Truncated Amyloid beta as triggers of Alzheimer's disease pathology: Recent advances on their production mechanisms and toxicology

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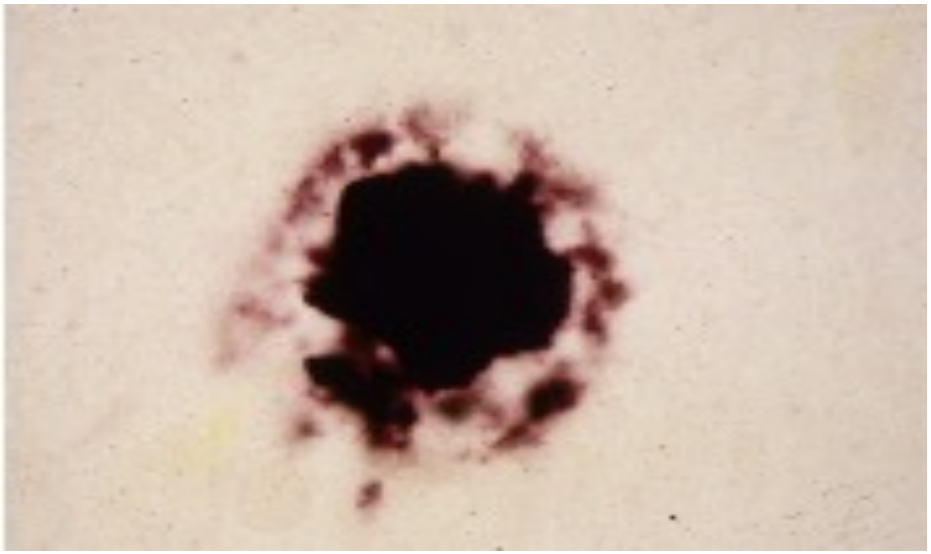
USP
9 novembre 2023

Canonical macroscopic lesions in Alzheimer disease: The senile plaque



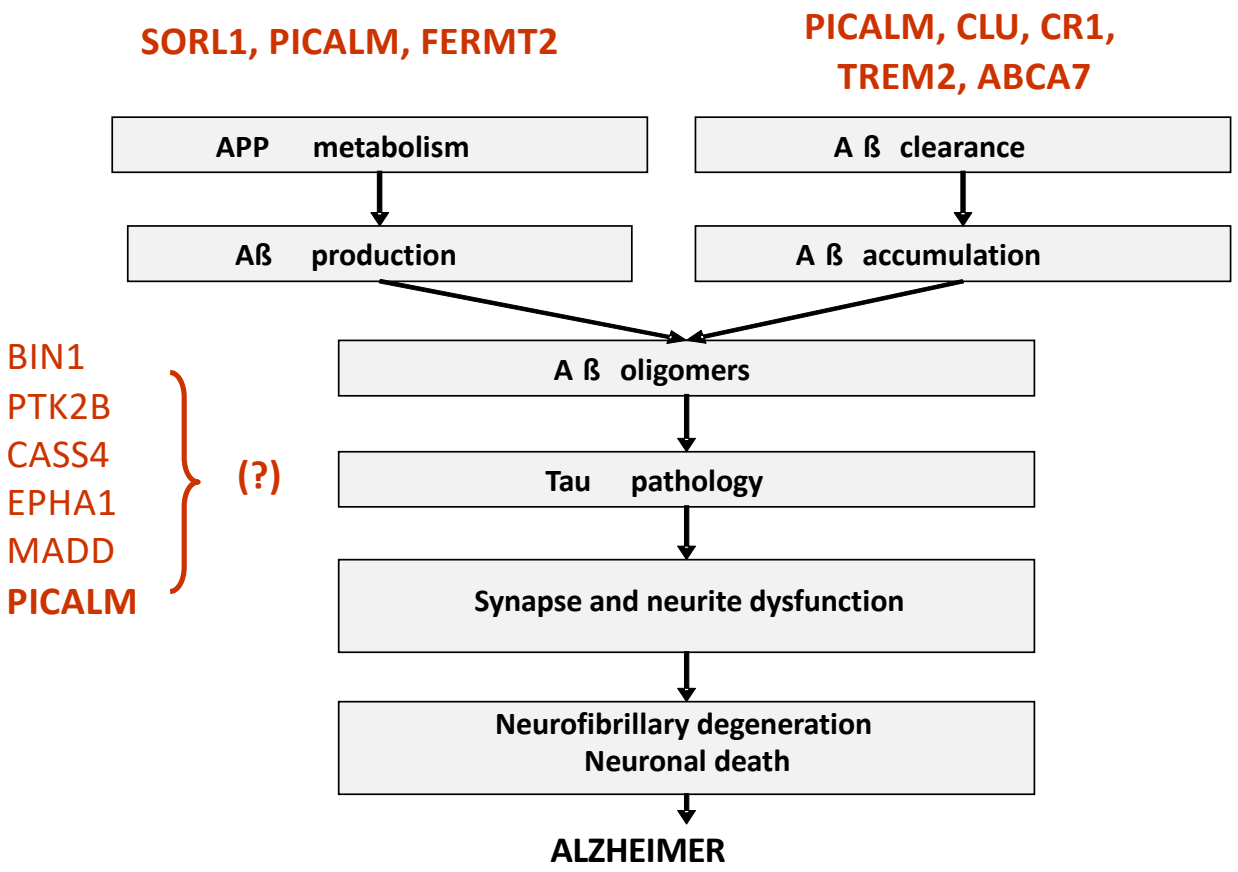
A few words about genetics…..

Monogenic forms of AD are due to mutations on three genes

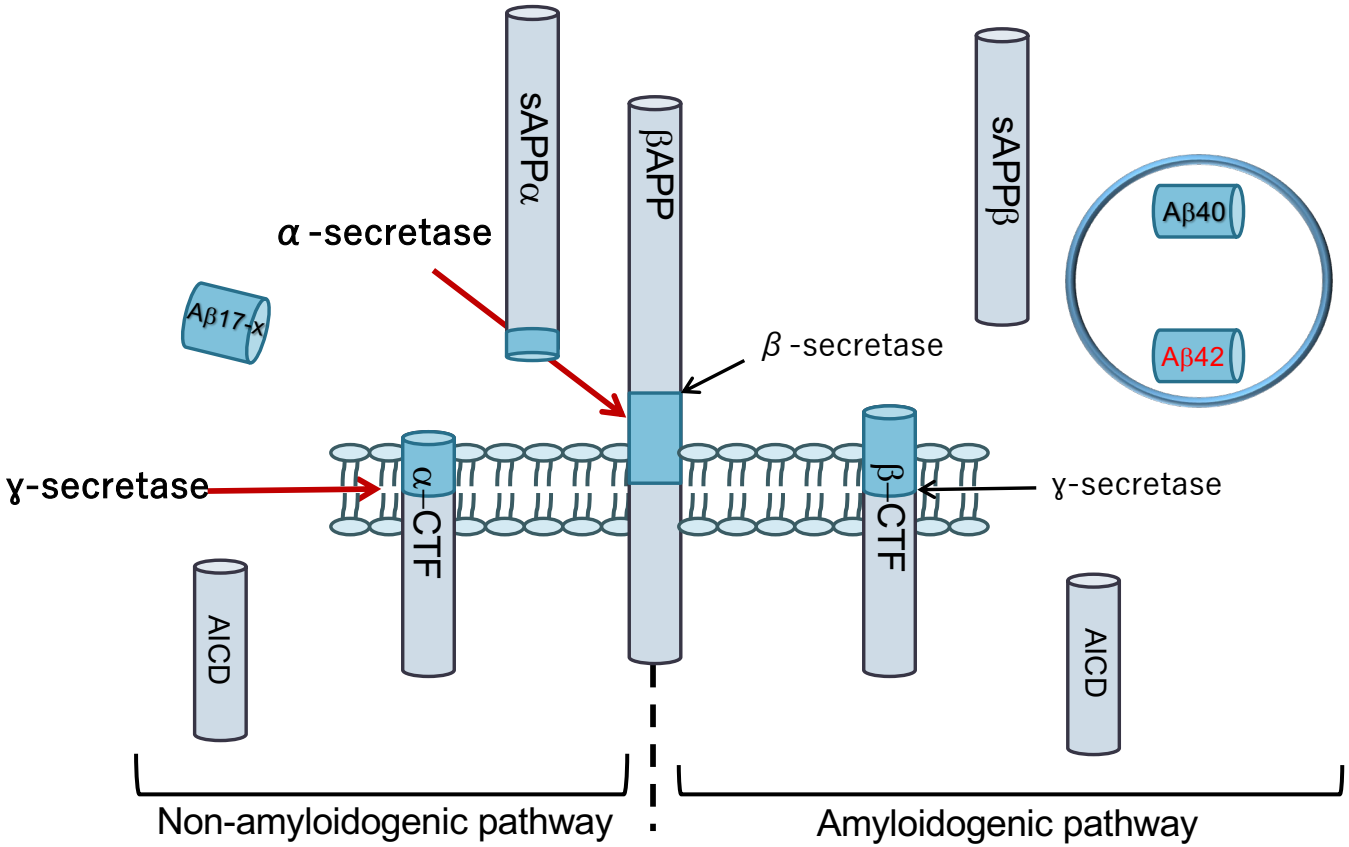
Presenilin 1 (chromosome 1)
Presenilin 2 (chromosome 2)
βAPP (chromosome 21)

All familial mutations with mandelian autosomal inheritance affect APP biology or that of enzymes involved in its catabolism

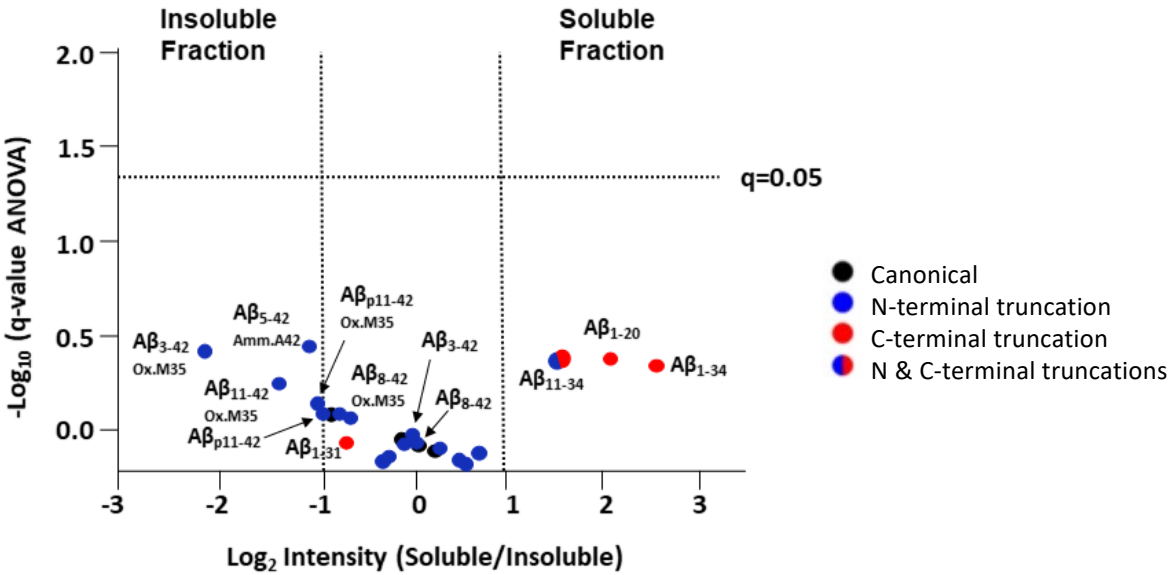
GWAS identified risk factors that also participate at various levels to the amyloid cascade



Proteolytic maturation of β APP



N-truncated Aβ species in human brains



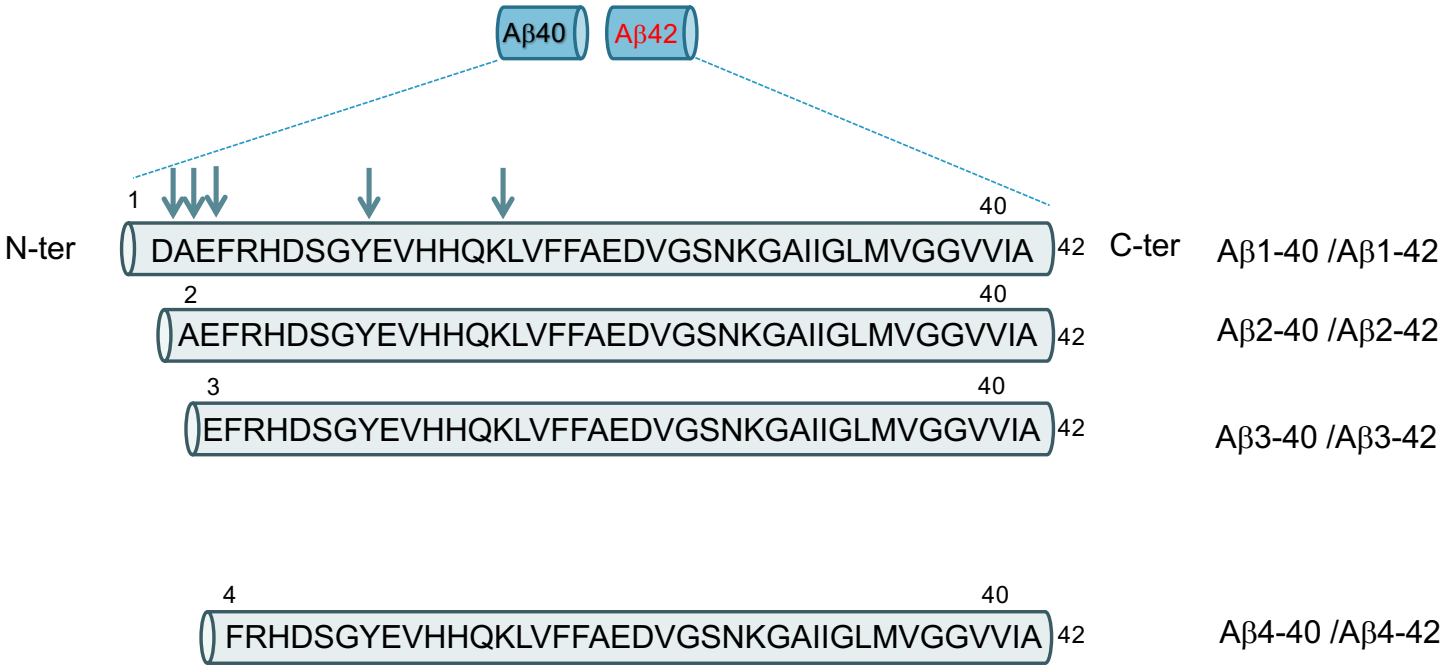
Wildburger et al, Scientific reports 2017

Aβ-peptides	Brain	CSF	Plasma
Non-truncated forms			
1-42, 1-40	+	+	+
1-43	+		
C-terminal truncations			
1-39, 1-38, 1-37, 1-34, 1-20	+	+	+
1-33, 1-19, 1-18, 1-17, 1-15, 1-14		+	+
1-35			+
1-30, 1-28, 1-16, 1-13		+	
1-31	+		
N-terminal truncations			
3-40	+	+	+
11-40		+	+
6-40			+
5-40	+		+
2-42, 3-42, 4-42, 5-42, 7-42, 8-42, 9-42, 10-42, 11-42, 4-40, 8-40, 9-40	+		
N,C-truncations			
6-39, 6-38			+
3-19, 3-17, 3-15, 11-30		+	
2-38, 11-34	+		
PTMs			
1-40ox	+	+	+
1-39ox, 1-38ox, 1-37ox, 1-17-HHnSa$_2$, 1-15-HHnSa$_2$, 1-15-HHnSa$_3$		+	
1-42ox, pGlu3-42, 3-42ox, pGlu3-42ox, 4-42ox, 5-42ox, 8-42ox, pGlu11-42, pGlu11-42ox, pGlu3-40	+		

Modifications: ox – oxidated M35; pGlu – N-terminal pyroglutamate; HHnSa – O-glycans, H = Hex, Hn = HexNAc, Sa = sialic acid (Neu5Ac).

Zakharova et al, Expert review of proteomics,*2018*

Secondary cleavages



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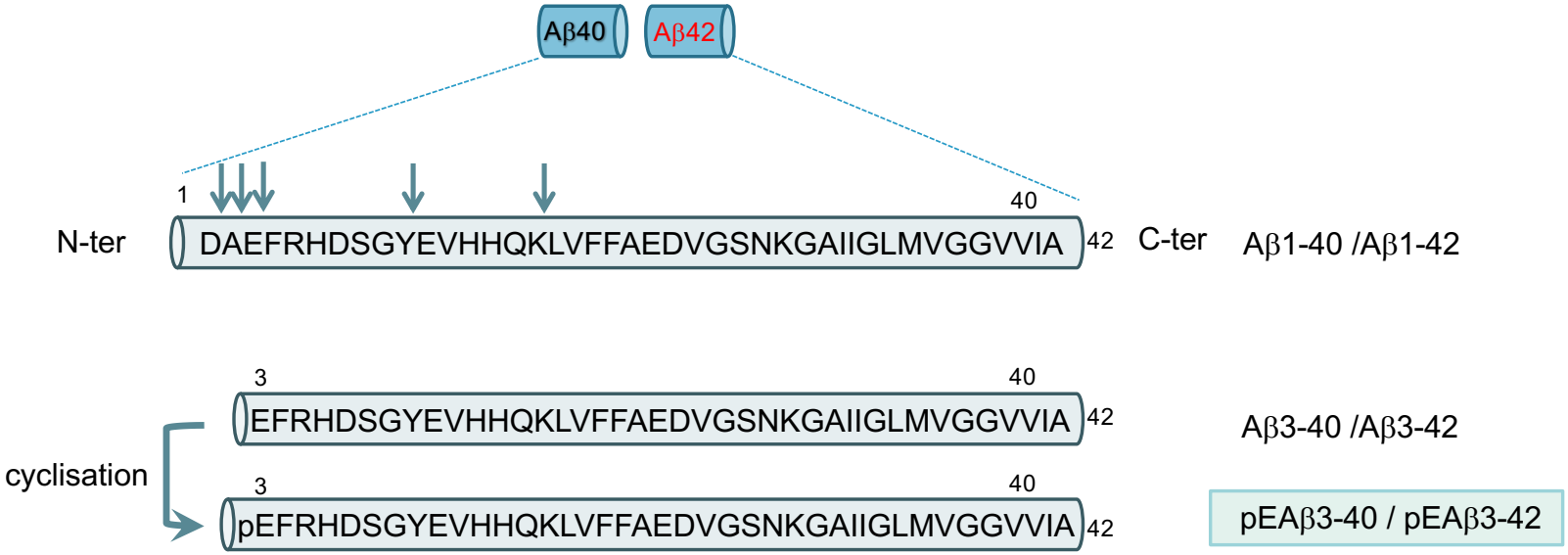
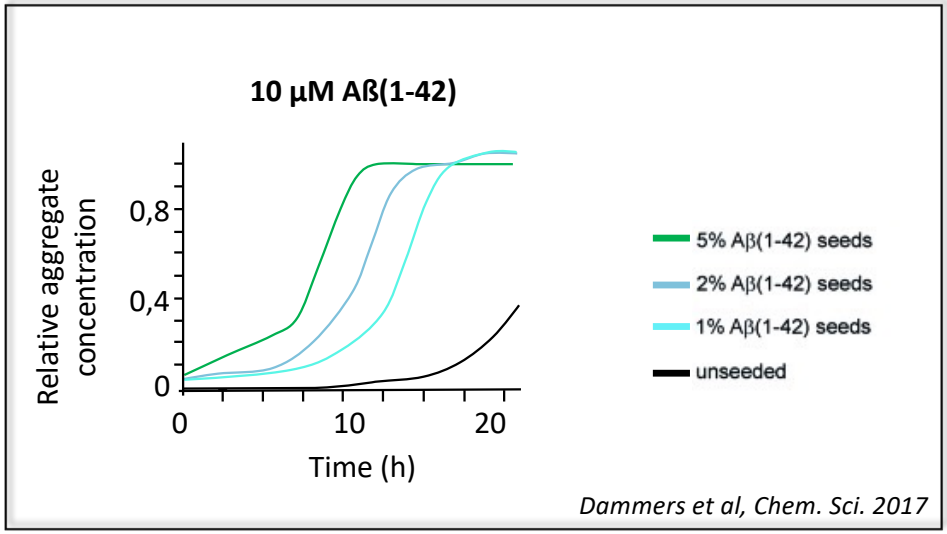


N-truncated Aβ : pE3- Aβ

- ✓ Accumulation of pE3-Aβ in AD but not in normal aging
- ✓ pE3-Aβ42 is neurotoxic
- ✓ pE3-Aβ42 increases the propensity of Aβ to aggregate



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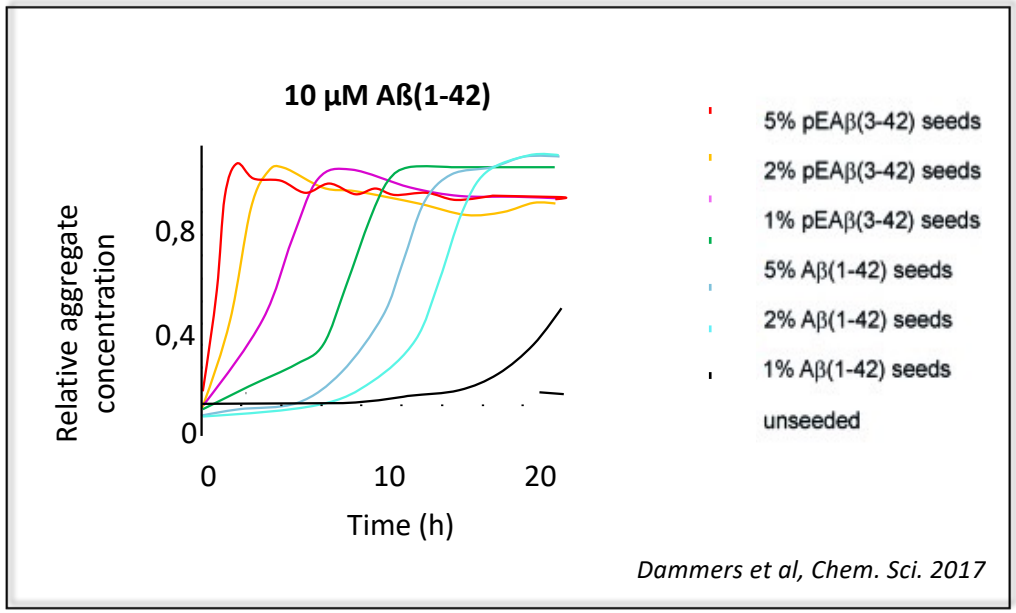
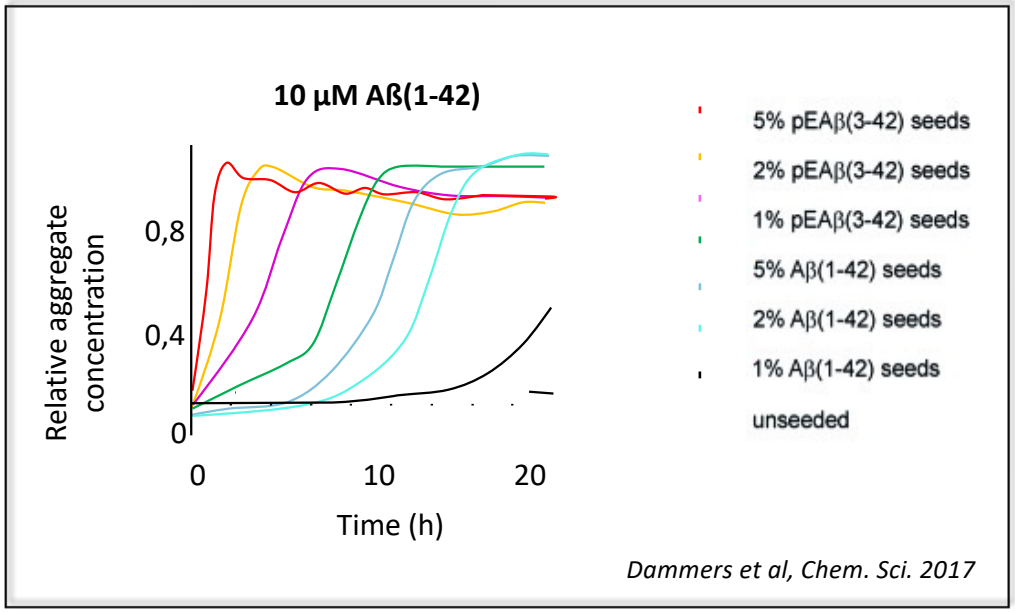


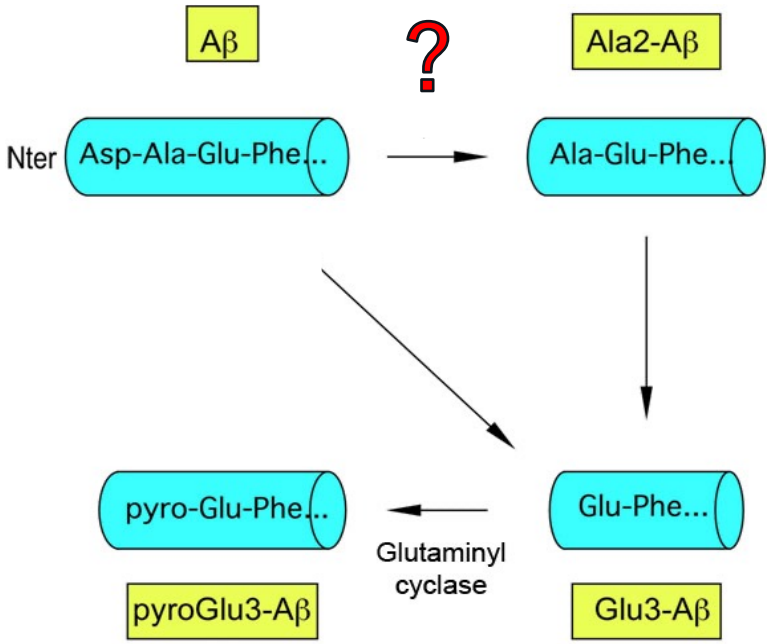
Dammers et al, Chem. Sci. 2017

N-truncated Aβ : pE3- Aβ



What are the enzymes responsible for pE3-Aβ production ?

An hypothesis about the nature of the enzymes Involved in Aβ truncation



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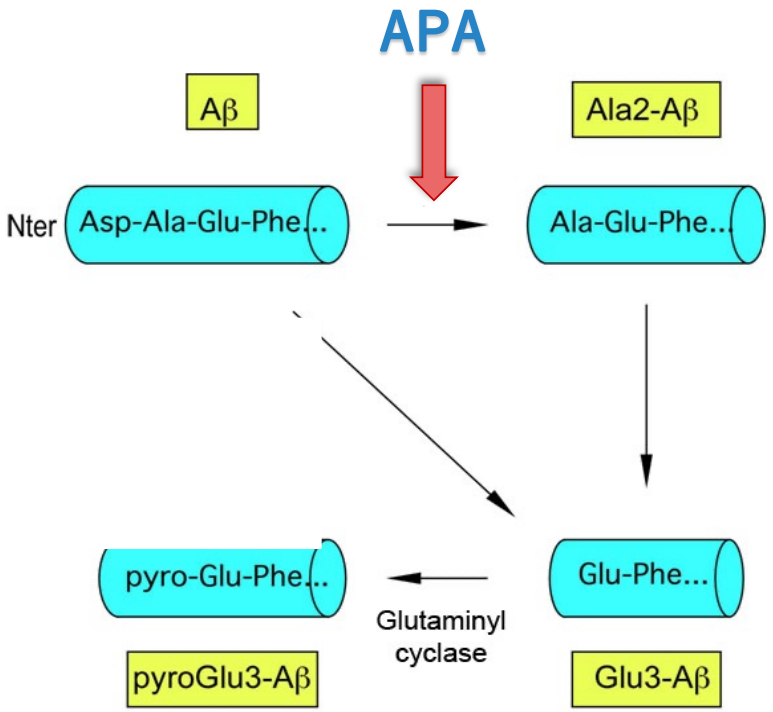

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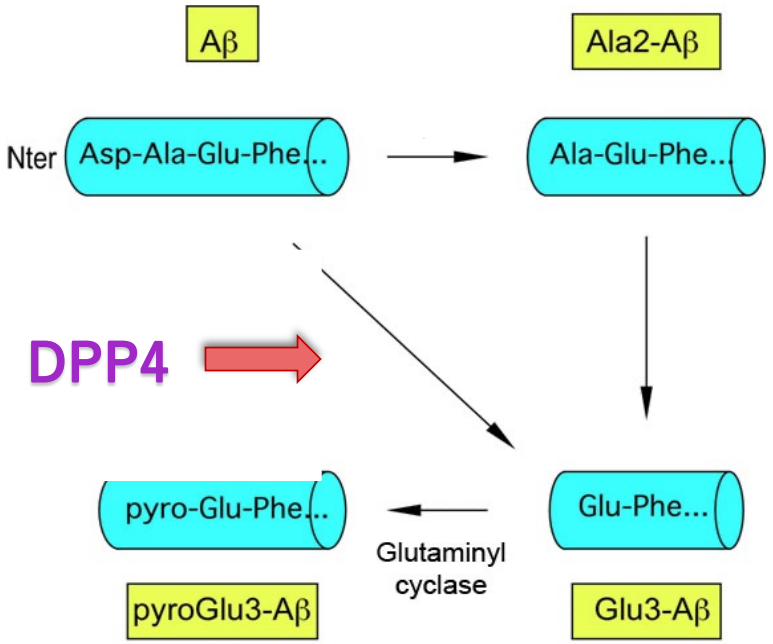
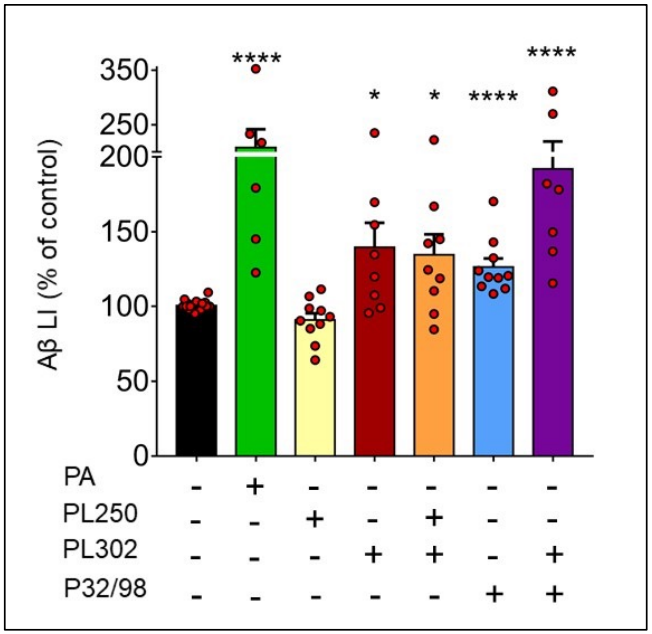


Pharmacological approach on cultured cells



Augmentation d'Aβ 1-x immunoreactivity in human cells expressing APPWT

APA and DPP4 inhibitors protect Aβ from degradation

Biochemical approach

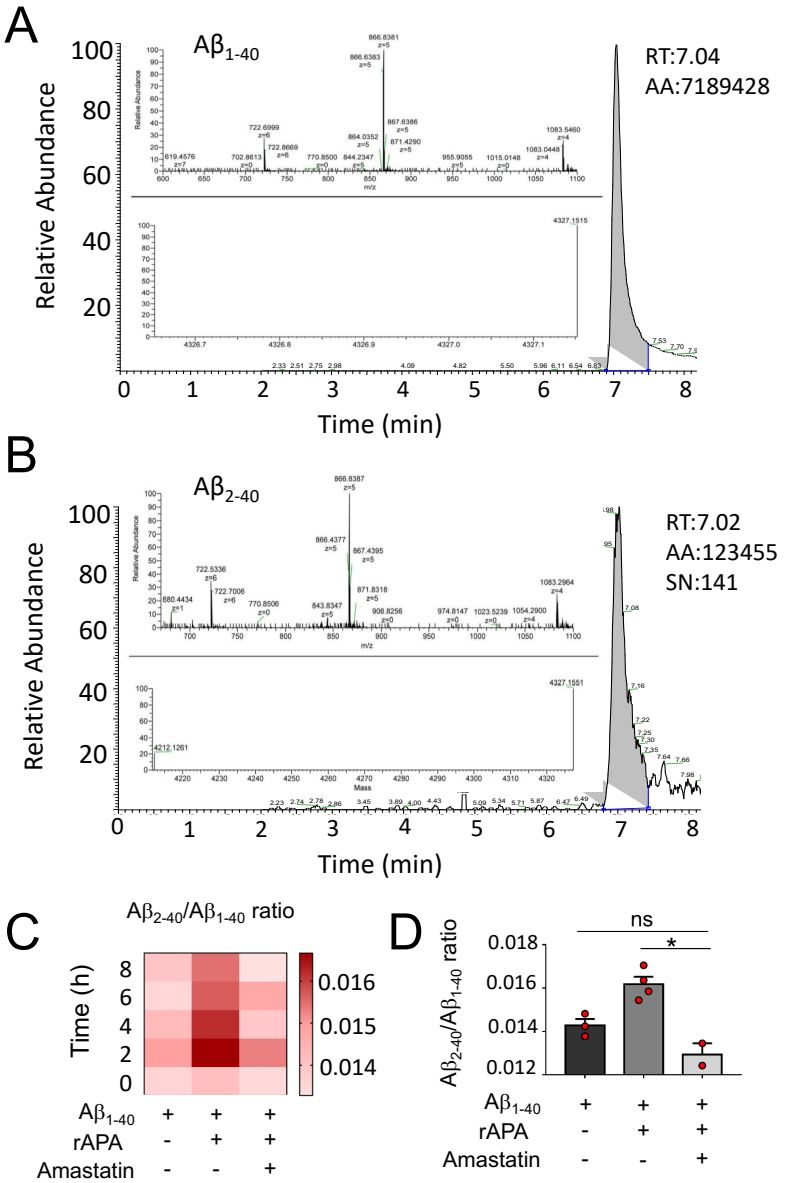
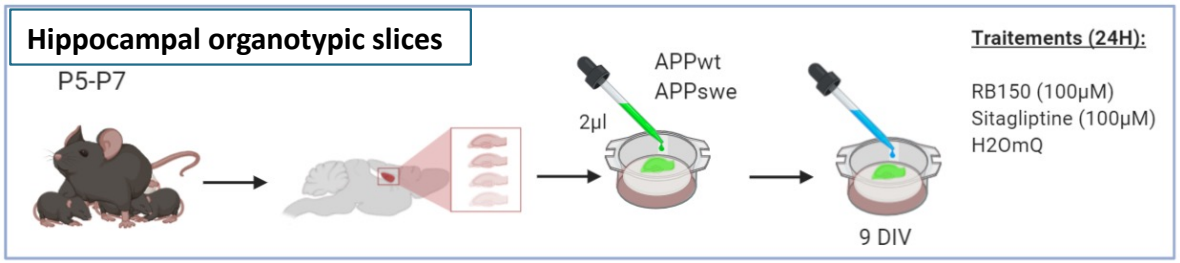


Figure 1. Valverde et al.

Impact of the modulation of APA and DPP4 on the maturation of dendritic spines: an *ex-vivo* approach.

Morphological study of dendritic spines



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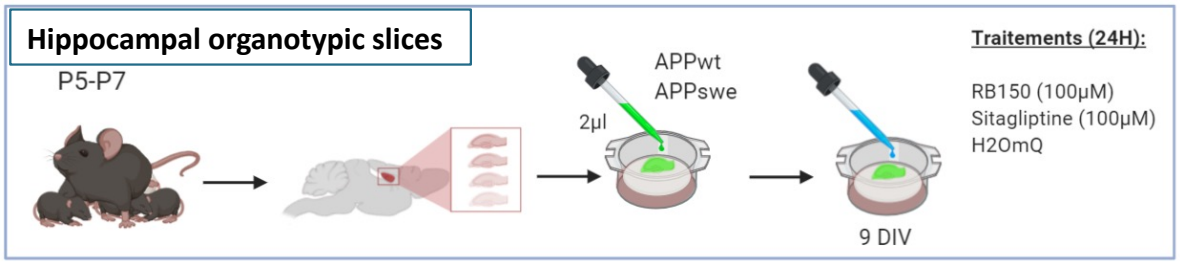

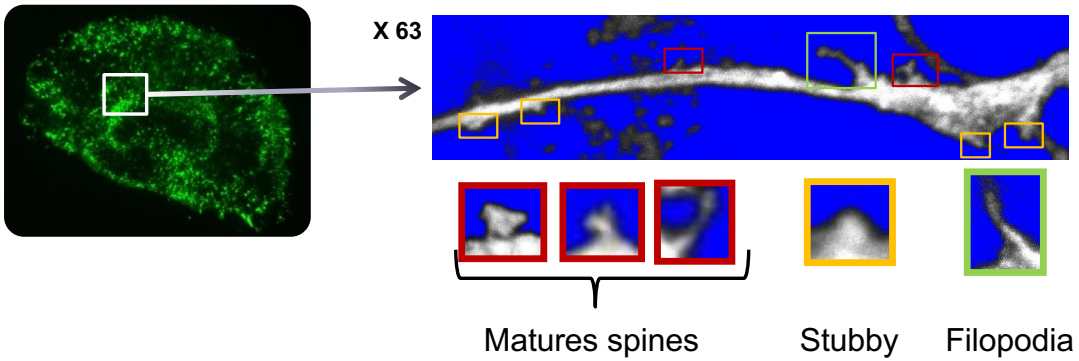

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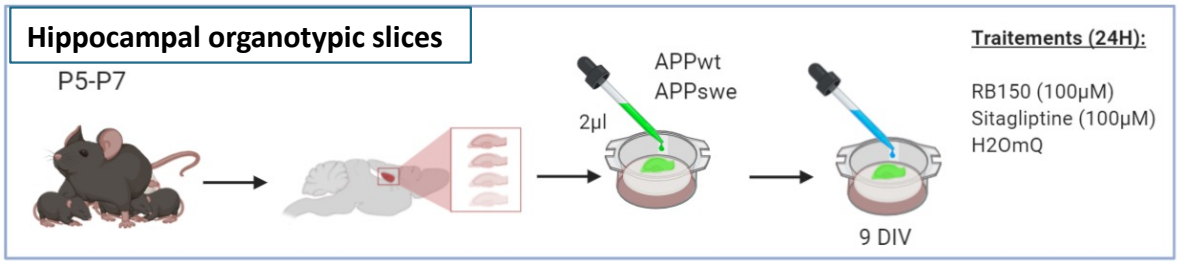

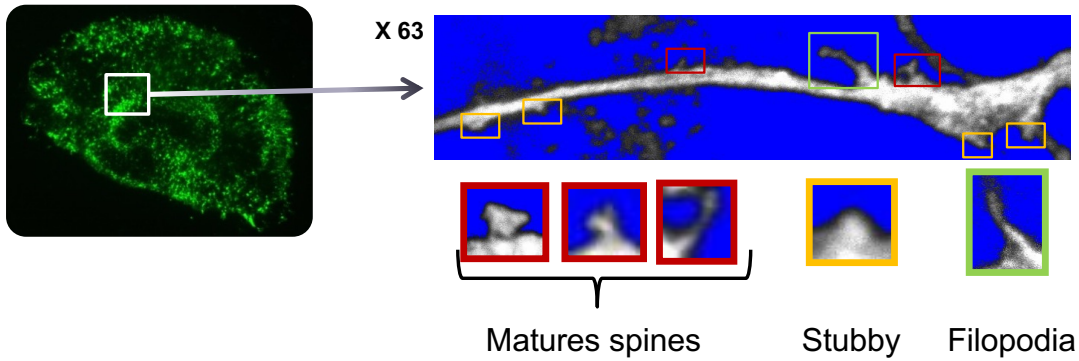

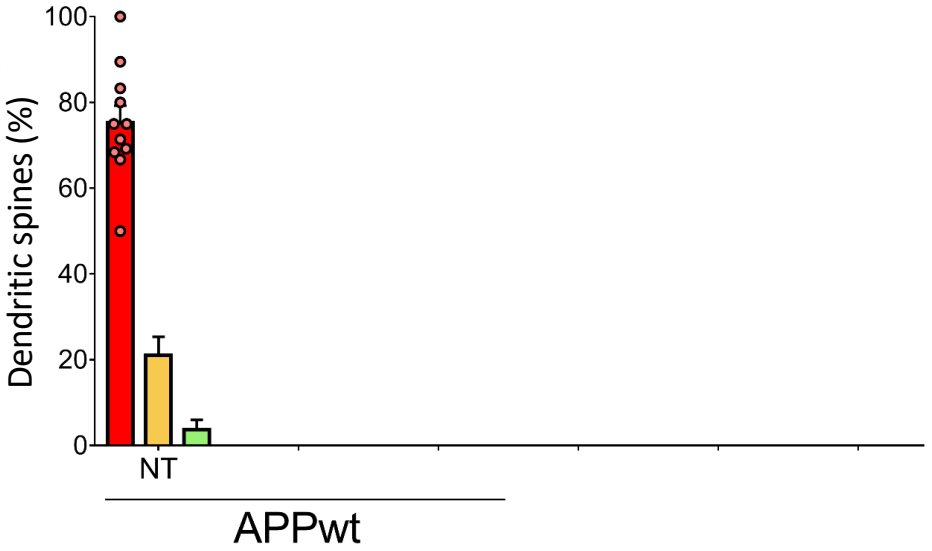

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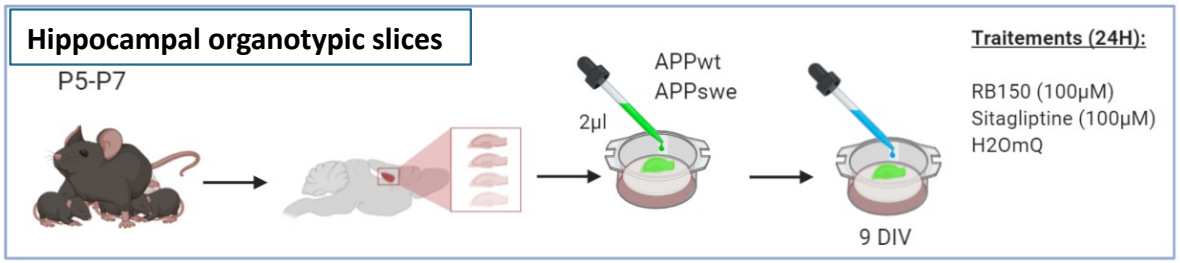

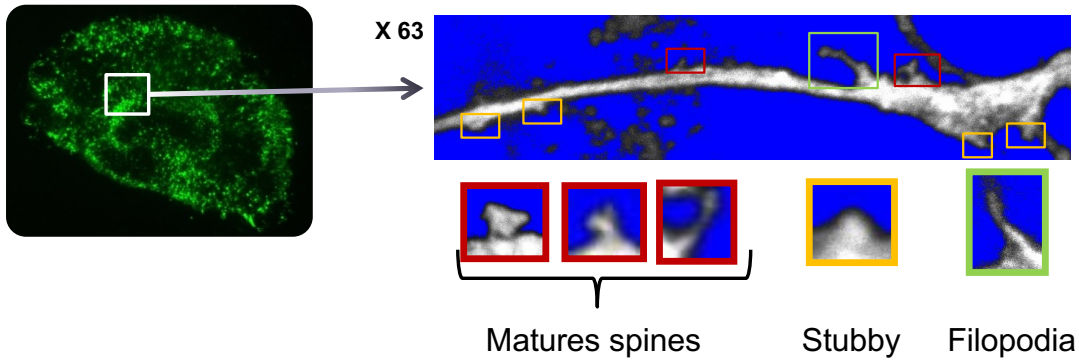

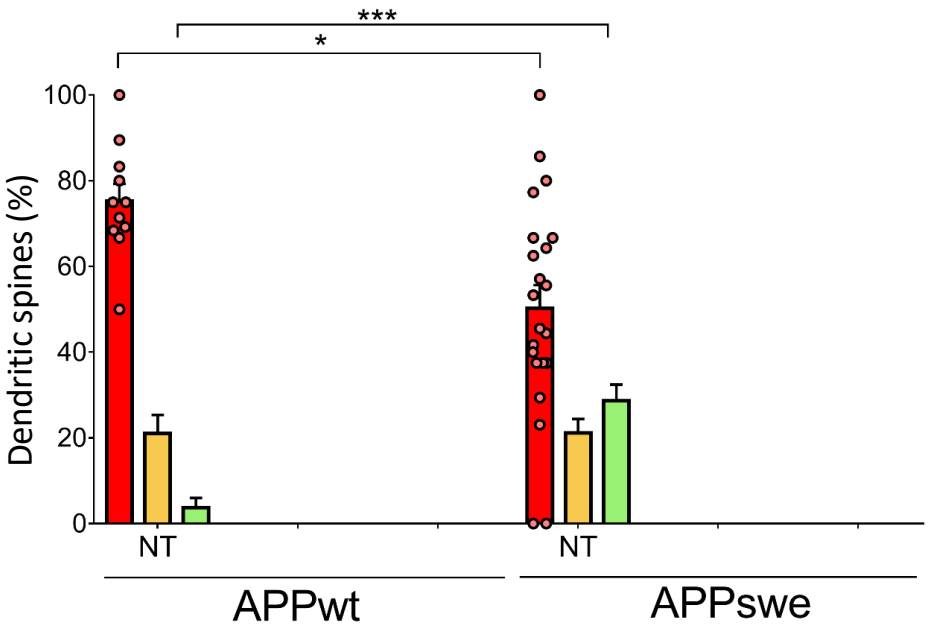

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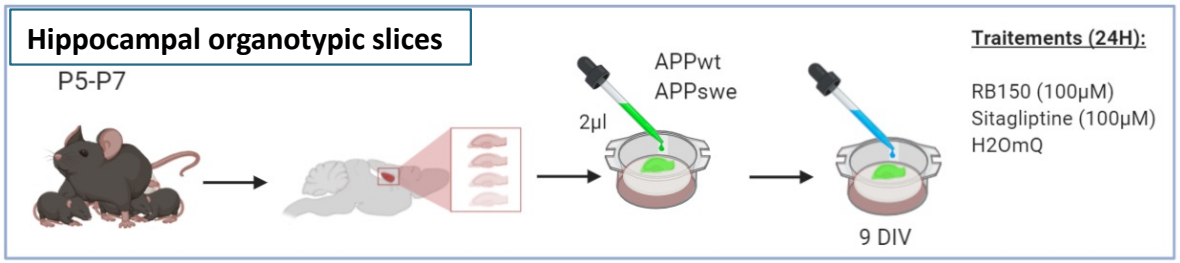
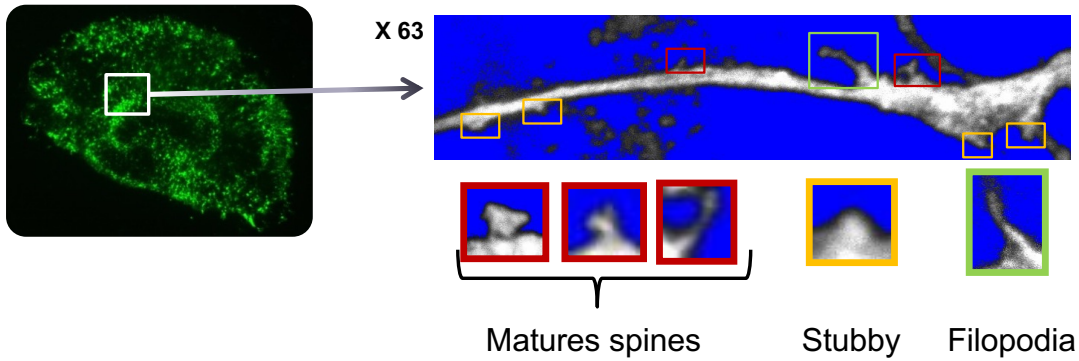
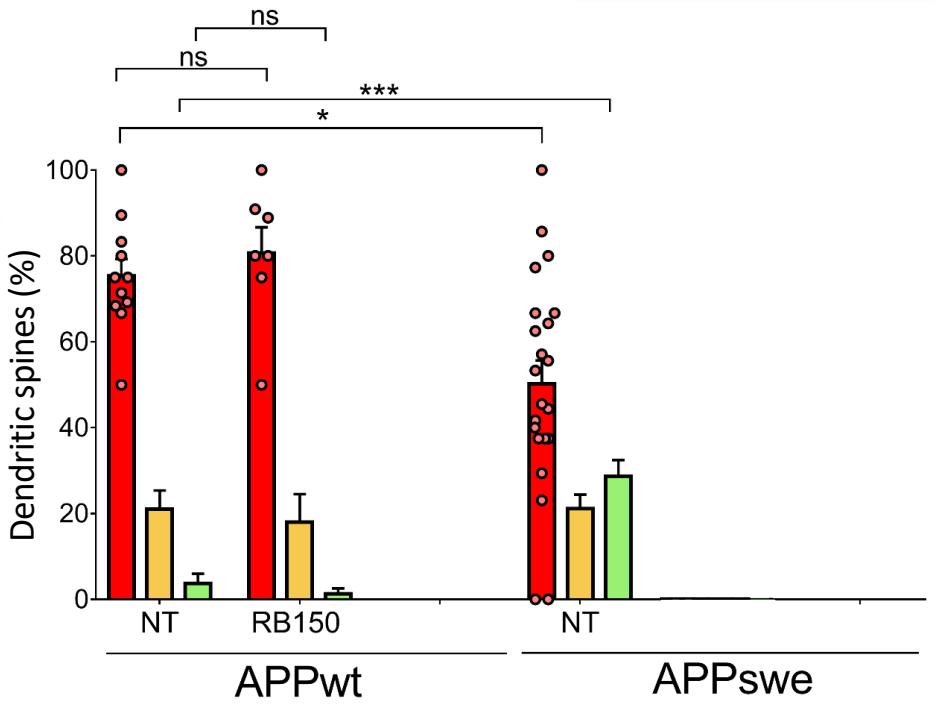
RB150 ⊣ APA







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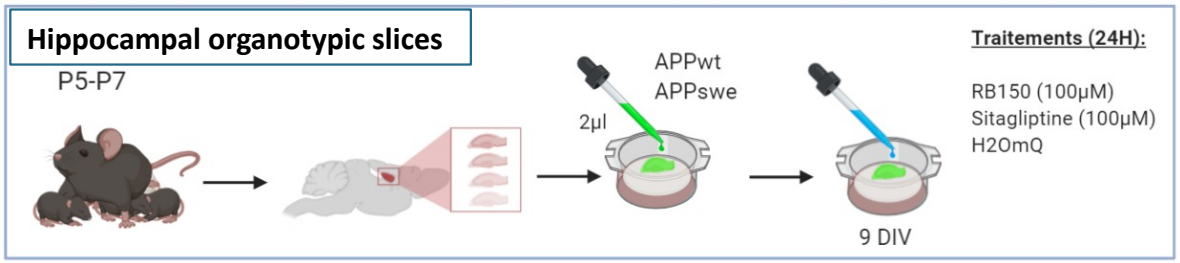

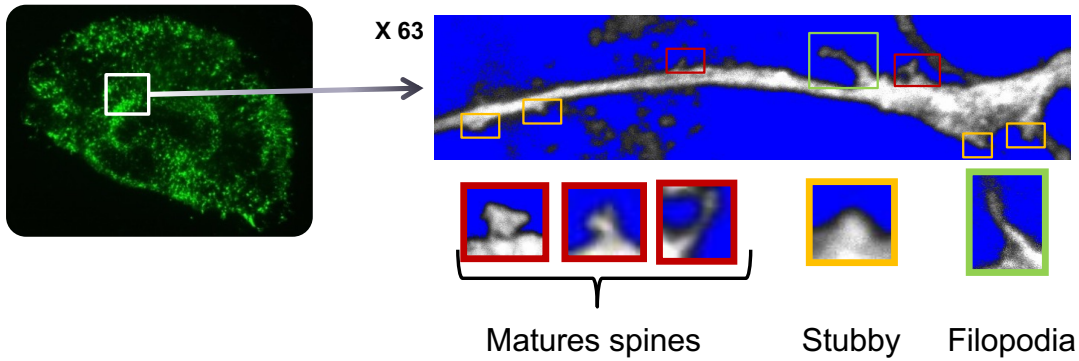

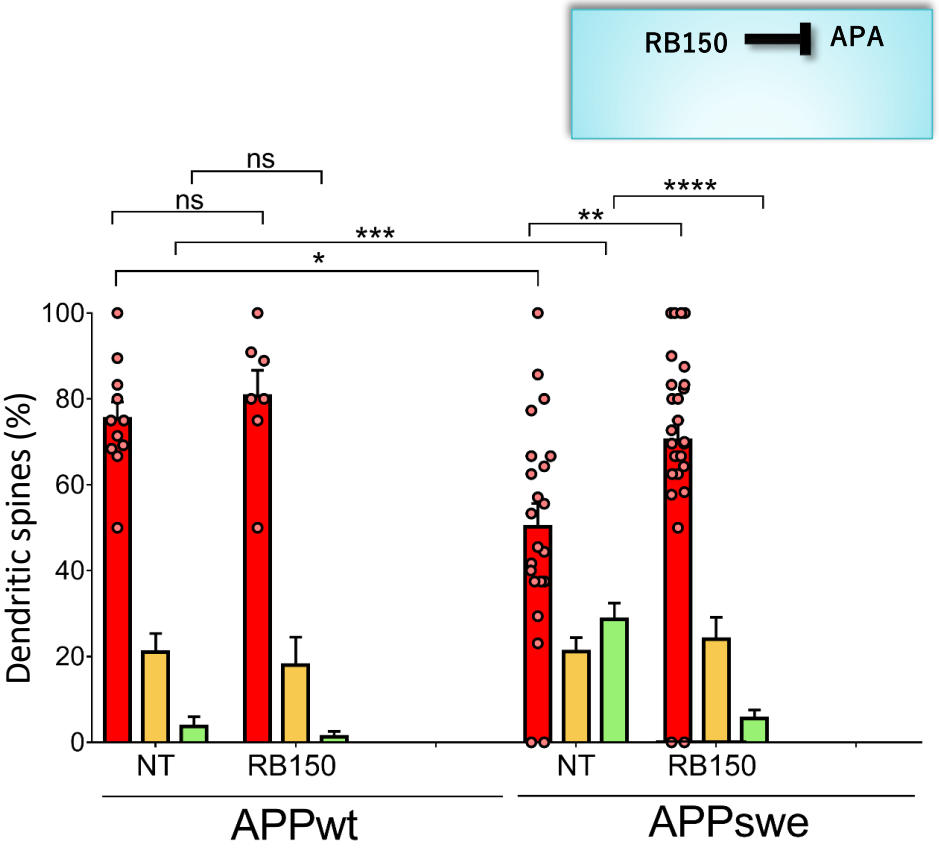

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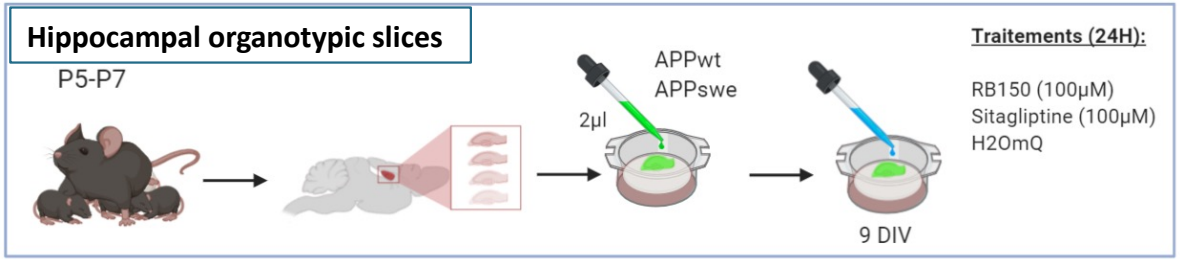

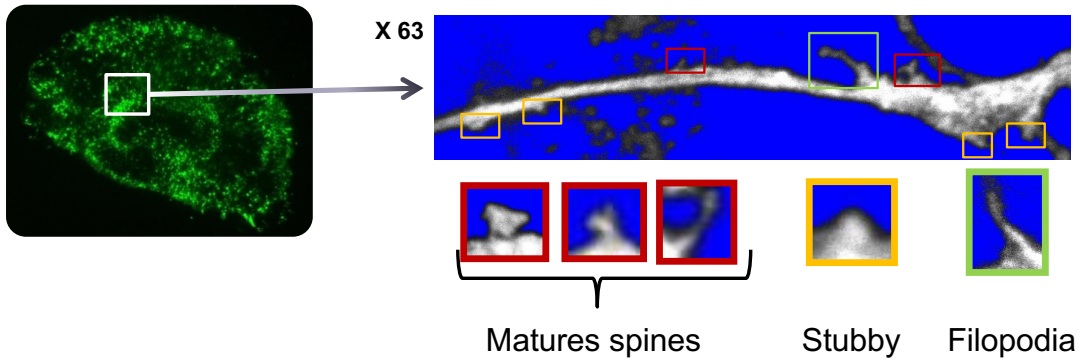

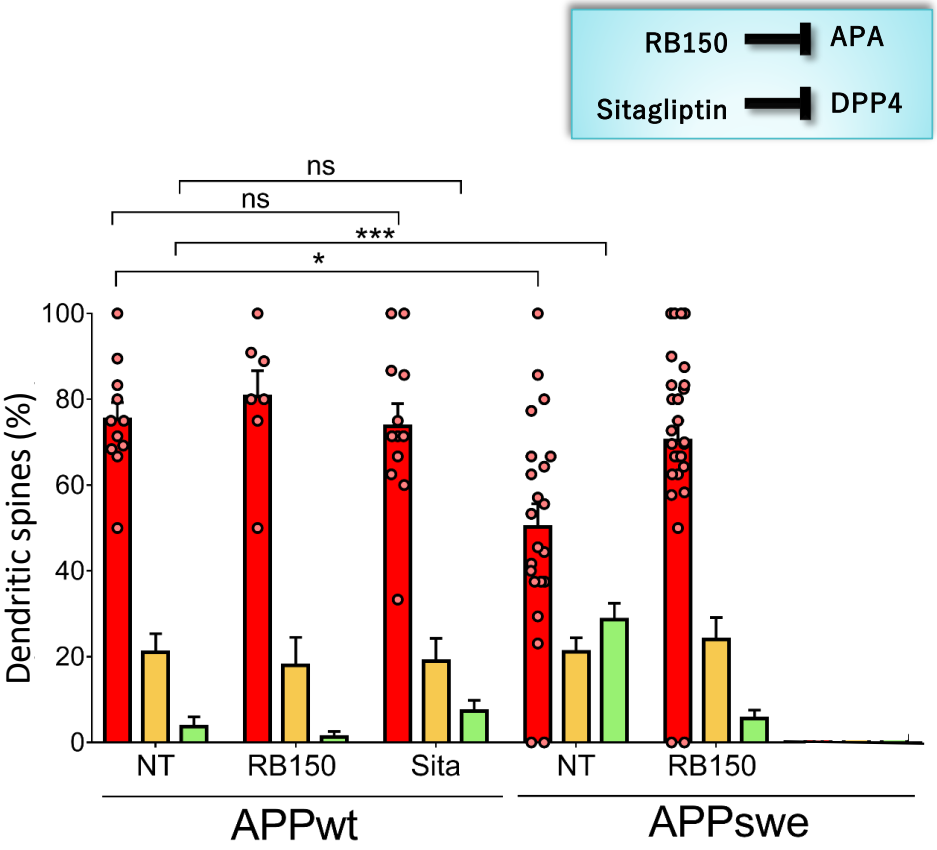

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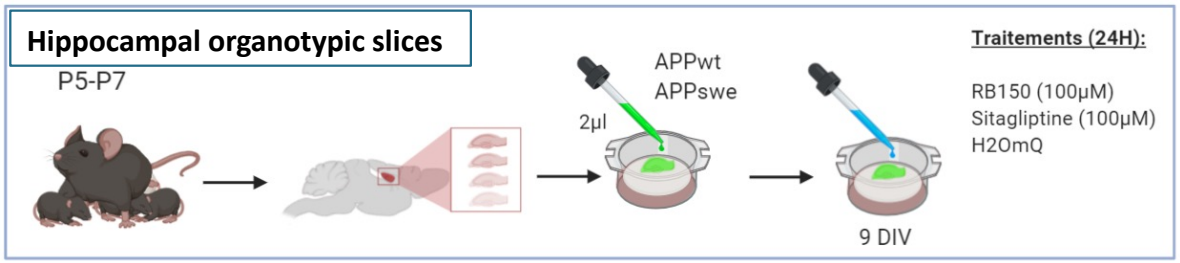
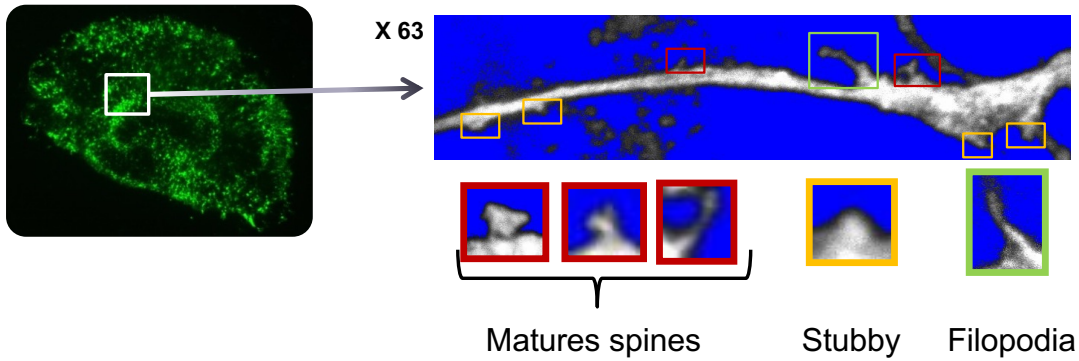
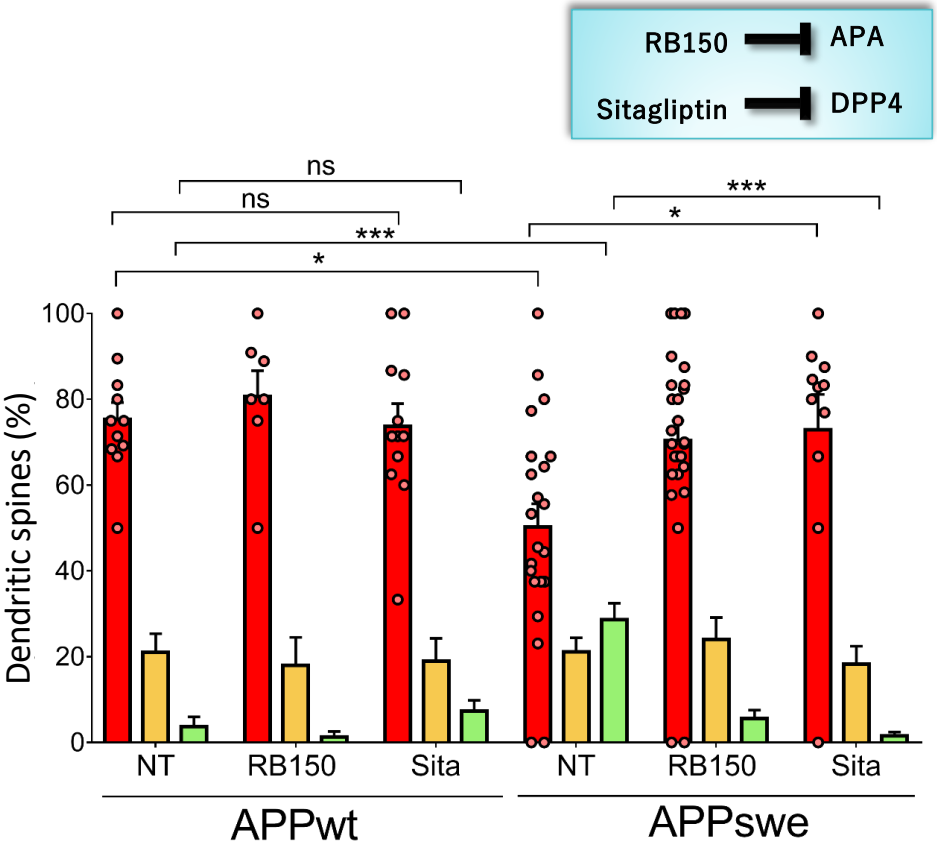






Conclusion #1

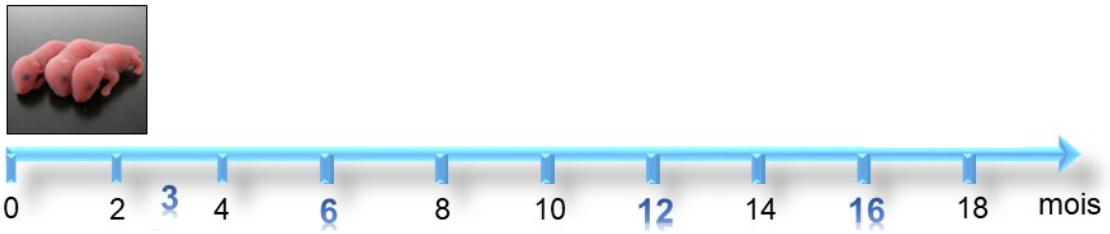
There is a beneficial effect of APA et DPP4 inhibitors on dendritic spines maturation

Influence of APA and DPP4 modulation on biochemical and anatomical lesions in a murine model of AD: Pharmacological and genetic approaches.

Influence of APA and DPP4 modulation on biochemical and anatomical lesions in a murine model of AD

In vivo approach: **WT and 3xTg-AD mice:**

$PS1_{M146V}/APP_{swe}/Tau_{P301L}$



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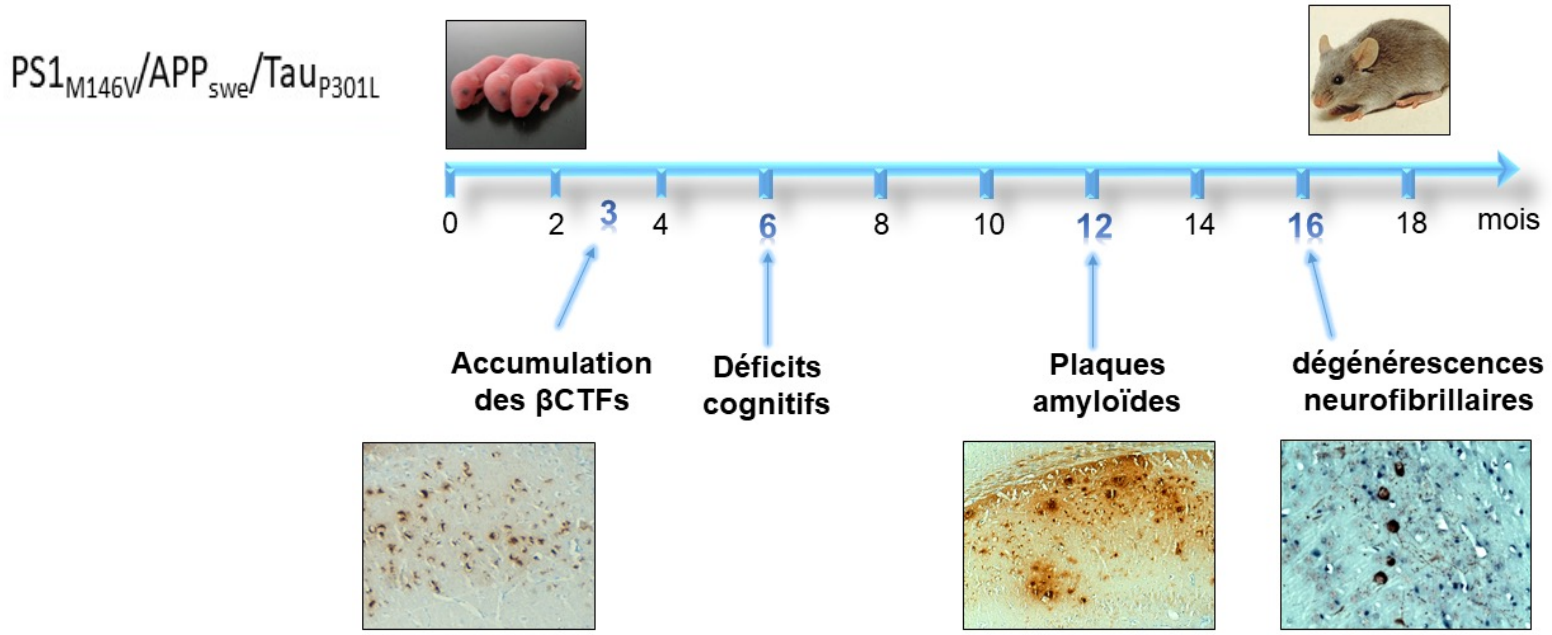

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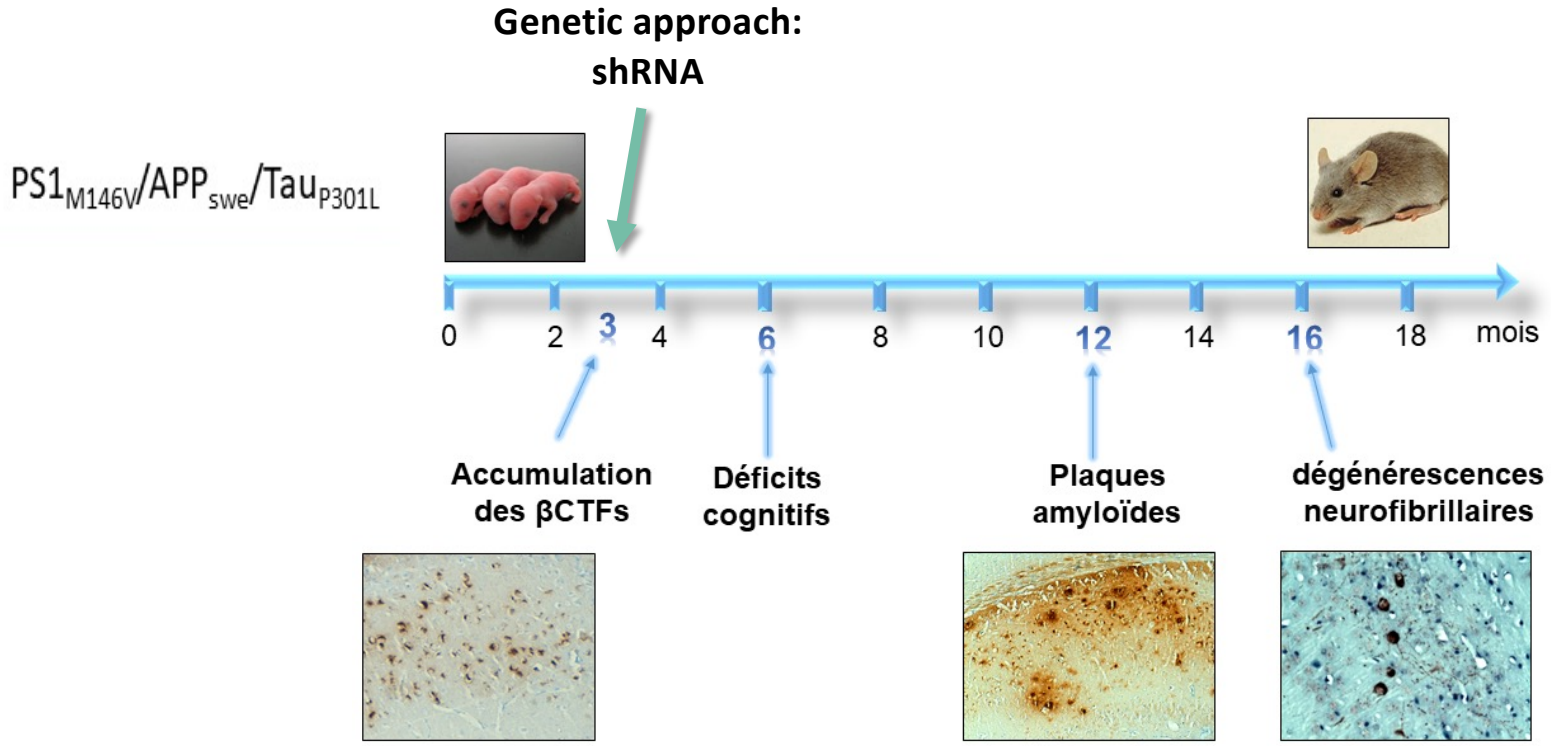

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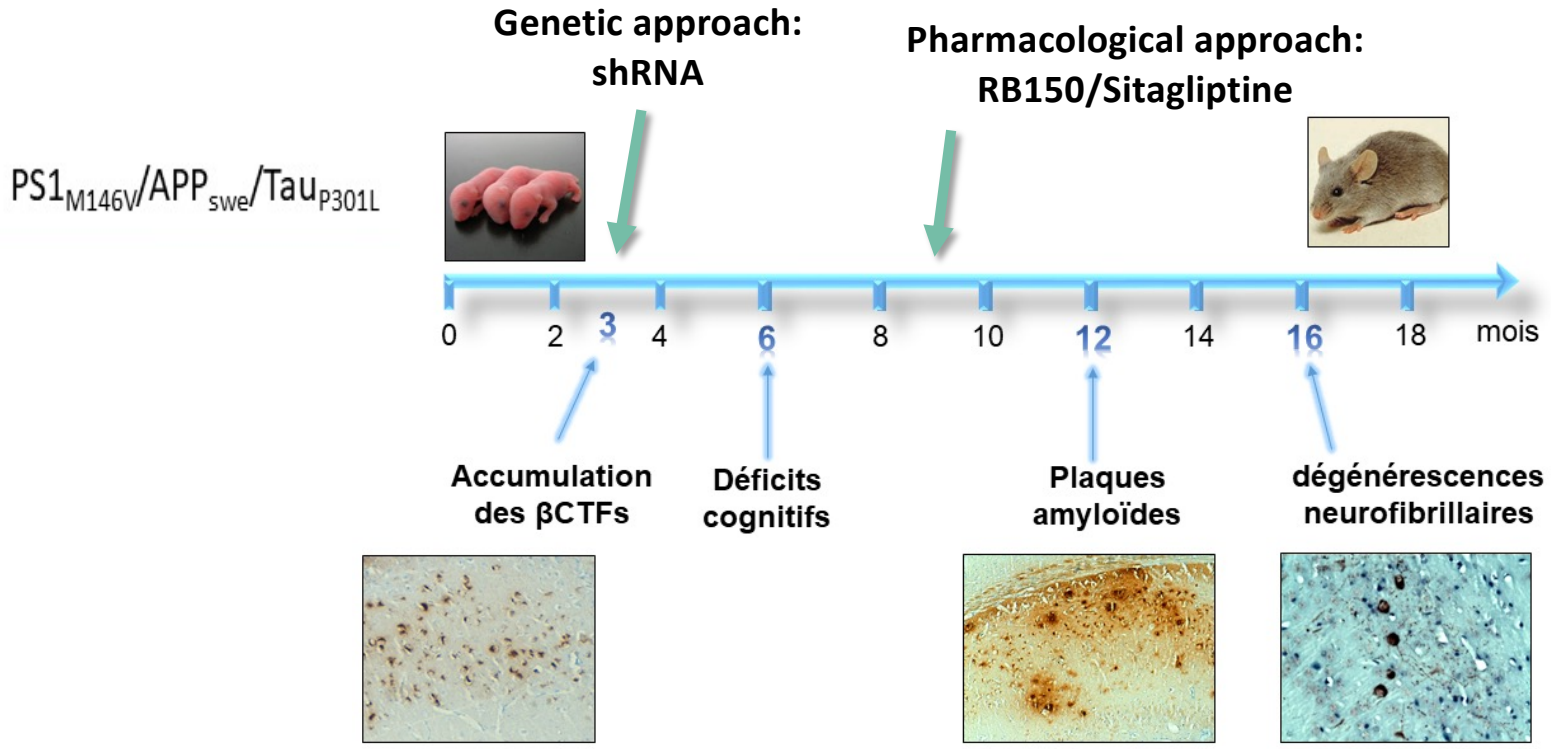

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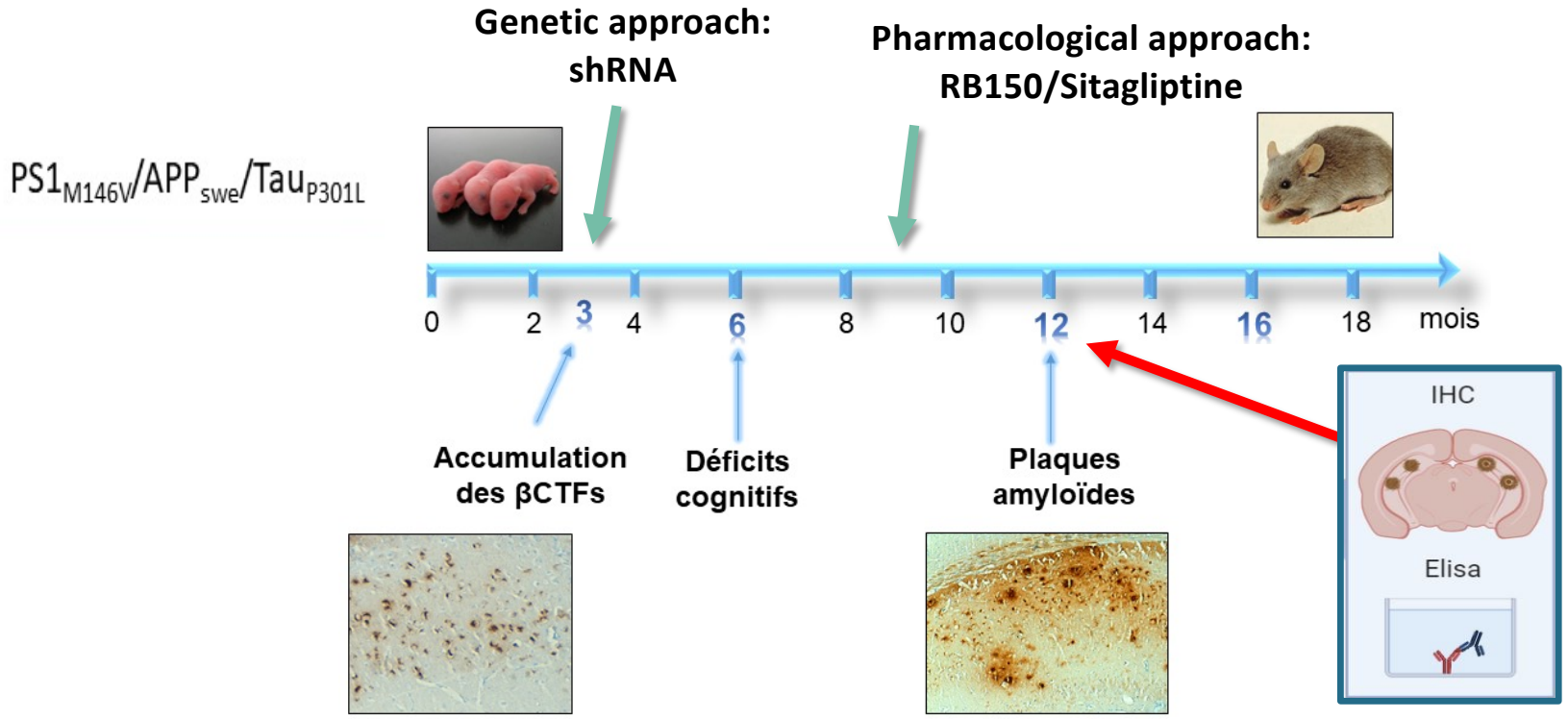


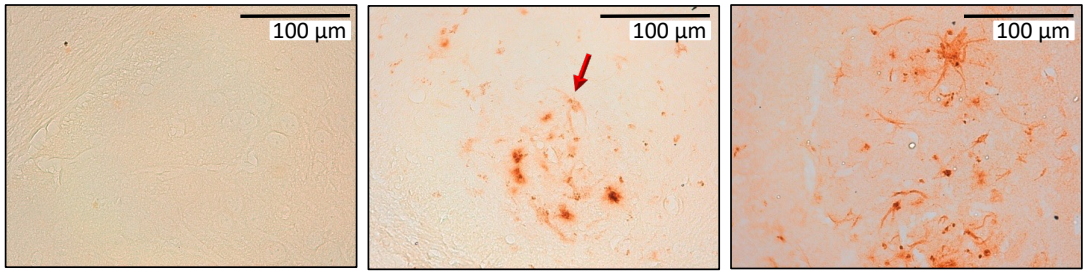
Influence of APA and DPP4 modulation on anatomical lesions in a murine model of AD
A genetic approach

pE3-Aβ x

WT | 3xTg-AD

12 months

shScr



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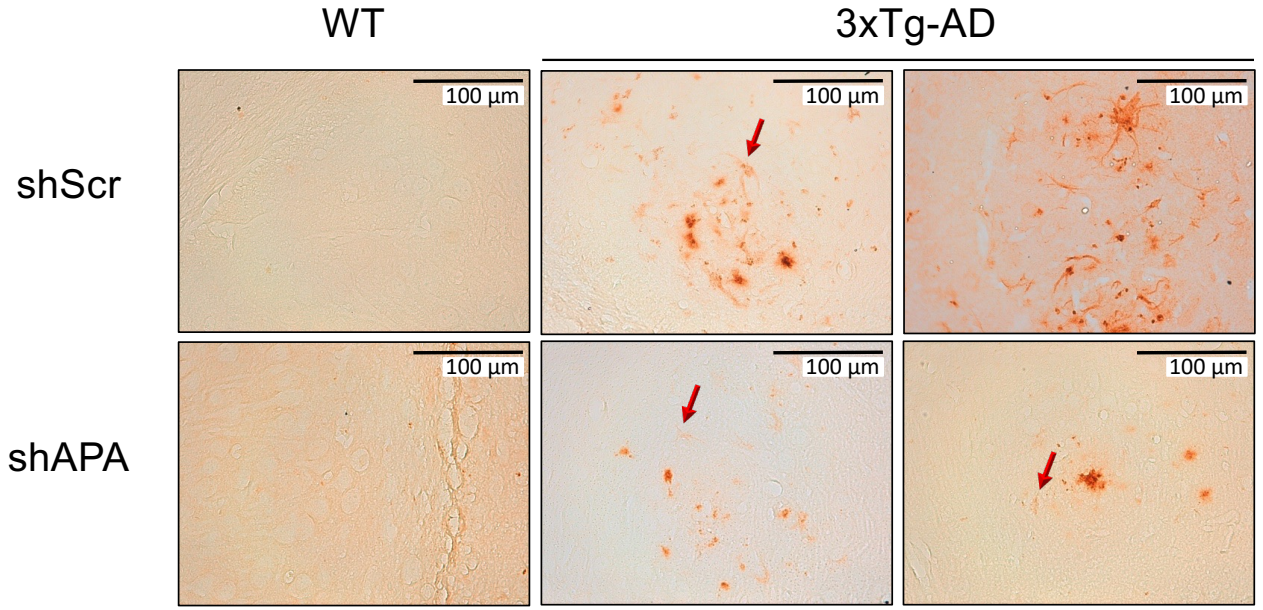

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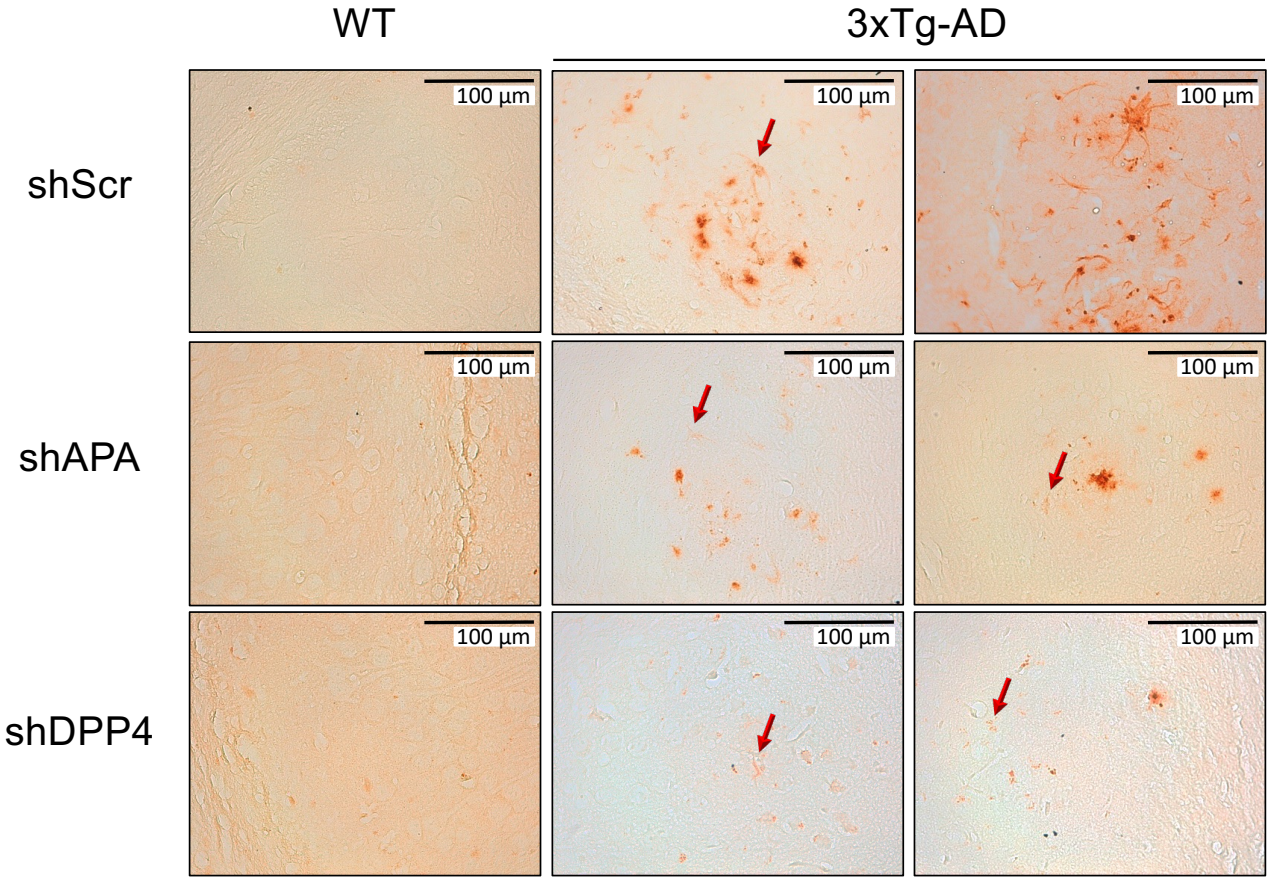

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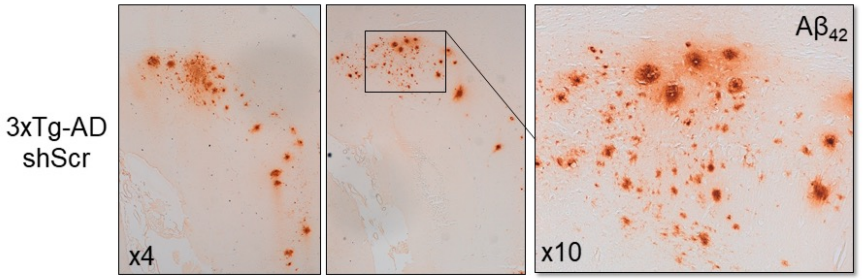

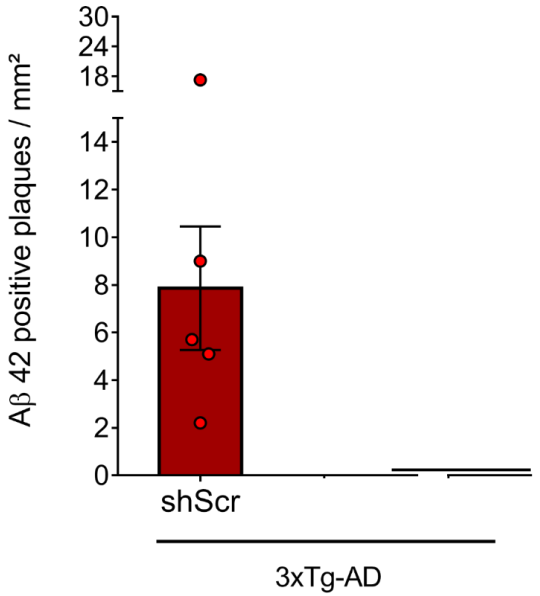

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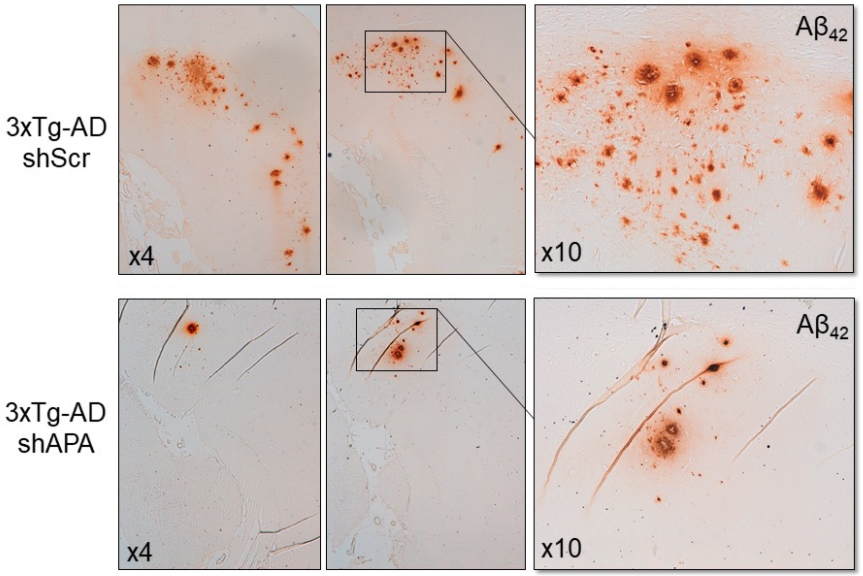

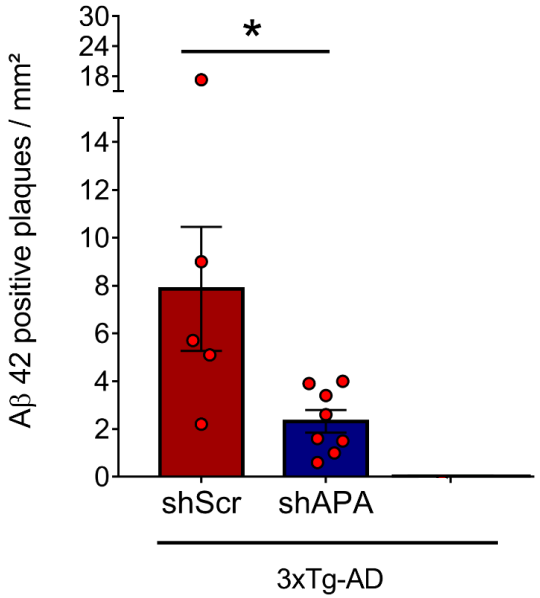

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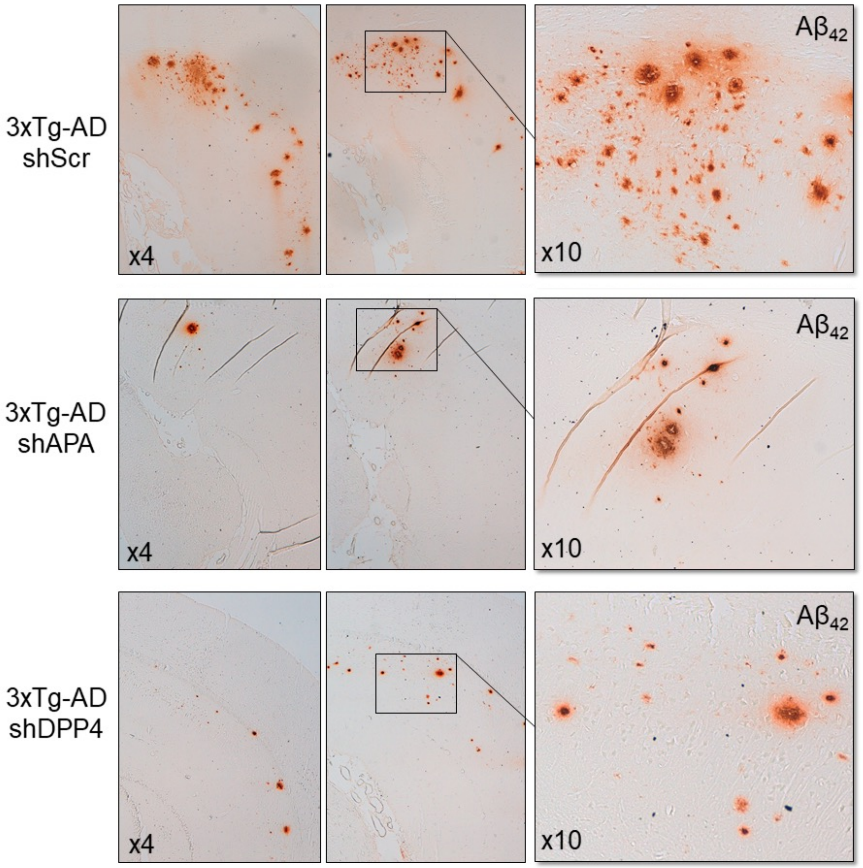

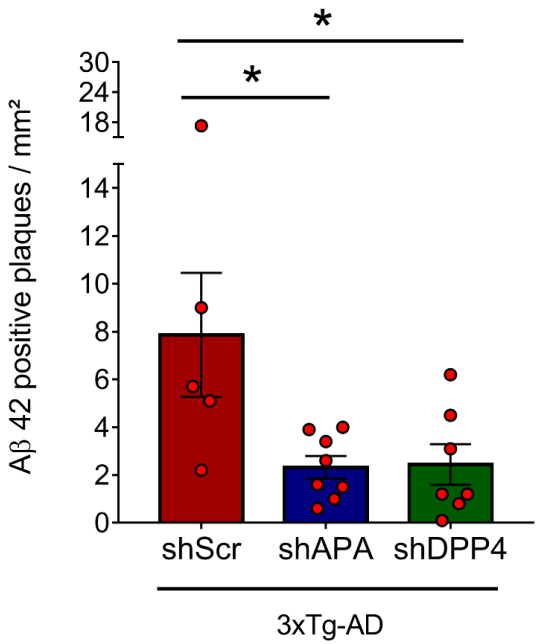

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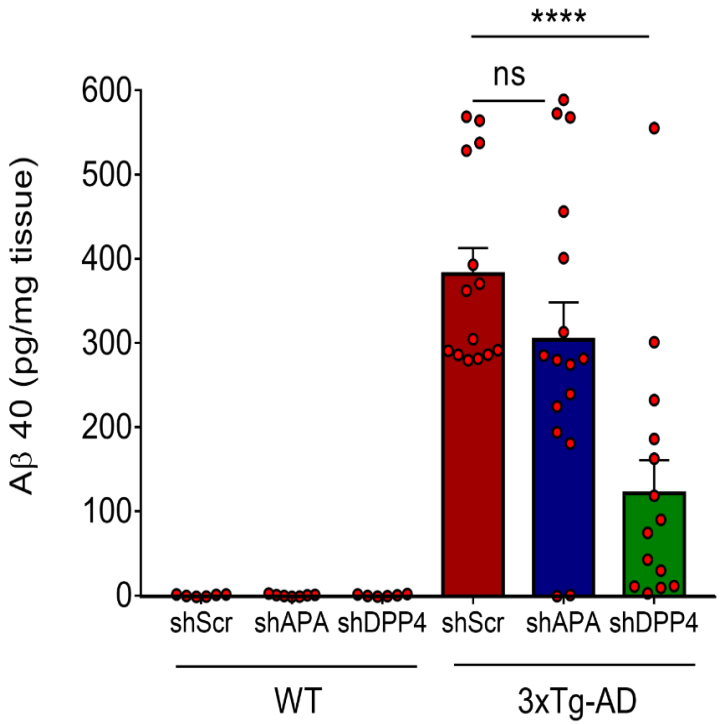
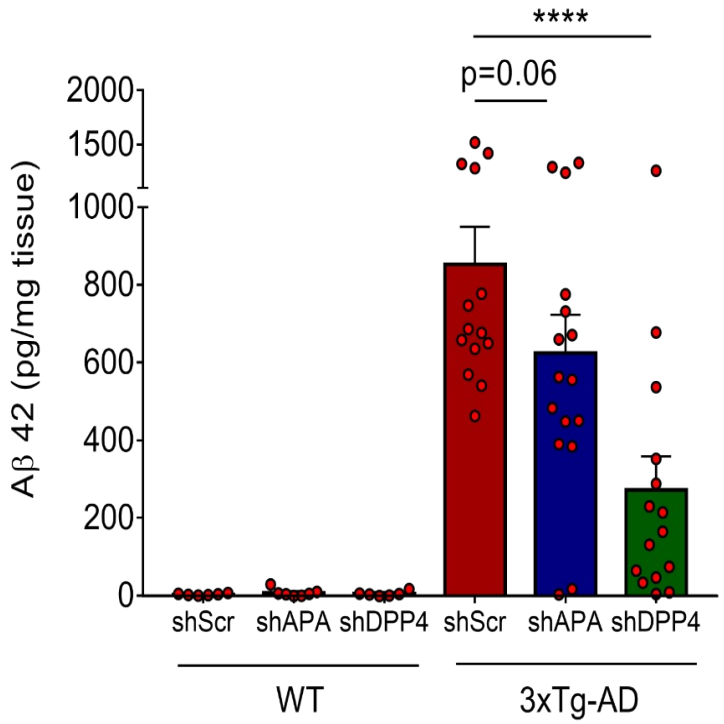
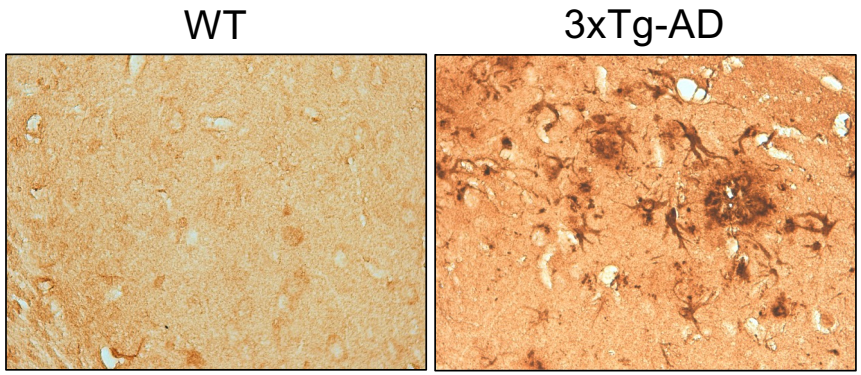
A genetic approach





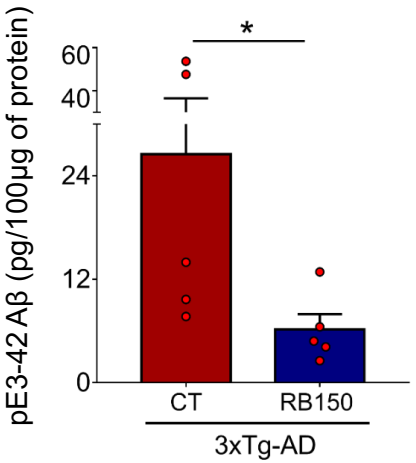
Influence of APA and DPP4 modulation: A pharmacological approach

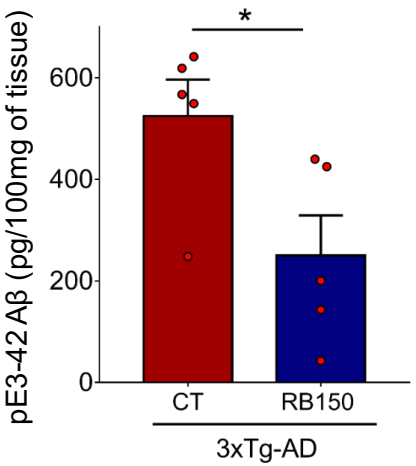
pE3-Aβ x



15 months

RB150 ⊣ APA

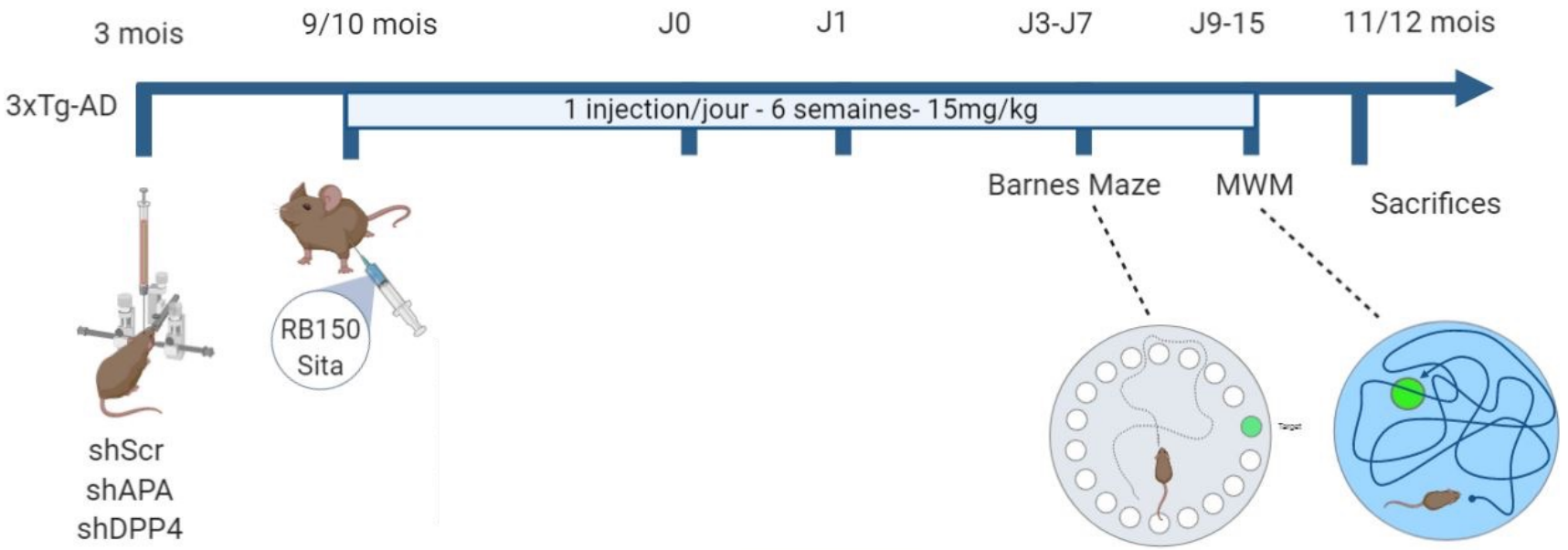




Influence of APA and DPP4 modulation on
biochemical and anatomical lesions in a murine model of AD

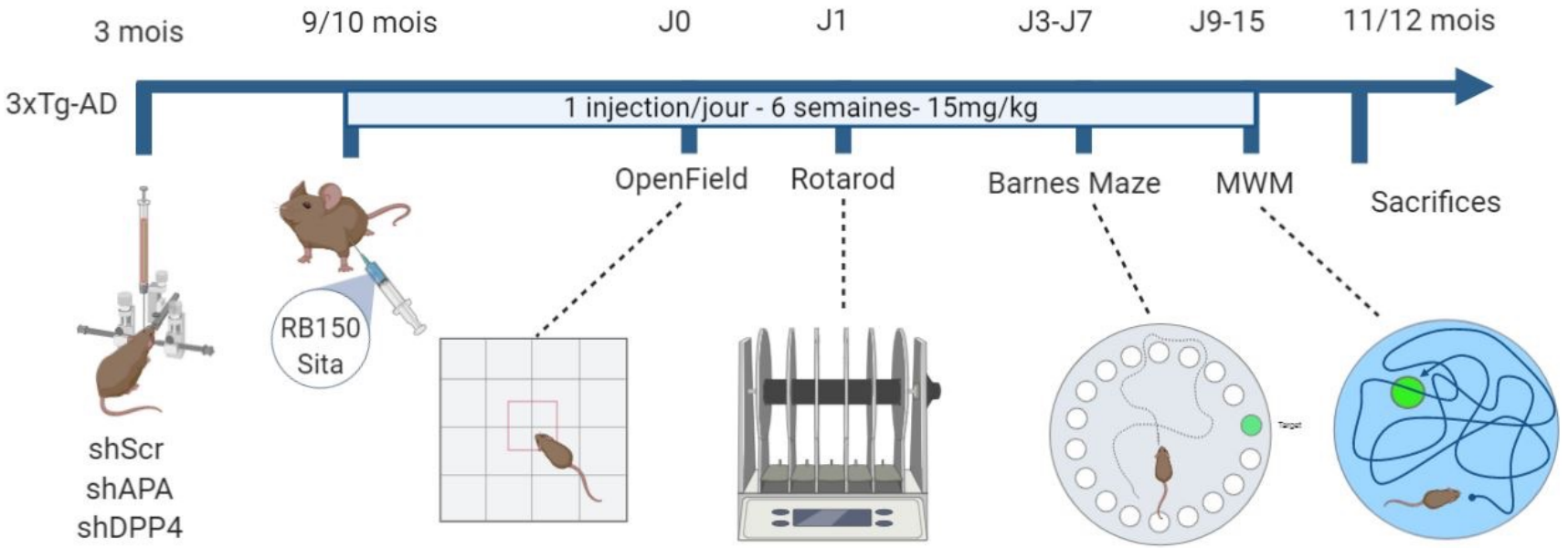
- **Beneficial effect of** APA and DPP4 reduction on both Aβ42- and pE3-Aβ42- positive plaques
- **Reduction** of Aβ load in 3xTg-AD by both pharmacological and genetic approaches
- **Lowering of** pE3-Aβx in treated 3xTg-AD mice

Influence of APA and DPP4 modulation on cognitive deficits in 3xTg-AD by pharmacological and genetic approaches.

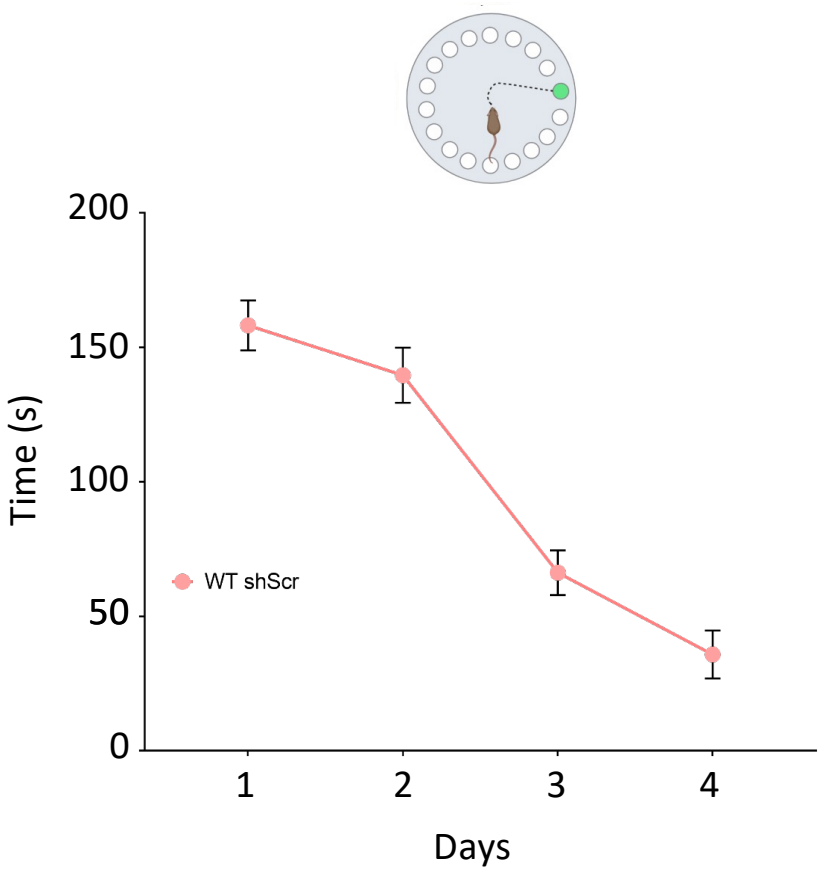


<u>Parameters</u>:

- Learning recording
- Number of entries in target zone»
- Number of entries in various quadrants
- Number of entries in various holes


3 mois
9/10 mois
J0
J1
J3-J7
J9-15
11/12 mois
3xTg-AD
1 injection/jour - 6 semaines- 15mg/kg
OpenField
Rotarod
Barnes Maze
MWM
Sacrifices
RB150
Sita
shScr
shAPA
shDPP4

Learning in Barnes Maze et MWM: genetic approach targeting APA



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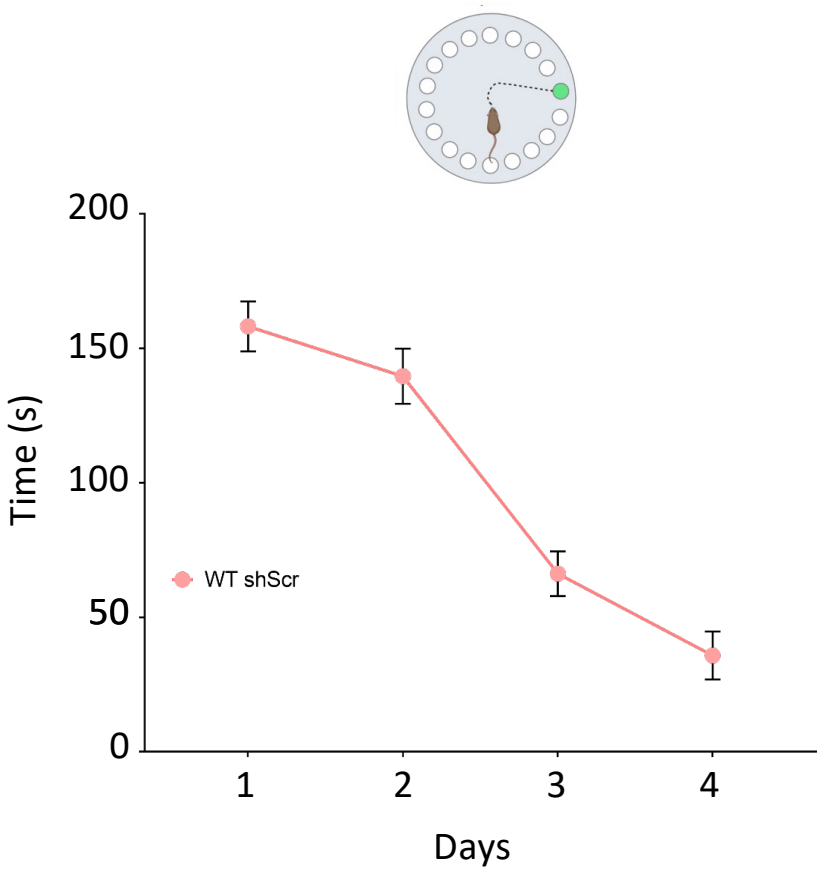

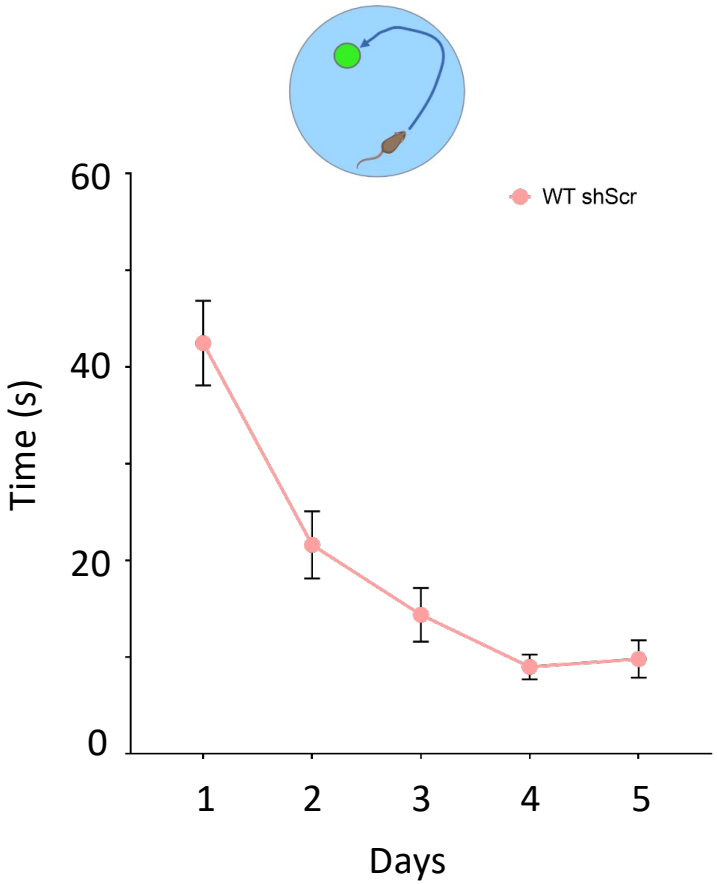

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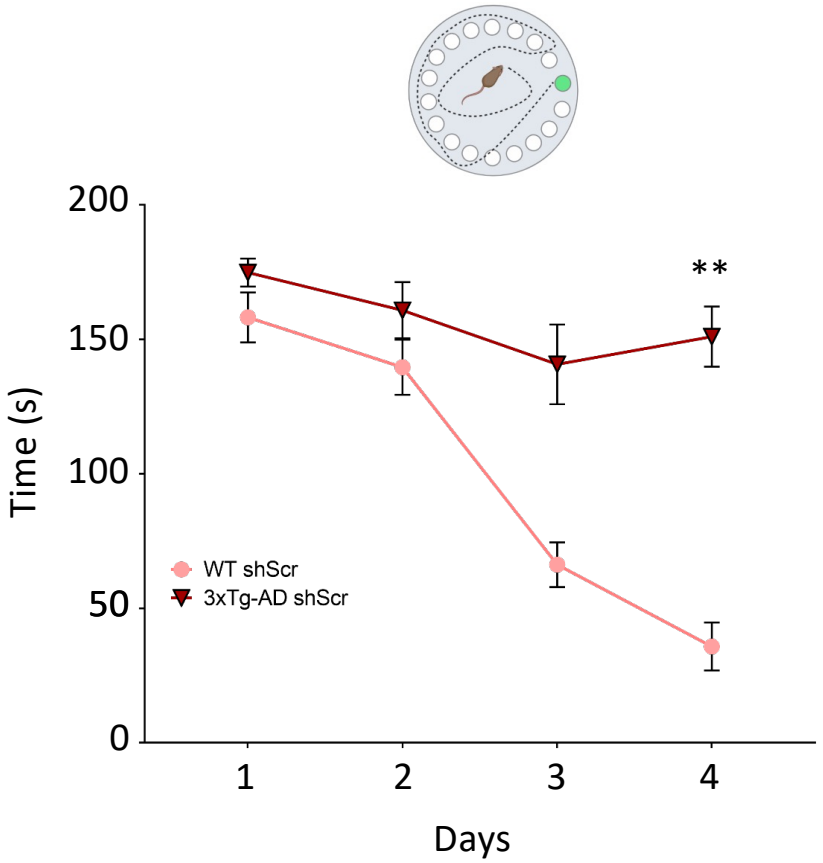

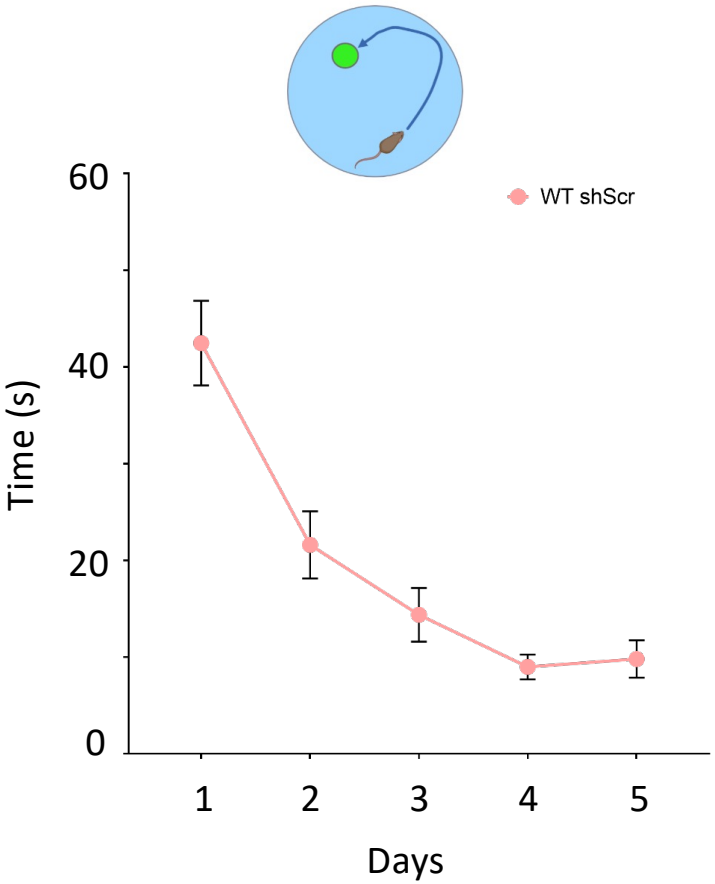

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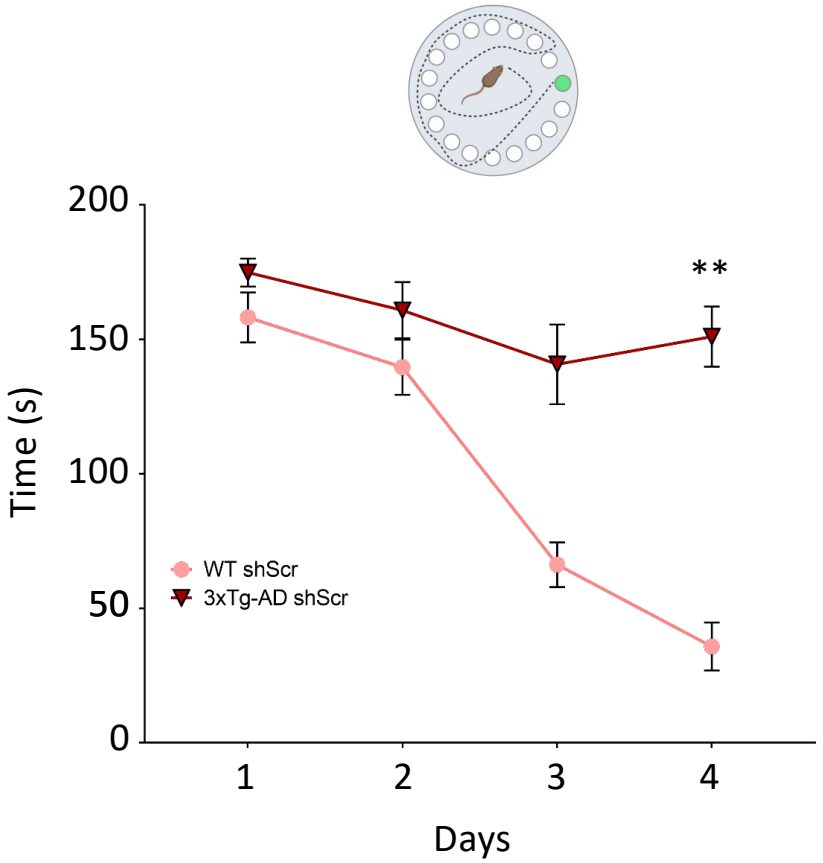

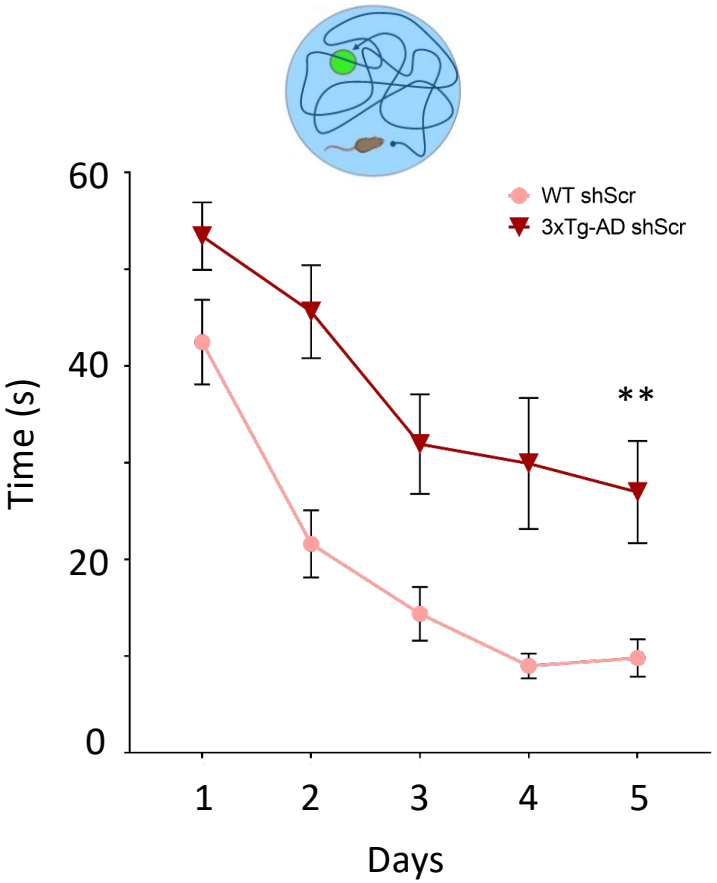

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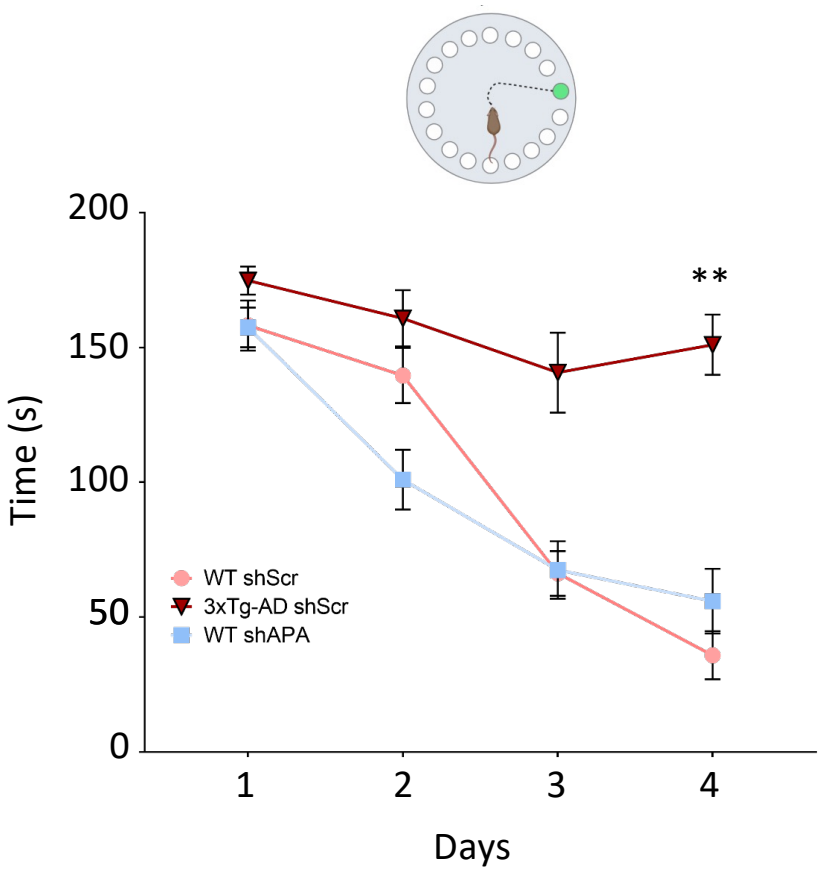
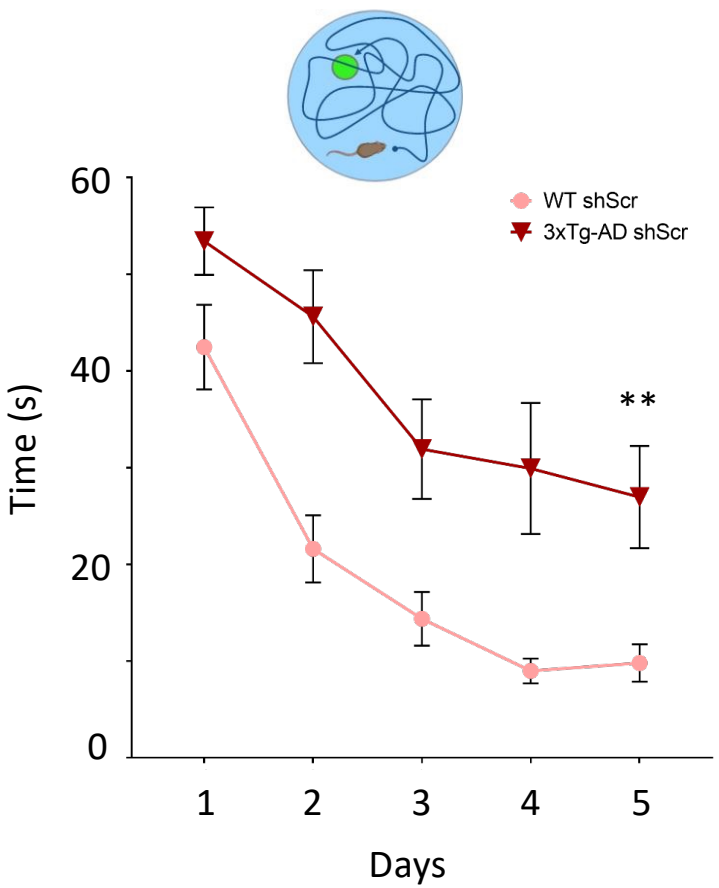
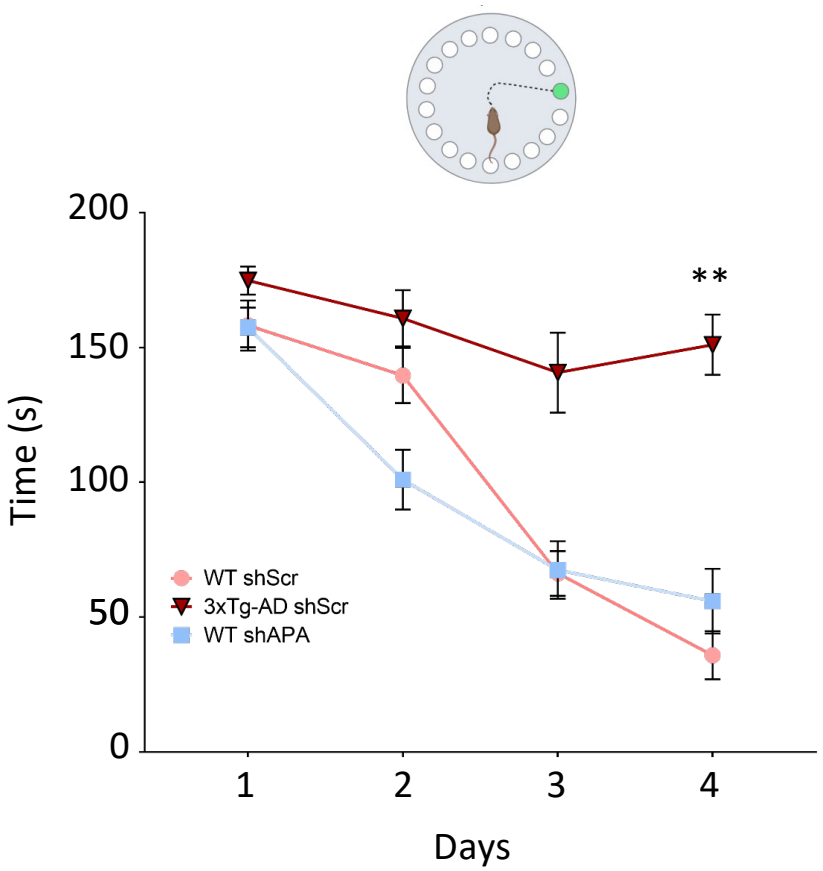
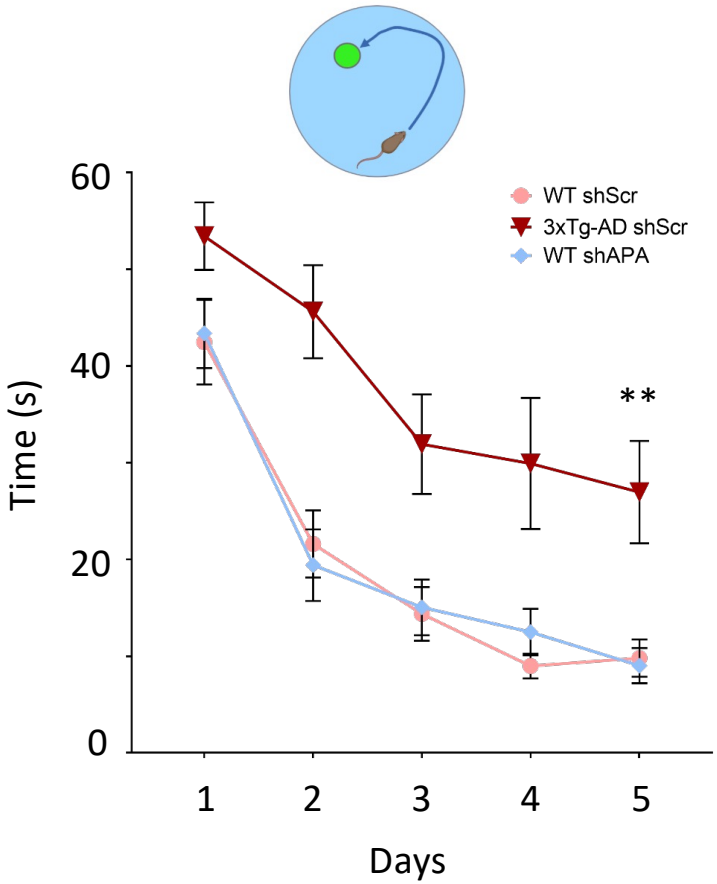




Learning in Barnes Maze et MWM: genetic approach targeting APA





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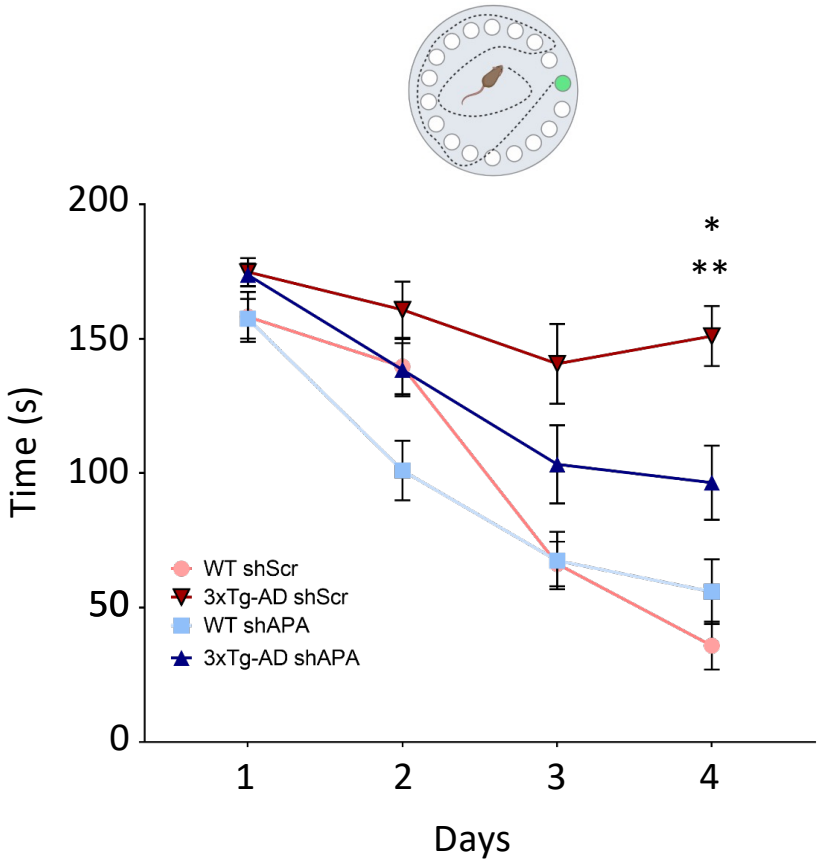
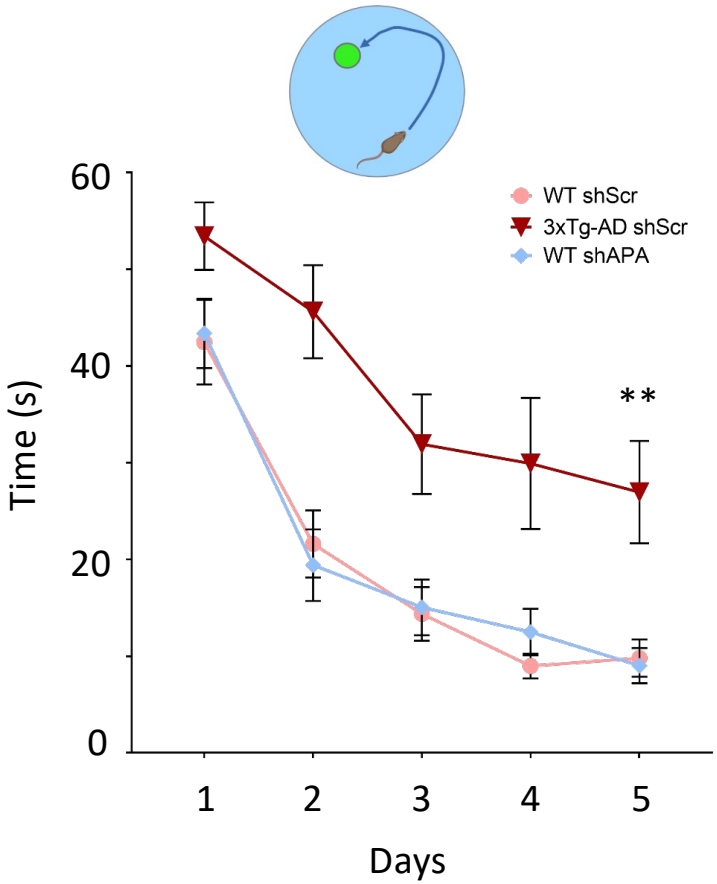
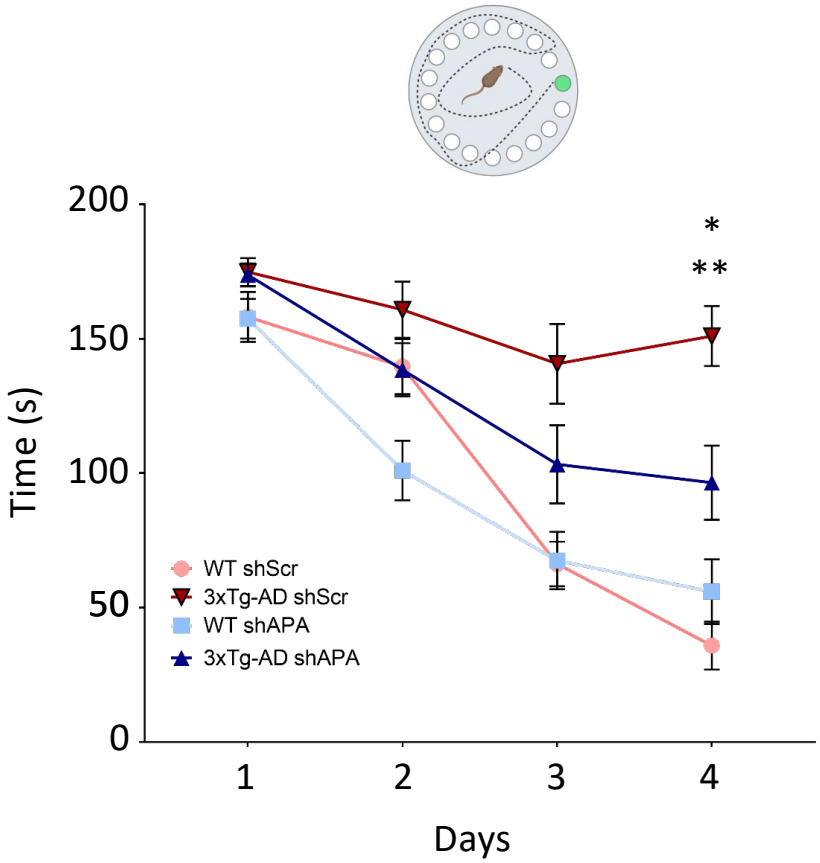
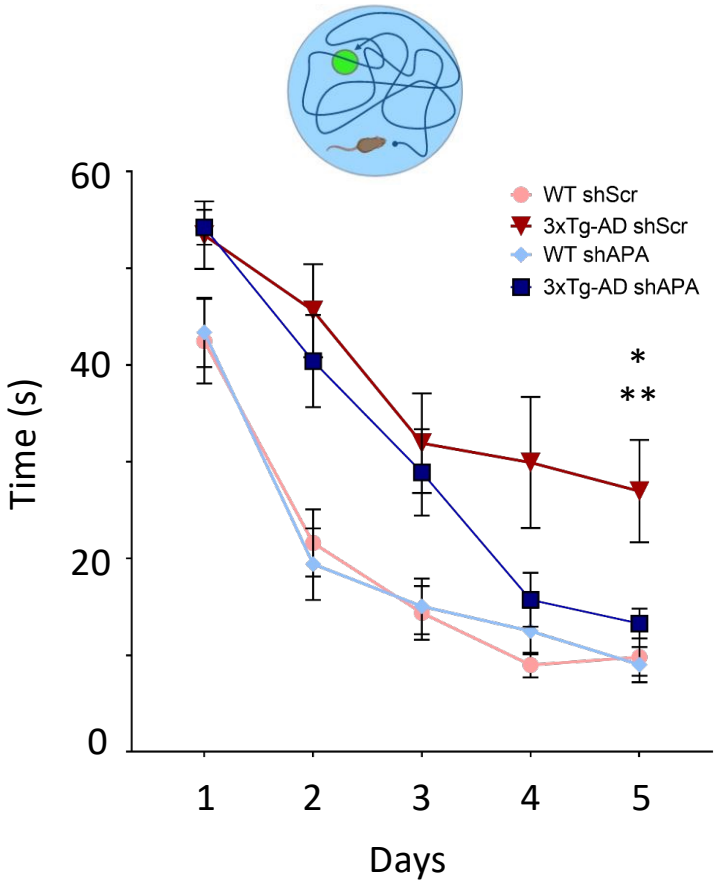




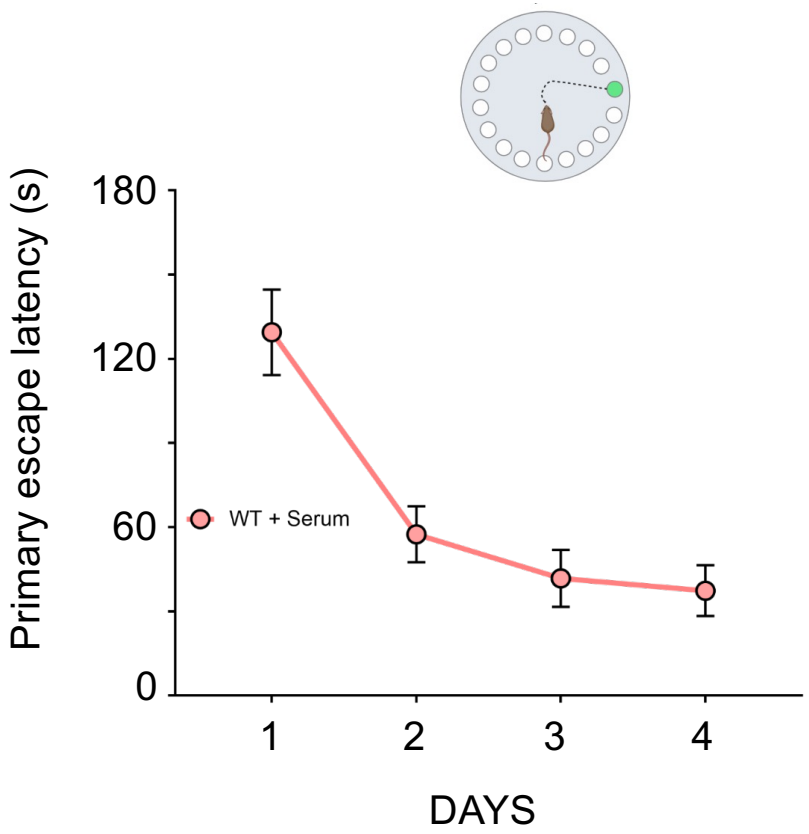
Learning in Barnes Maze et MWM: genetic approach targeting APA



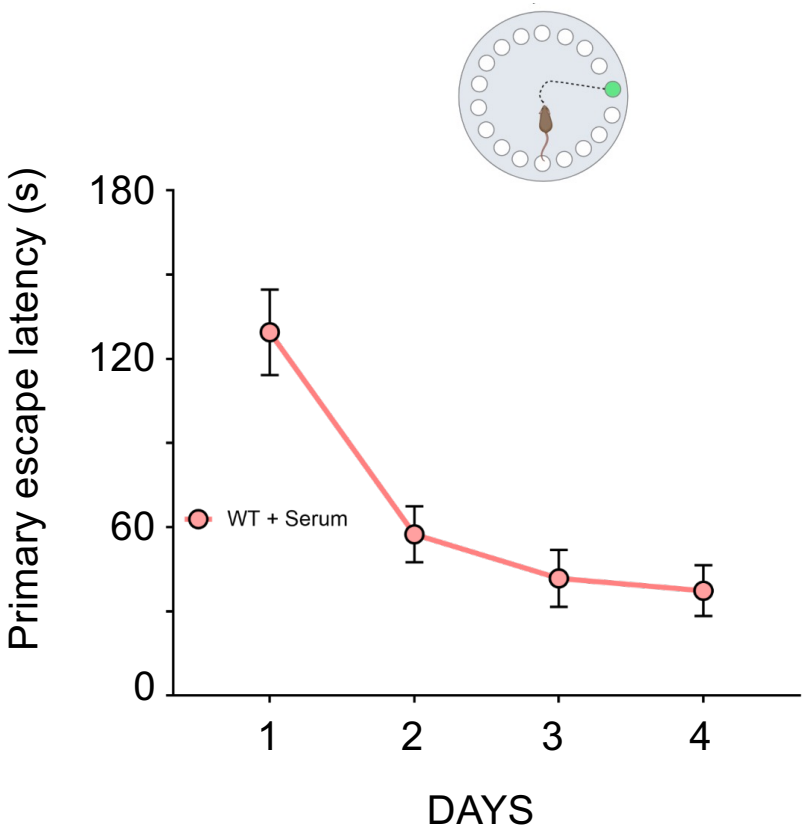


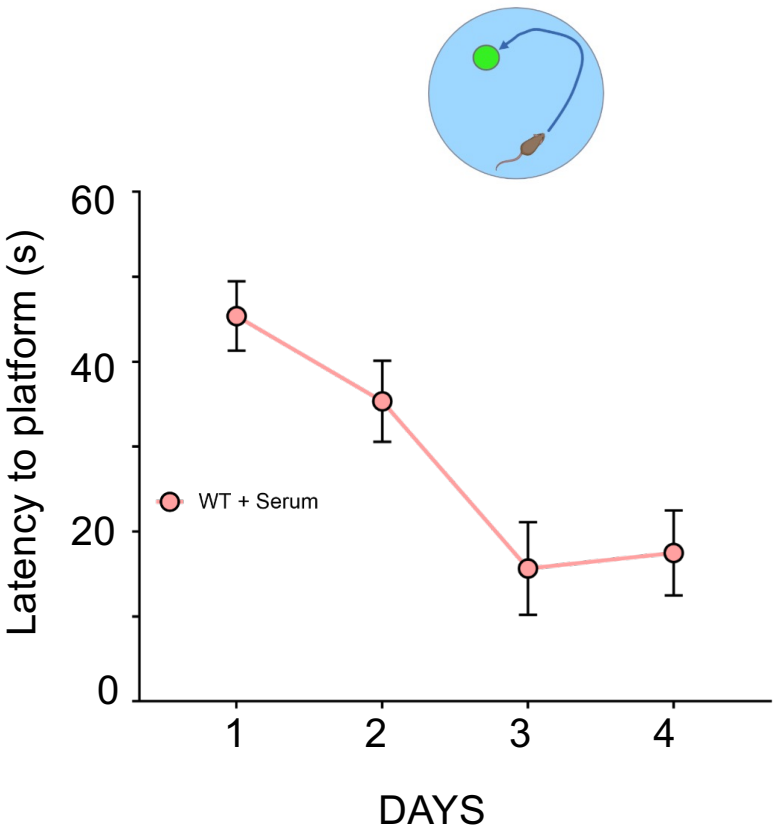
Learning in Barnes Maze and MWM: pharmacological targeting of APA

RB150

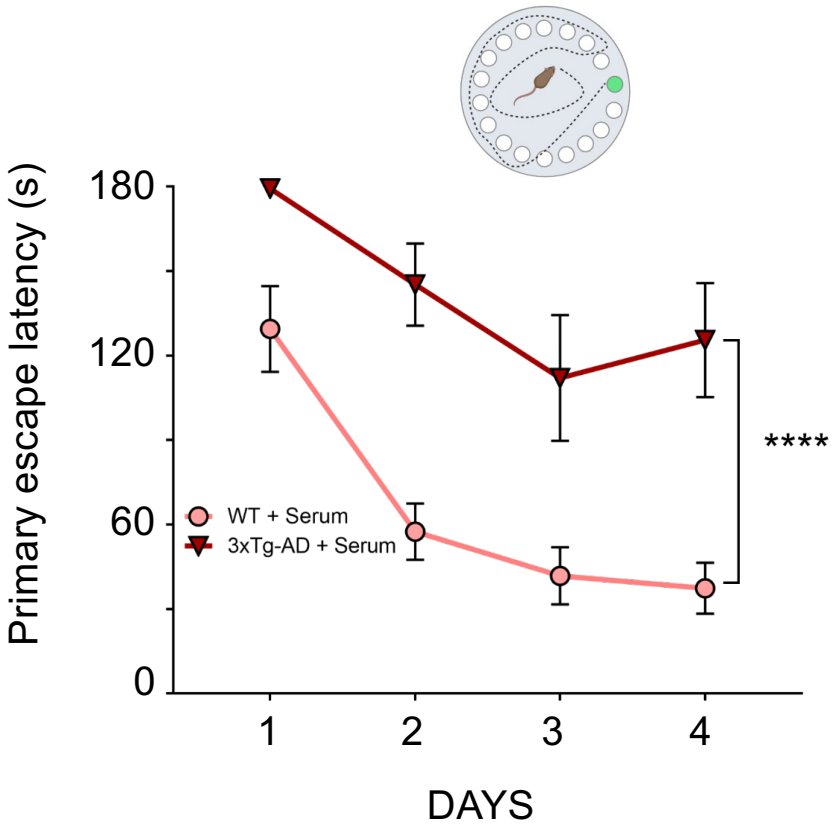


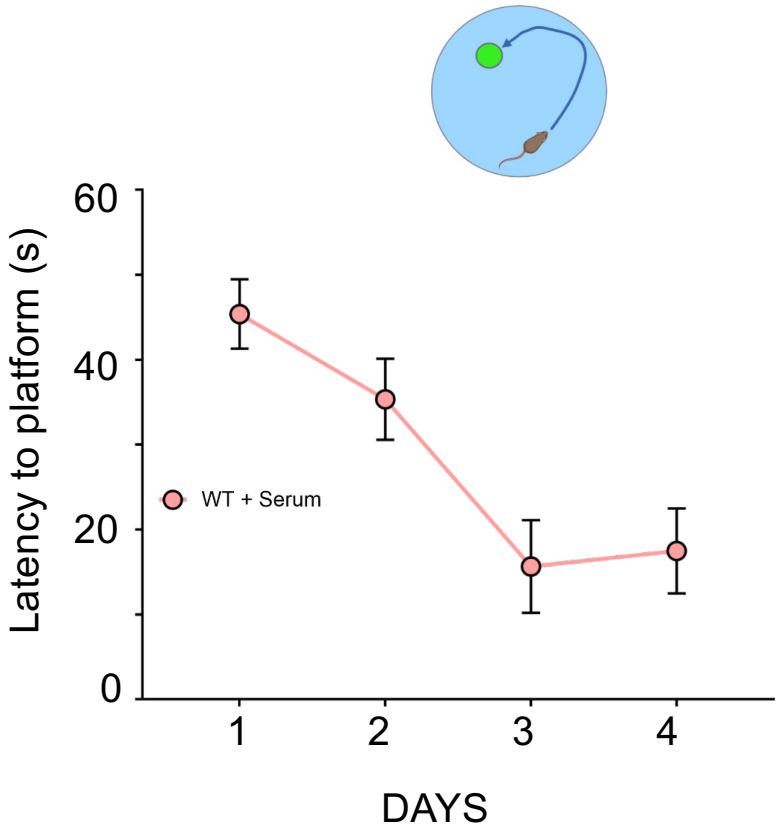
Learning in Barnes Maze and MWM: pharmacological targeting of APA



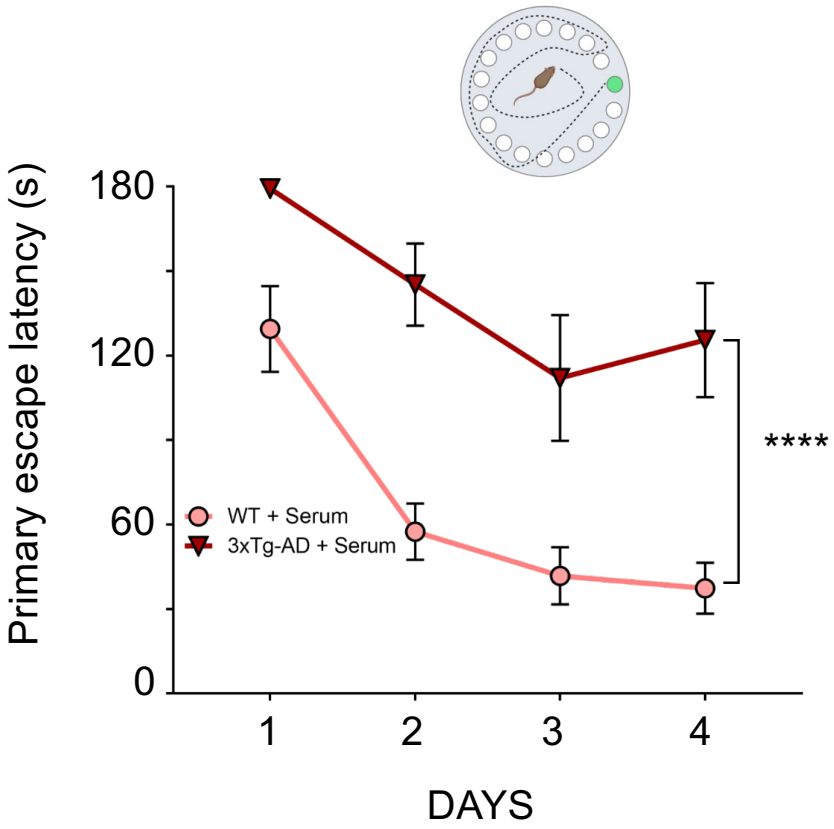


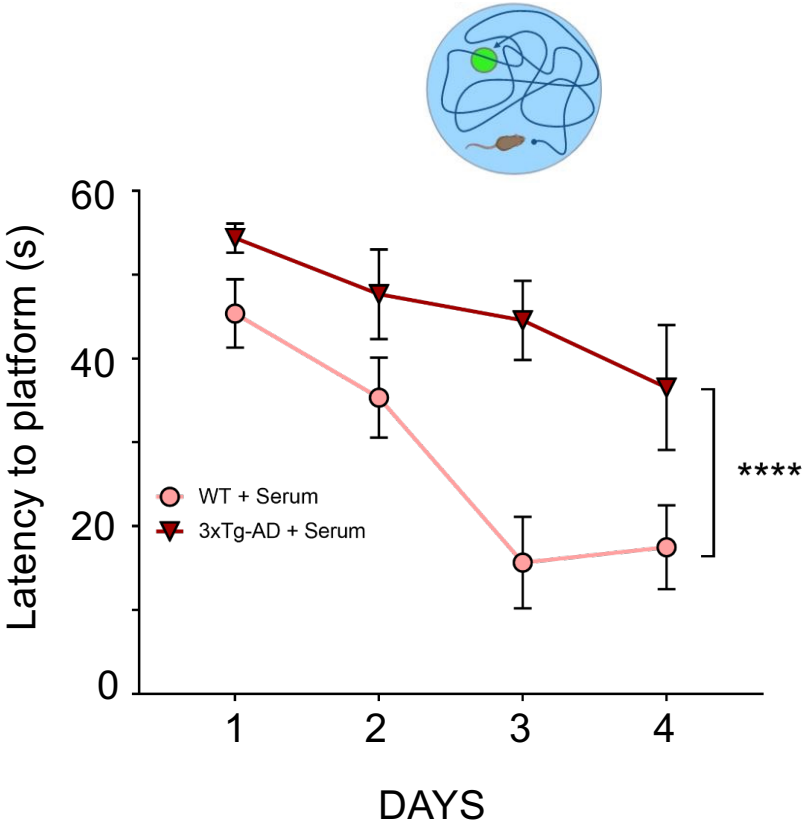
Learning in Barnes Maze and MWM: pharmacological targeting of APA



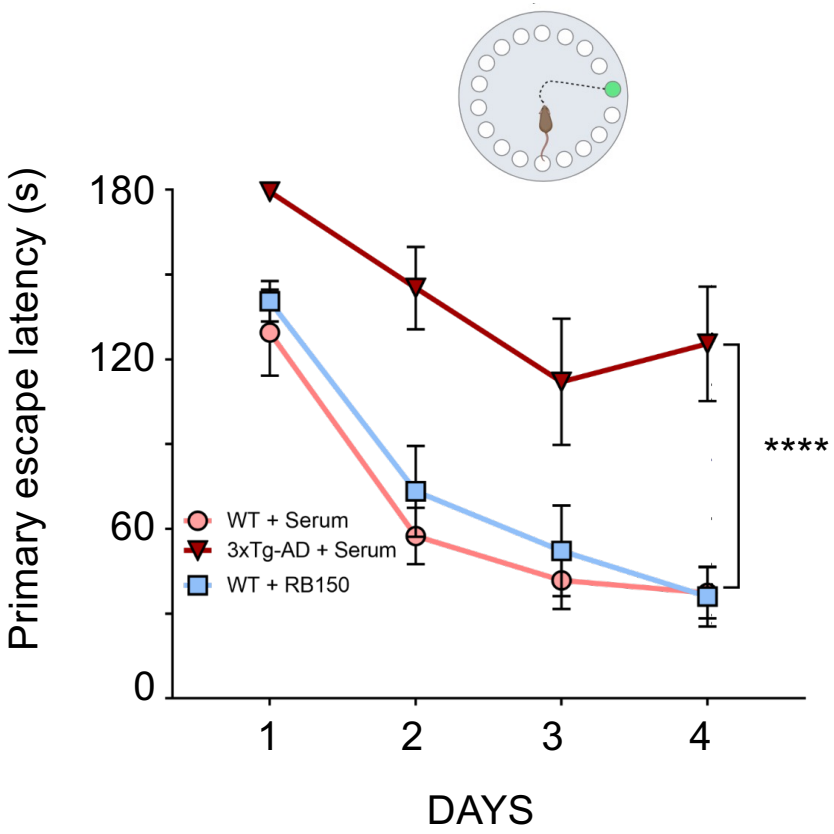


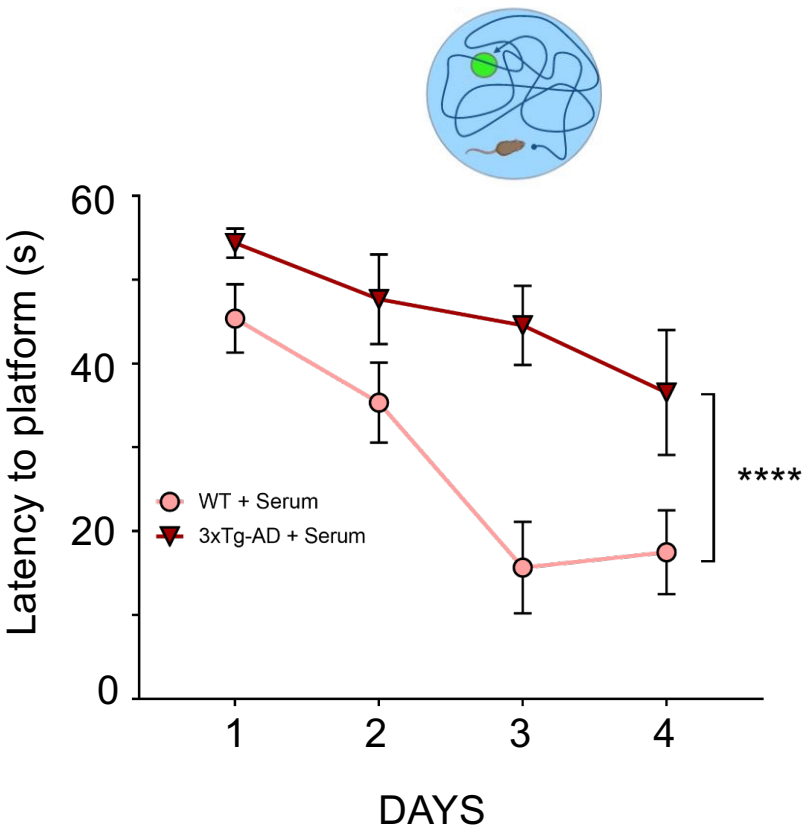
Learning in Barnes Maze and MWM: pharmacological targeting of APA



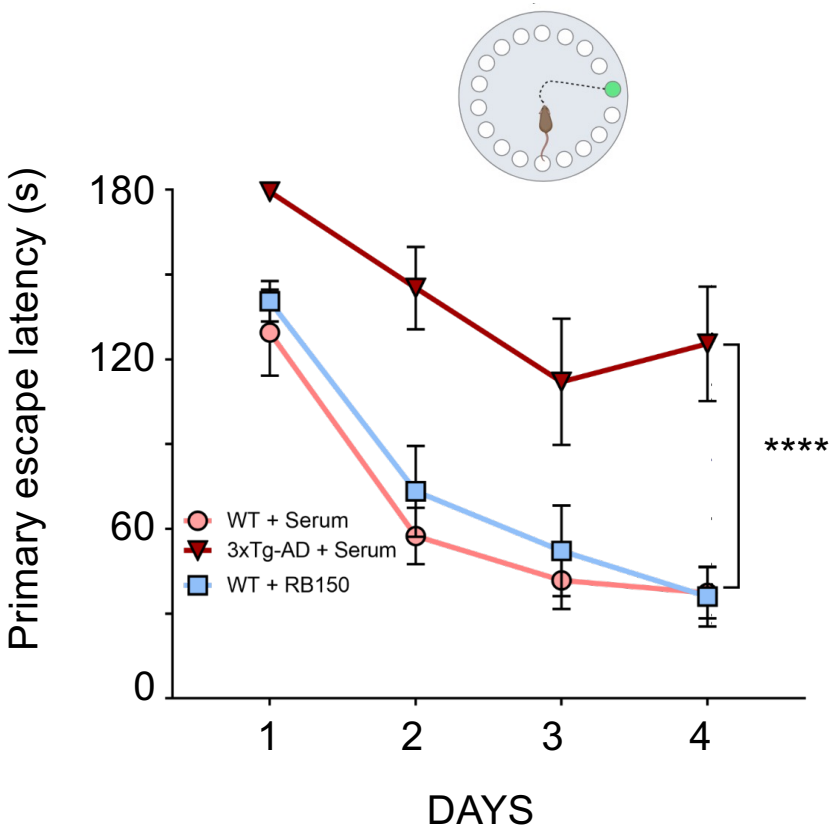


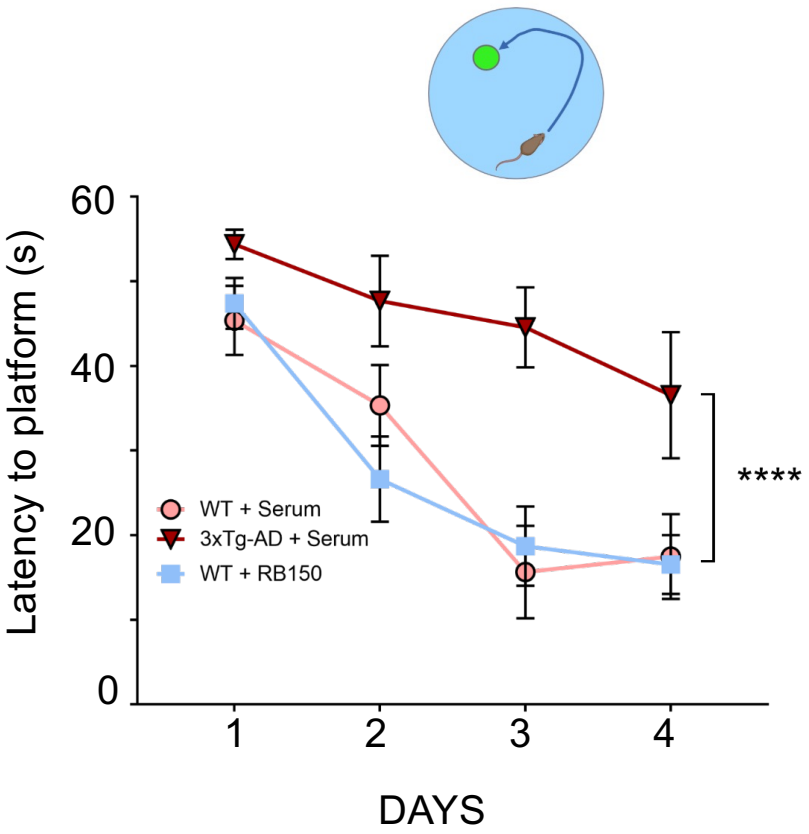
Learning in Barnes Maze and MWM: pharmacological targeting of APA



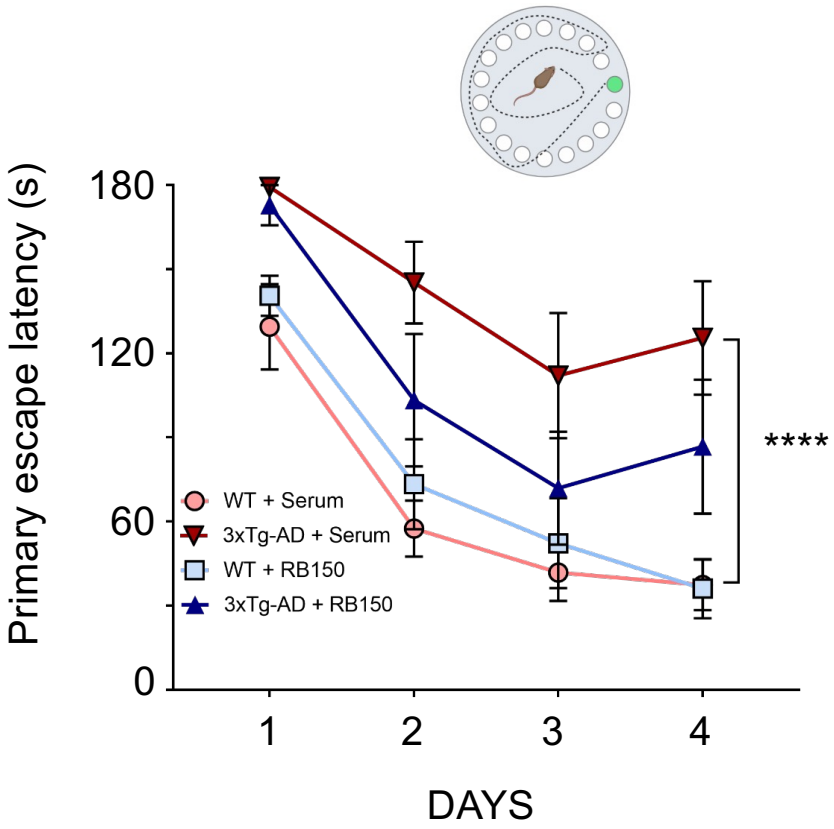


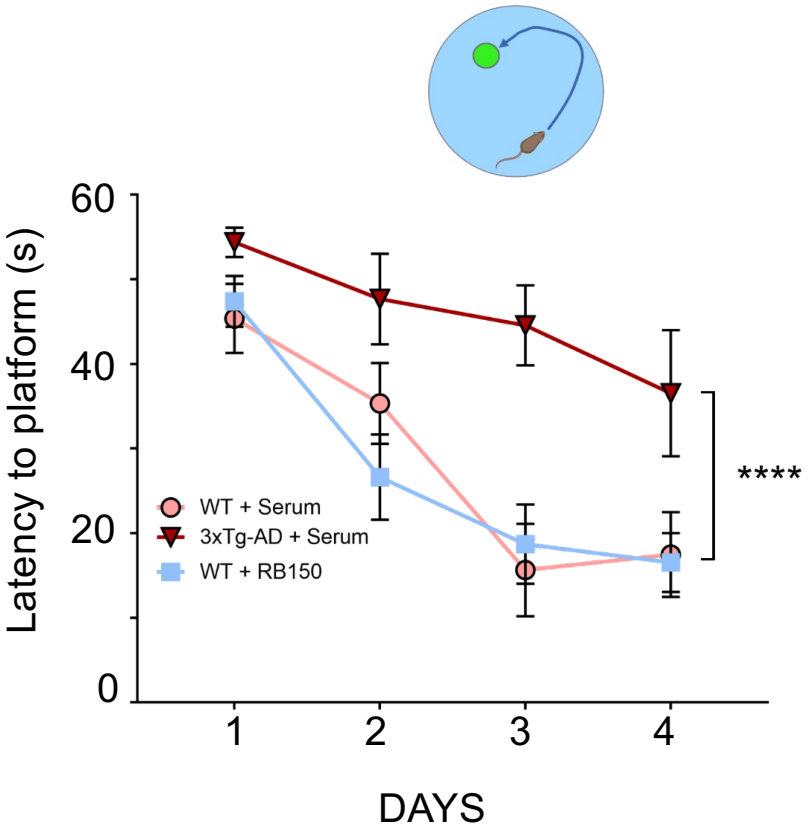
Learning in Barnes Maze and MWM: pharmacological targeting of APA



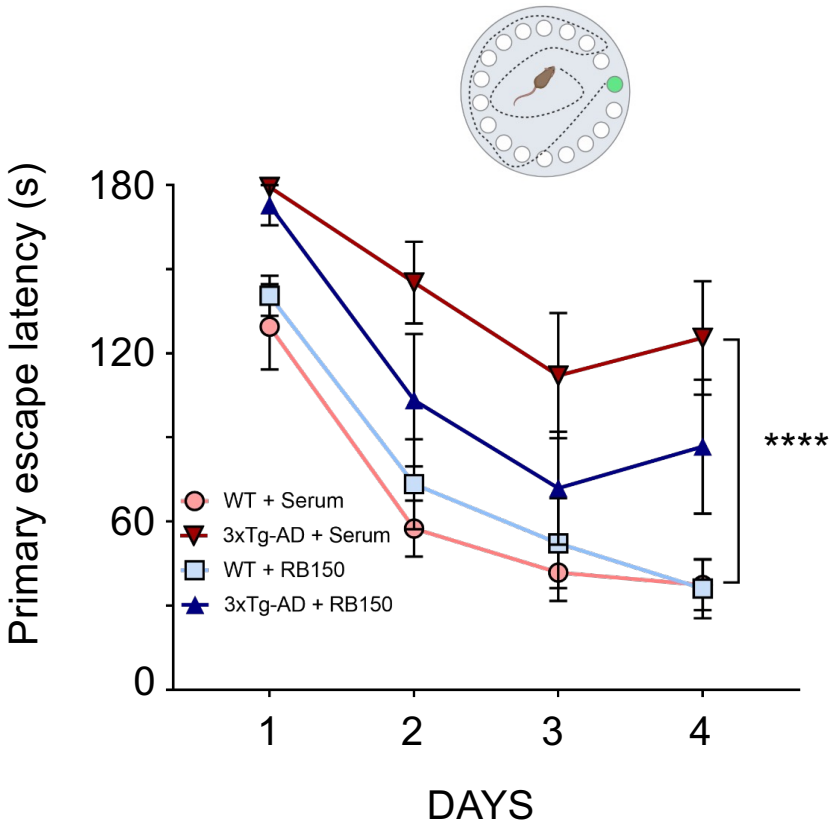


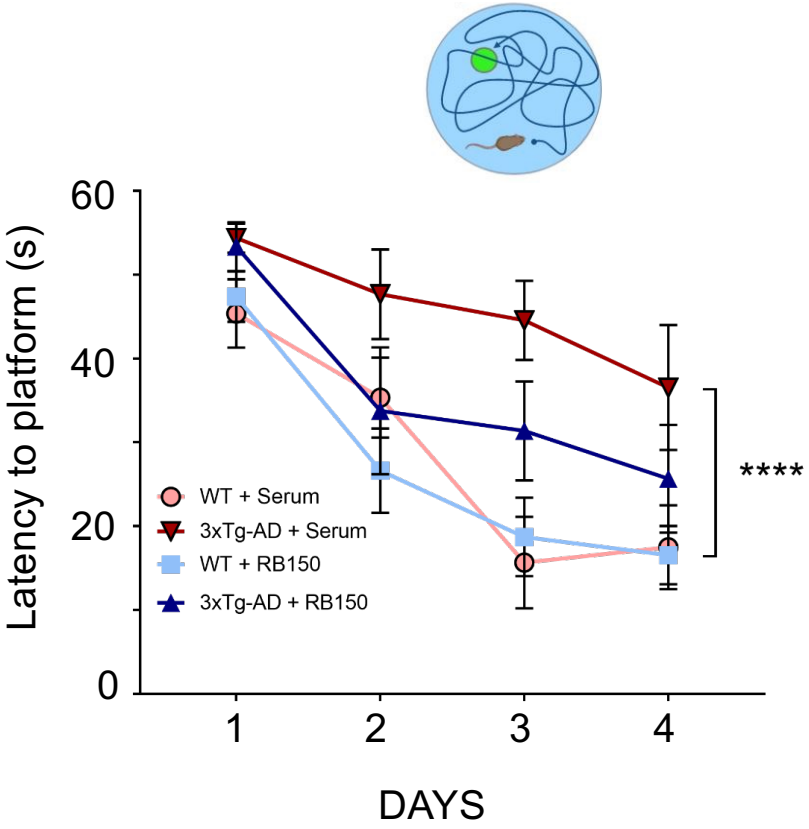
Learning in Barnes Maze and MWM: pharmacological targeting of APA





Learning in Barnes Maze and MWM: pharmacological targeting of APA





Conclusions

APA

→ Improvement of cognitive deficits in Barnes Maze and MWM by both genetic and pharm

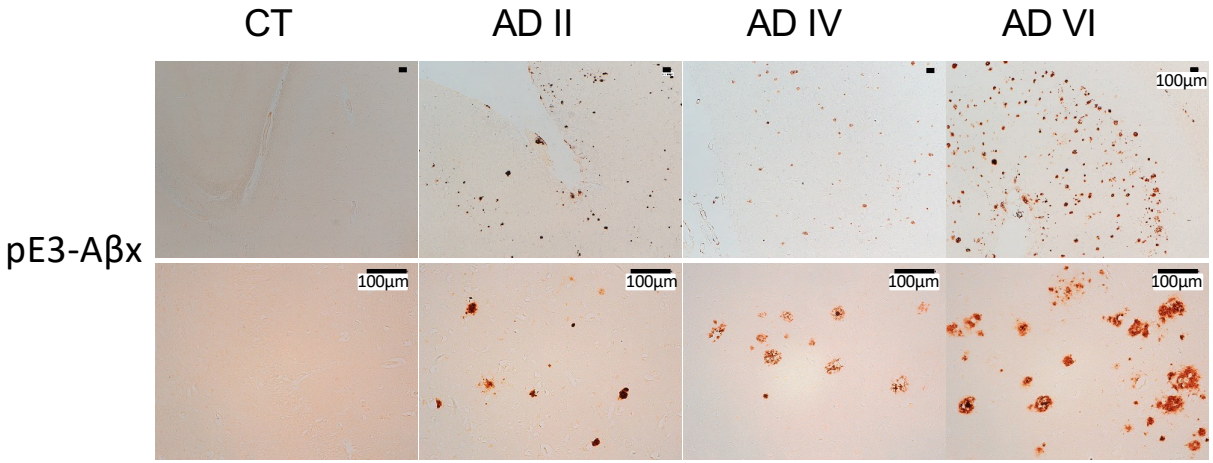
DPP4

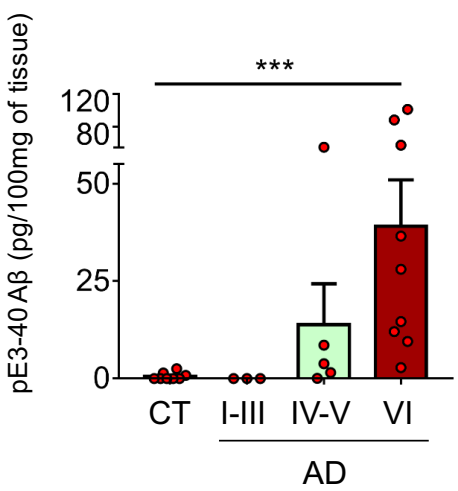
→ Improvement of cognitive defects in the MWM by genetic approach

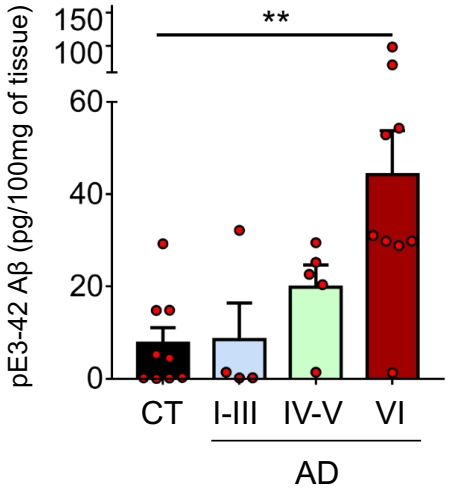
→ Improvement of cognitive defects in the Barnes Maze by pharmacological approach

Measurements of APA and DPP4 activities in sporadic AD brains.

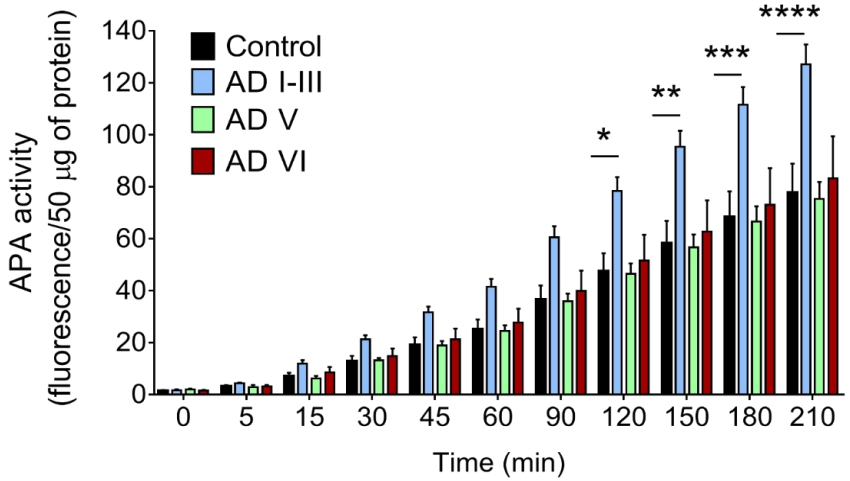
Truncated Aβ AD-affected brains

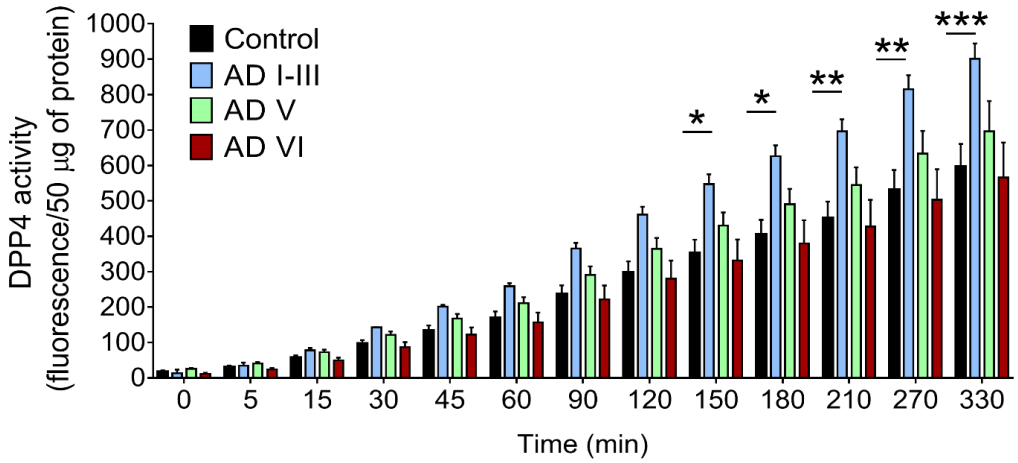






APA and DPP4 activities in sporadic AD brains.





Targeting Aβ truncation, an alternative therapeutic strategy in AD

Aminopeptidase A contributes to biochemical, anatomical and cognitive defects in Alzheimer's disease mice and is increased at early stage of sporadic Alzheimer's disease. (Acta Neuropathologica)

A.Valverde, J.Dunys, D.Debayle, T.Lorivel, AS.Gay , B.Roques, S.Lacas-Gervais, M.Chami et F.Checler. ***Acta Neuropathologica***, 2021 Jun;141(6):823-839

Dipeptidyl peptidase 4 accounts for Alzheimer's disease-like defects in a mouse model and its activity is increased in sporadic Alzheimer's disease brains.

A.Valverde, J.Dunys, C.Caillava, D.Debayle, T.Lorivel, AS.Gay , M.Chami et F.Checler, 2021
Journal of Biological Chemistry, Aug;297(2):100963

Remerciements

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Centre Commun de Microscopie

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