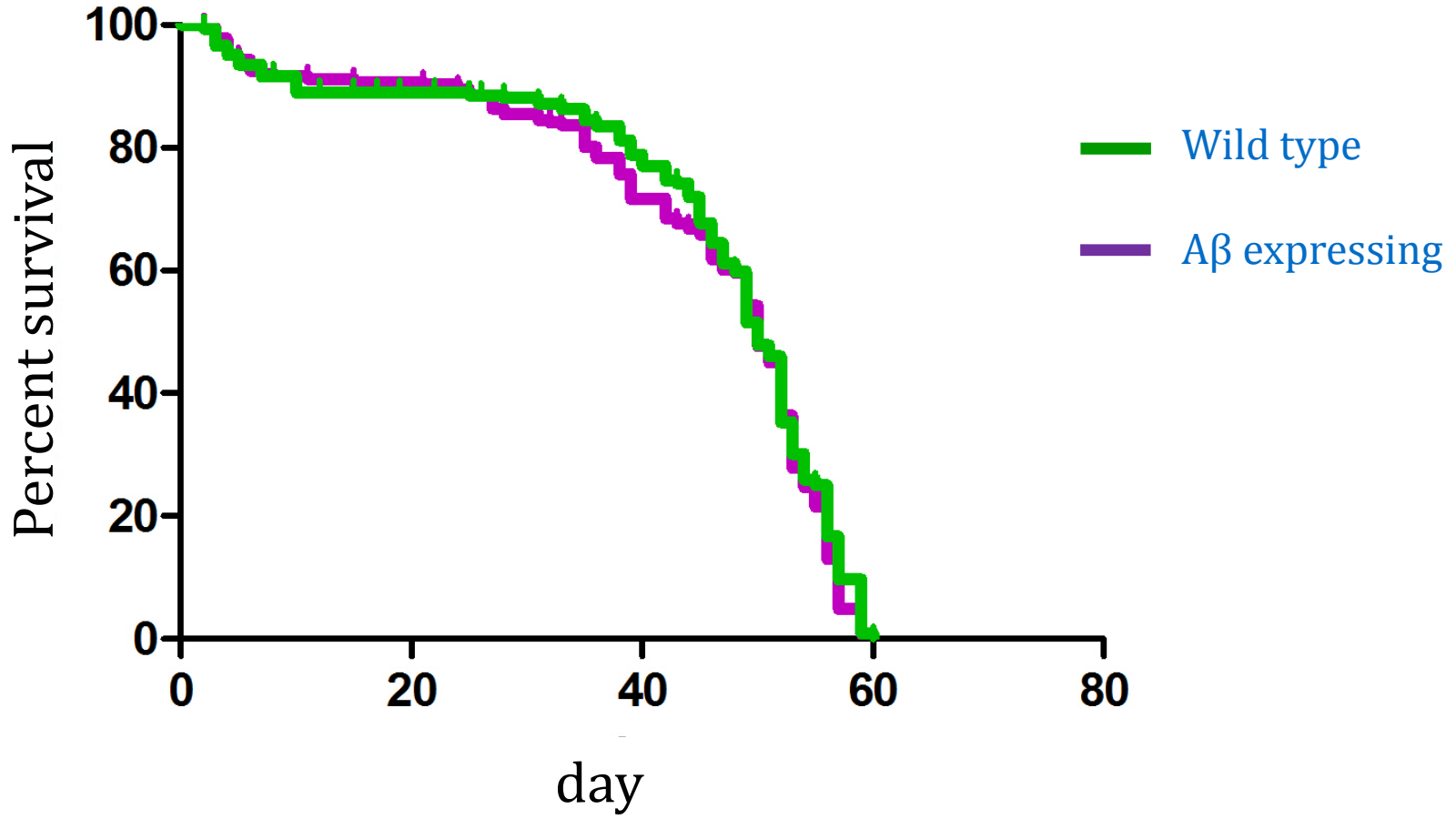


Plaque like deposits in the brain

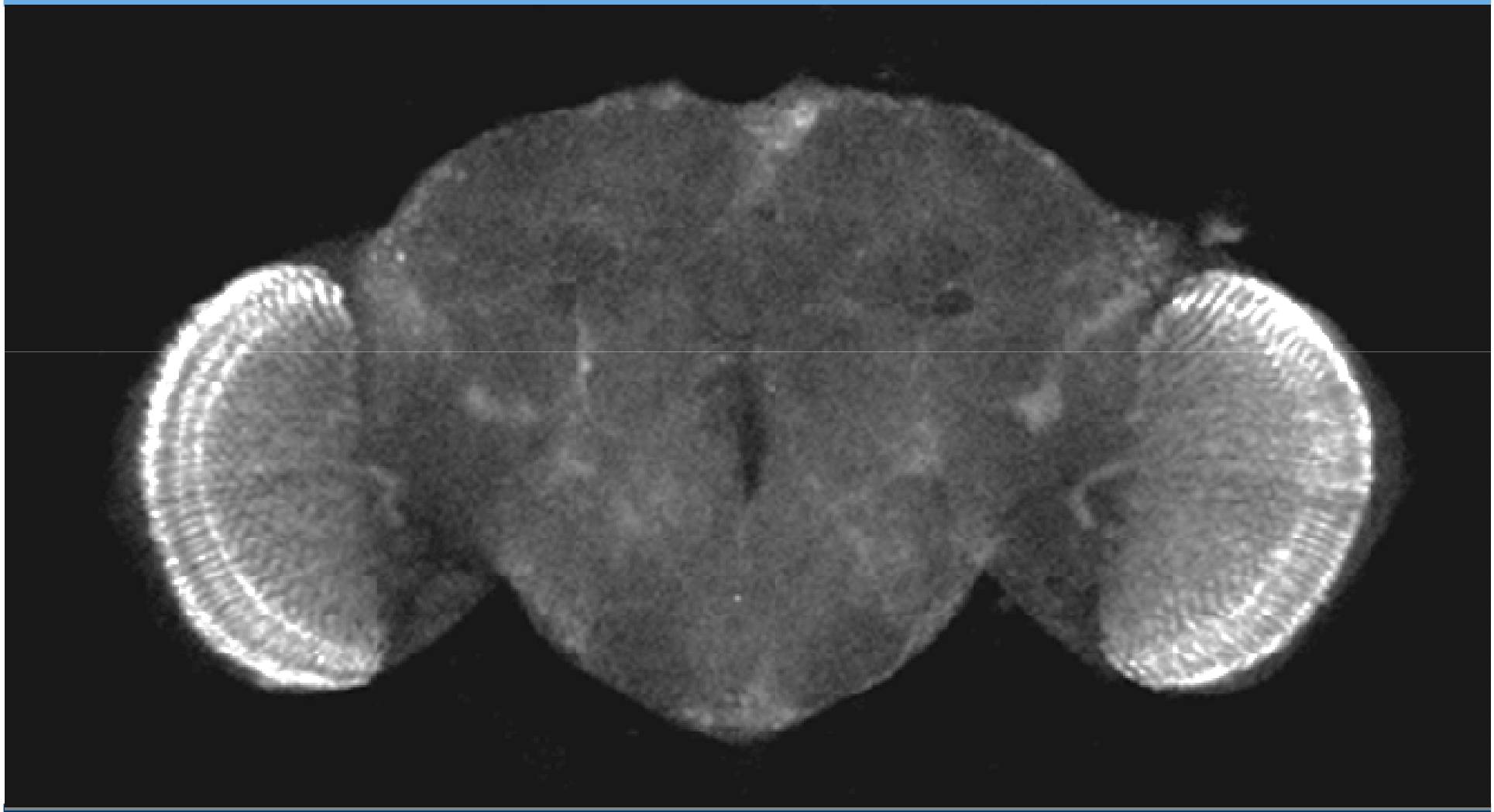


Without SSP, Aβ is expressed in cytoplasm

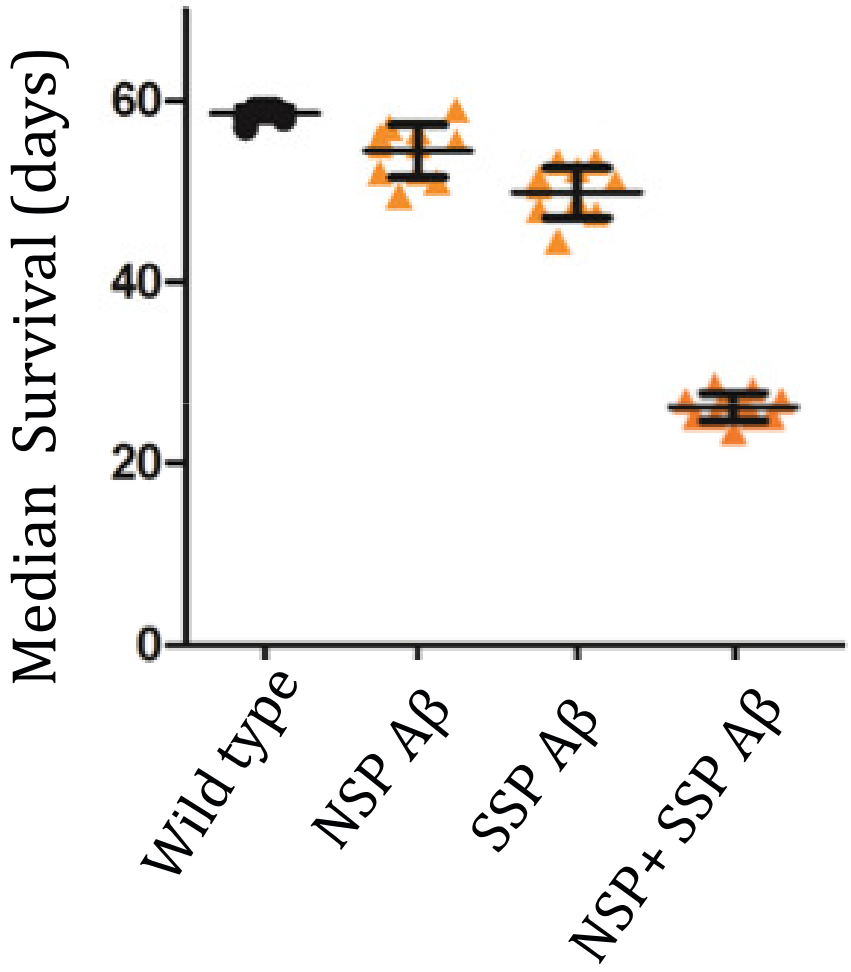
...but Cytoplasmic Aβ is non-toxic



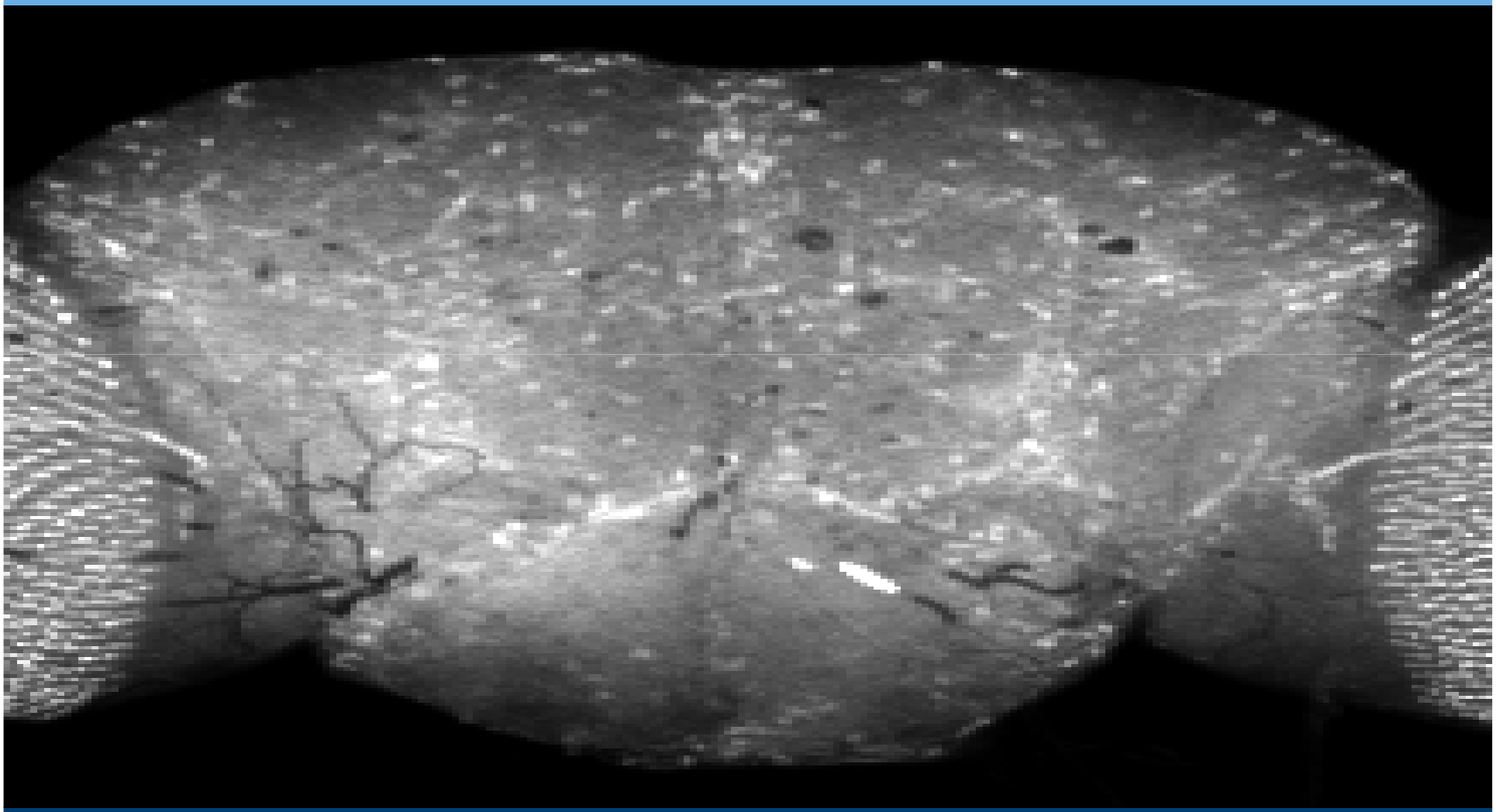
No plaque like deposits



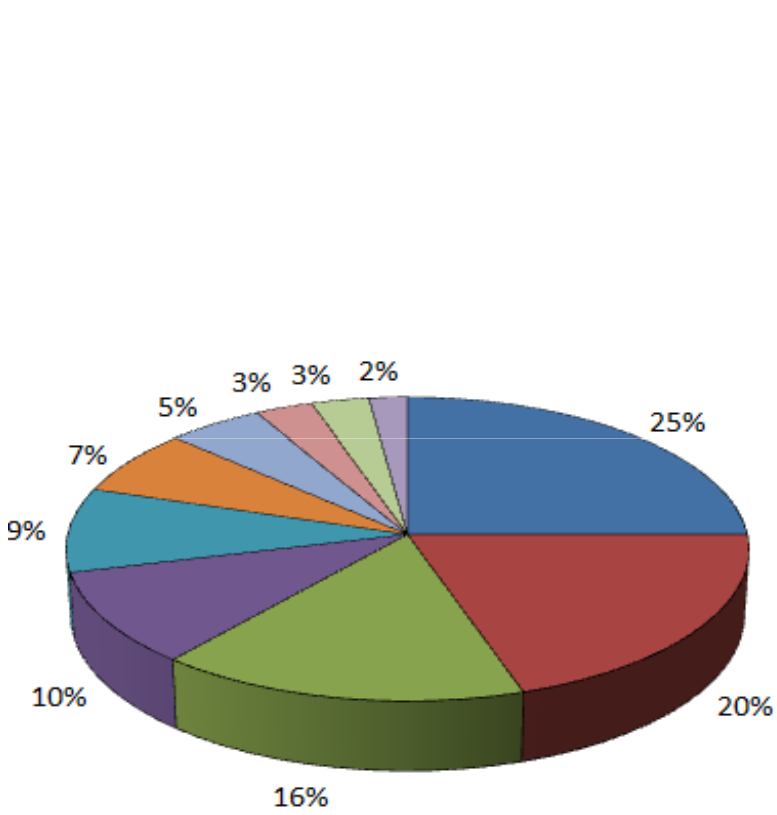
What happens if we co-express these constructs?



Increase in plaque deposition

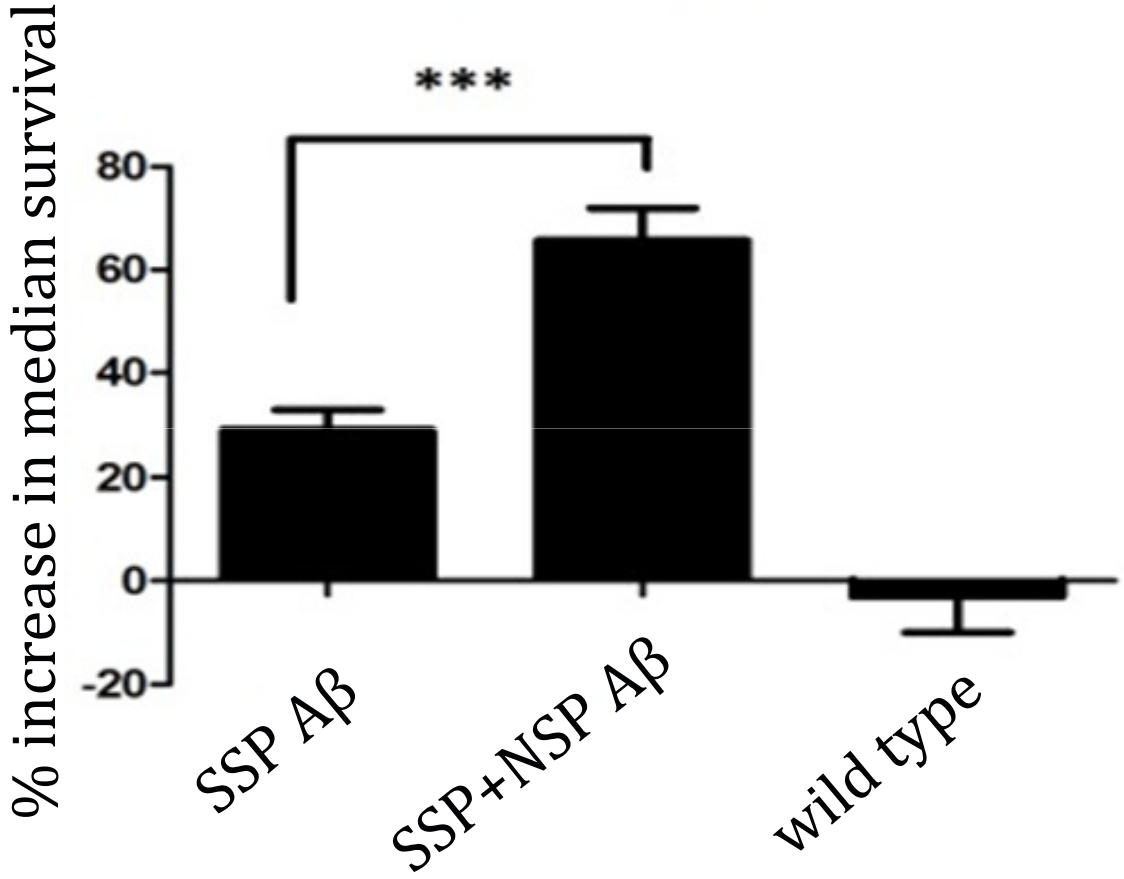


Which pathways are facilitating this synergy?

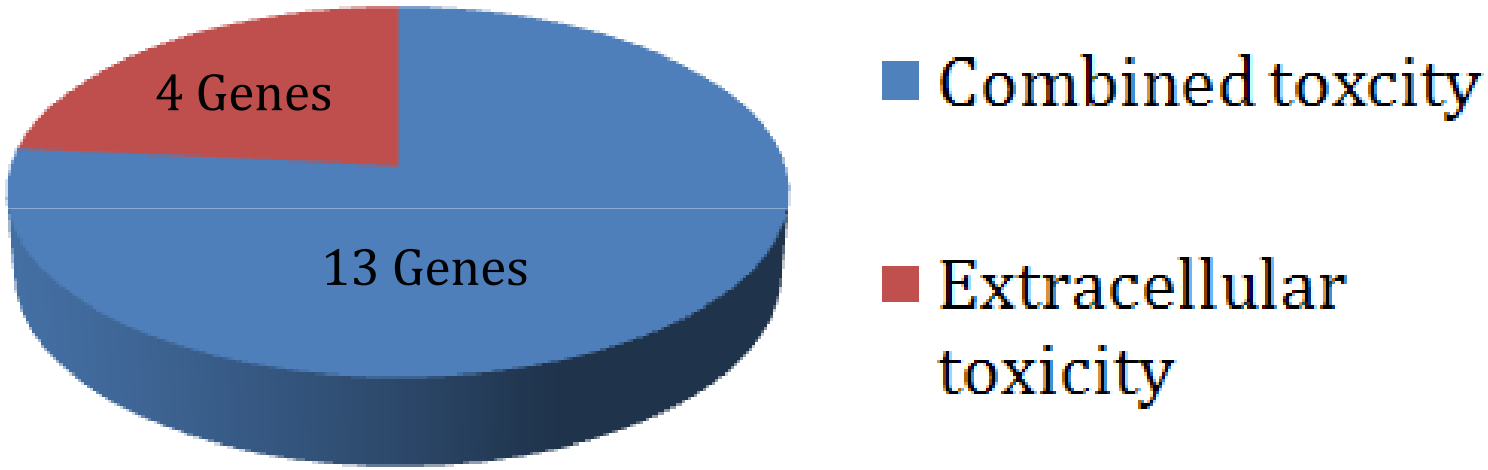


- Endo-/Exocytosis Clatrin-mediated
- Genes from GWAS Studies
- Macropinocytosis and other non-clatrin-mediated Endocytosis
- ERAD
- Autophagy
- Endosomal Sorting
- Vesicular Formation
- Vesicular Transport
- Membrane Secretion
- AB Transporters

An example……CG1824 siRNA



RNAi screen outcome



Conclusion

- There is a synergistic relationship between extracellular and Cytoplasmic Aβ
- Gene knockdown at interface of the cells, modifies Aβ toxcity.
- We are trying to replicate this effect in mammalian cells and study the pathways involved

Many thanks to…

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