Targeting the p75 Receptor to Inhibit Degenerative Signaling and Tau Phosphorylation/Misfolding/ Missorting: Preclinical through Phase 1

ADC Directors Meeting, April 18th 2015

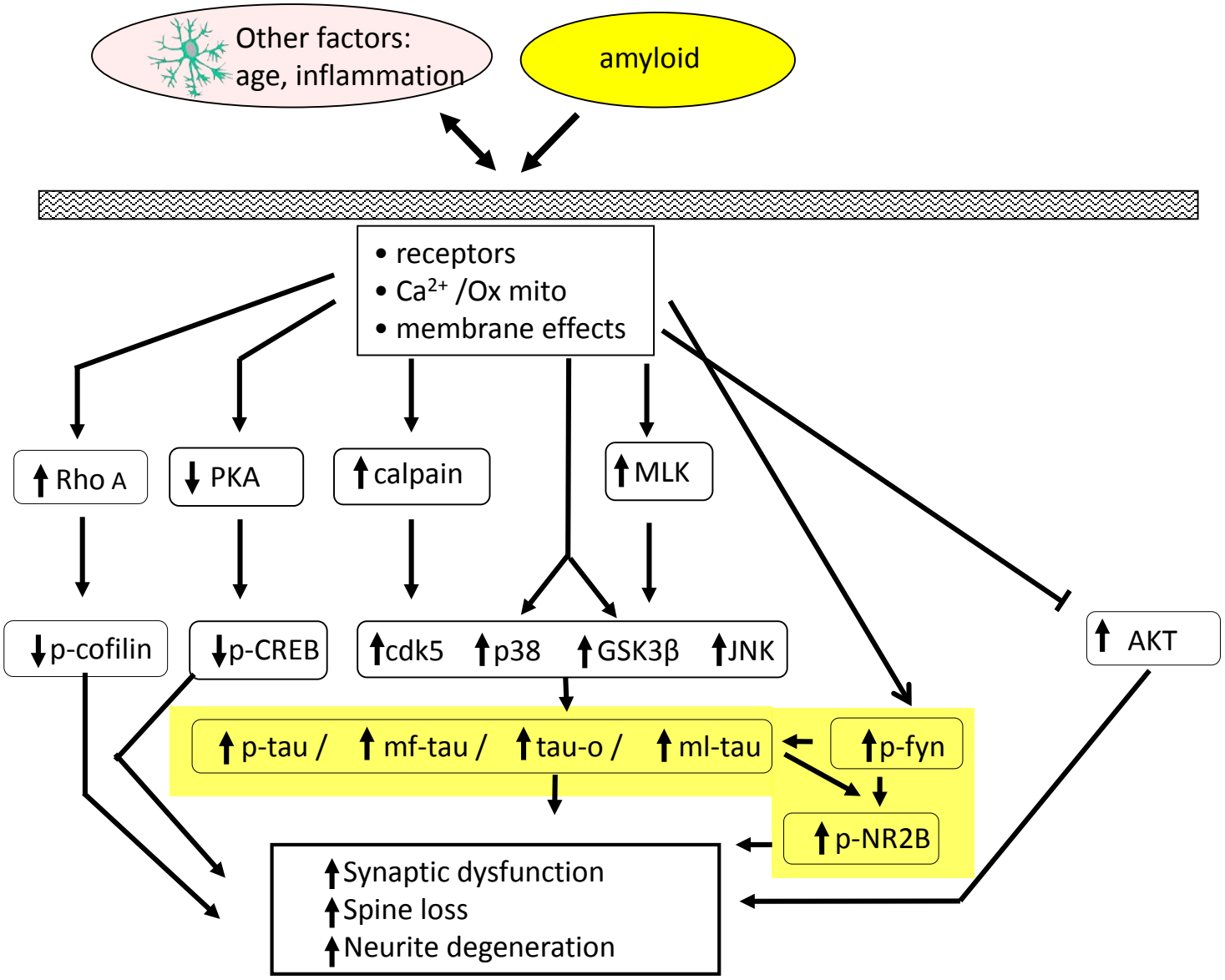
Frank M. Longo, Stanford University

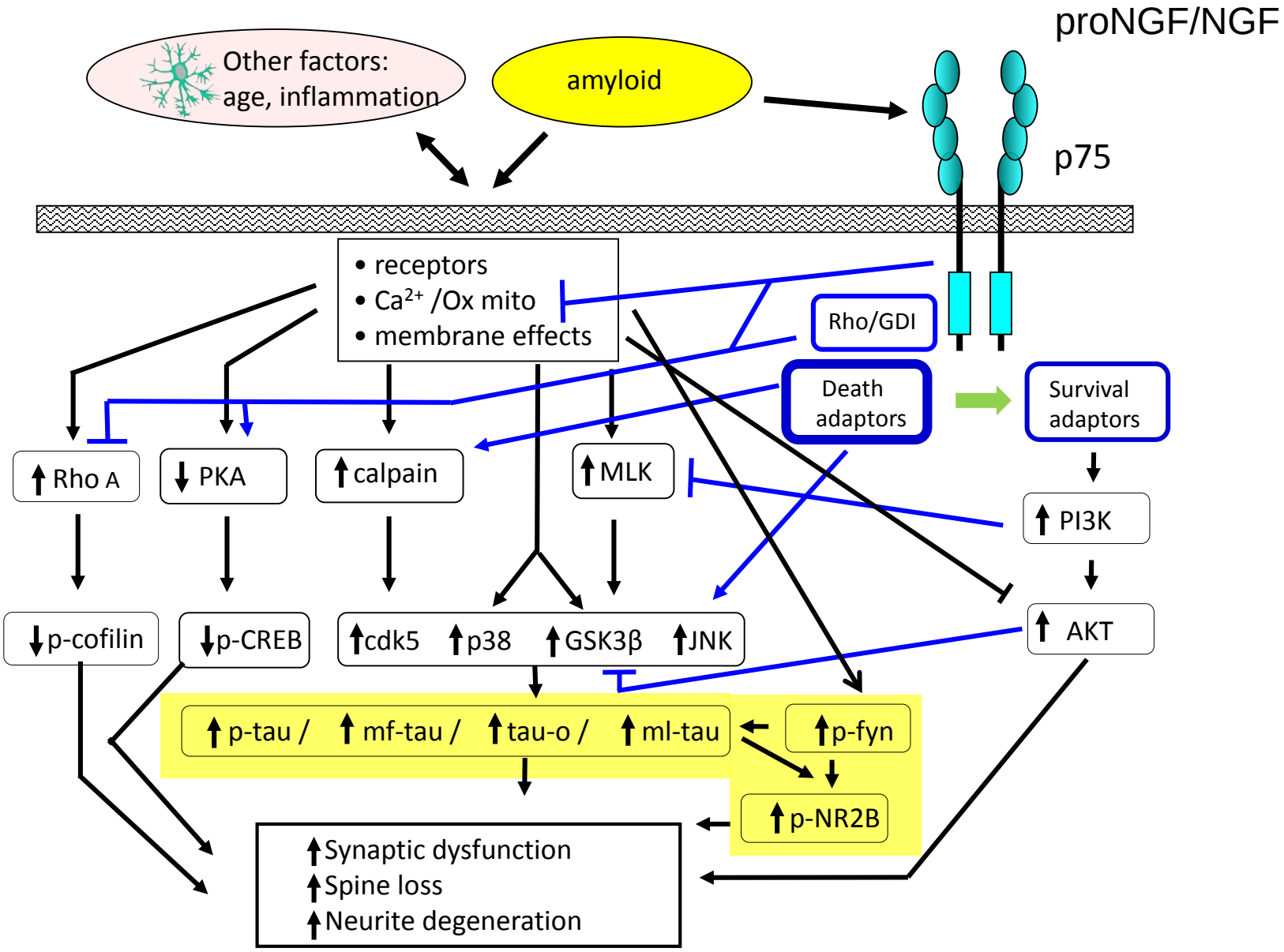
UNC/UCSF → PharmatrophiX

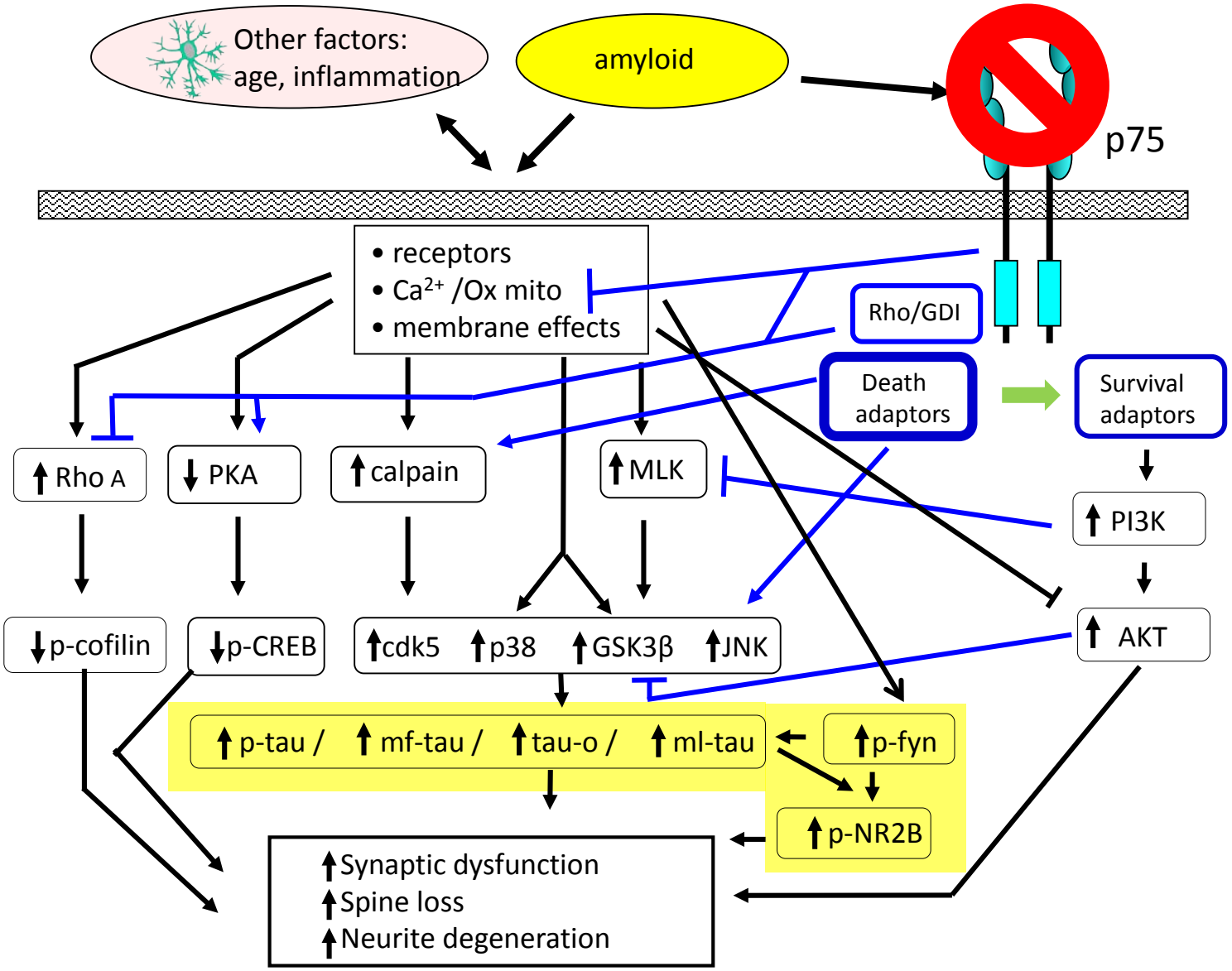
Stanford → Academic/mechanistic studies

Also: Steve Massa, MD, PhD at UCSF

ADDF
Alzheimer's Association
NIA U01
NINDS R21
Taube Family
Koret Fdn
Jean Perkins Fdn
Horngren Family


Other factors:
age, inflammation
amyloid
• receptors
• Ca2+ /Ox mito
• membrane effects
Rho A
PKA
calpain
MLK
p-cofilin
p-CREB
cdk5
p38
GSK3β
JNK
AKT
p-tau /
mf-tau /
tau-o /
ml-tau
p-fyn
p-NR2B
Synaptic dysfunction
Spine loss
Neurite degeneration

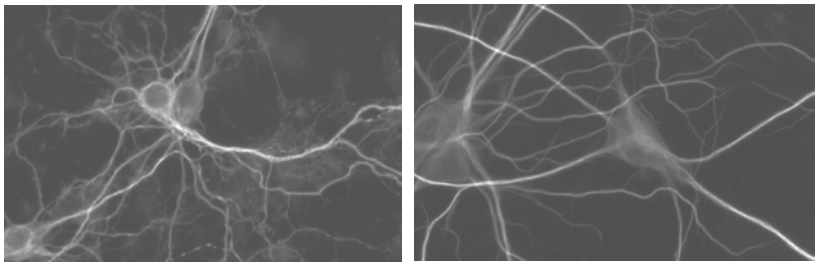

proNGF/NGF
Other factors:
age, inflammation
amyloid
p75
• receptors
• Ca2+ /Ox mito
• membrane effects
Rho/GDI
Death
adaptors
Survival
adaptors
Rho A
PKA
calpain
MLK
PI3K
p-cofilin
p-CREB
cdk5
p38
GSK3β
JNK
AKT
p-tau /
mf-tau /
tau-o /
ml-tau
p-fyn
p-NR2B
Synaptic dysfunction
Spine loss
Neurite degeneration

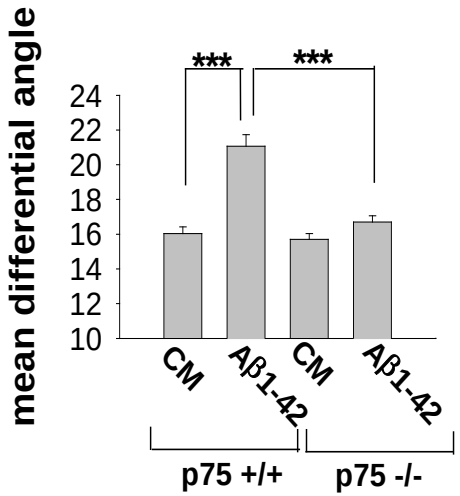

Other factors:
age, inflammation
amyloid
p75
• receptors
• Ca2+ /Ox mito
• membrane effects
Rho/GDI
Death adaptors
Survival adaptors
Rho A
PKA
calpain
MLK
PI3K
p-cofilin
p-CREB
cdk5
p38
GSK3β
JNK
AKT
p-tau /
mf-tau /
tau-o /
ml-tau
p-fyn
p-NR2B
Synaptic dysfunction
Spine loss
Neurite degeneration

Aβ-induced degeneration is p75 dependent

oligomeric-Aβ + 21 div HC neurons

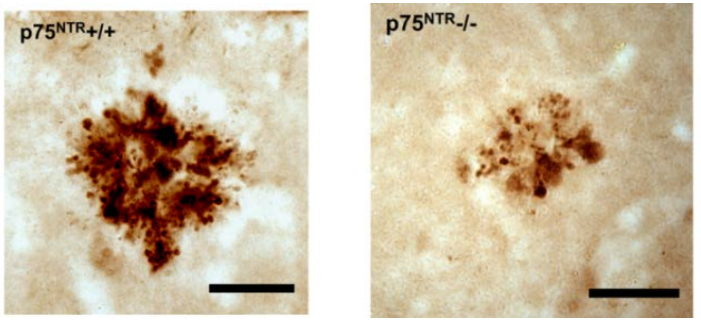
p75+/+ p75-/-

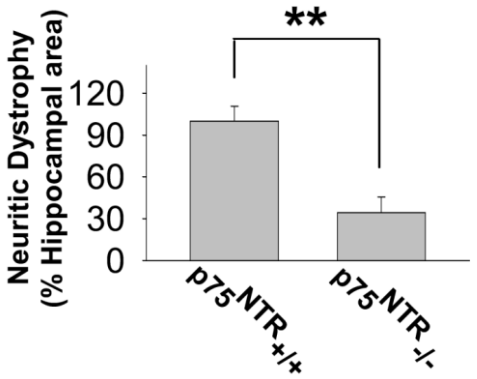




APP-L/S X p75 -/- dystrophic neurites (APP IHC)

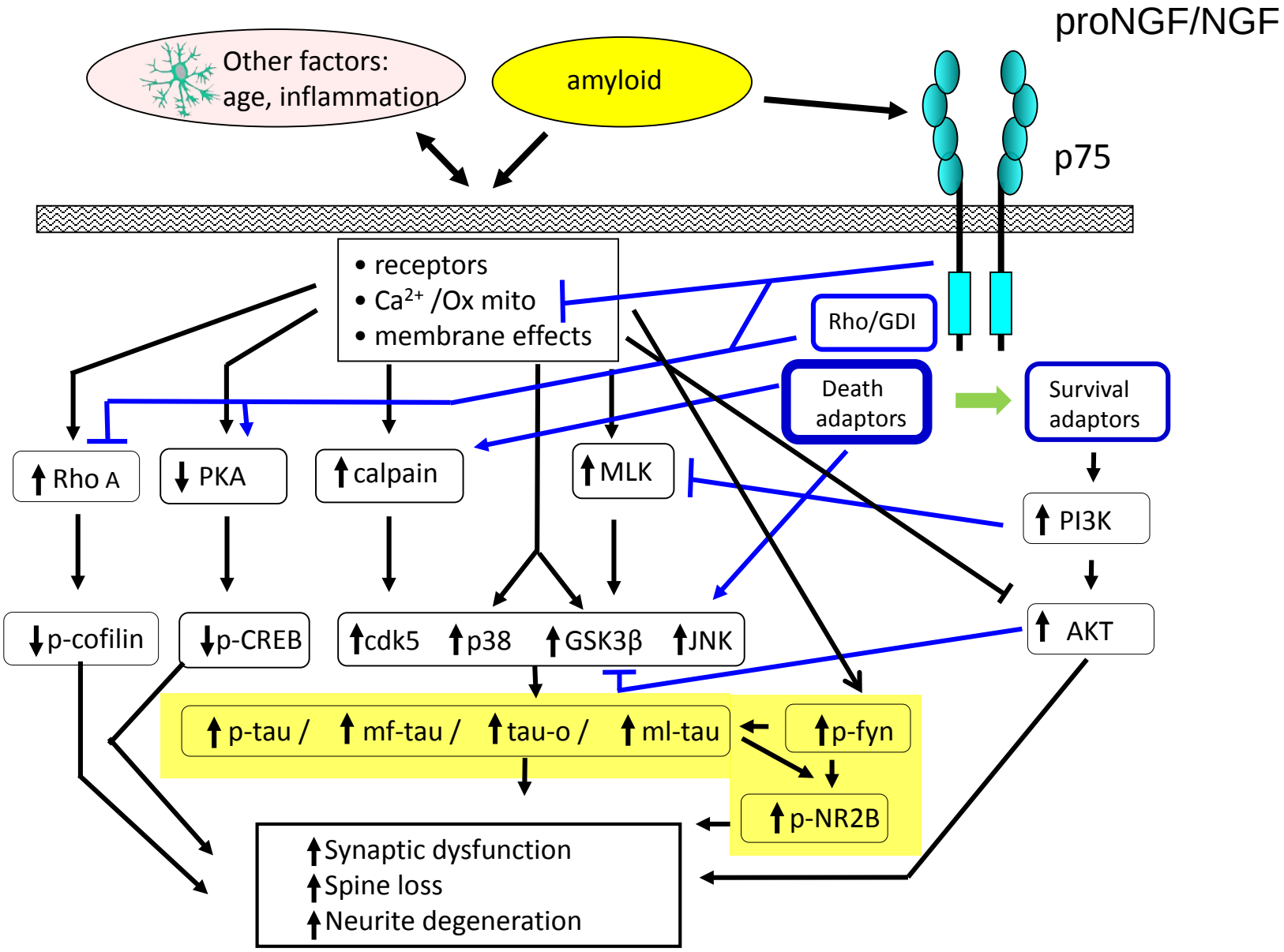
p75+/+ P75-/-



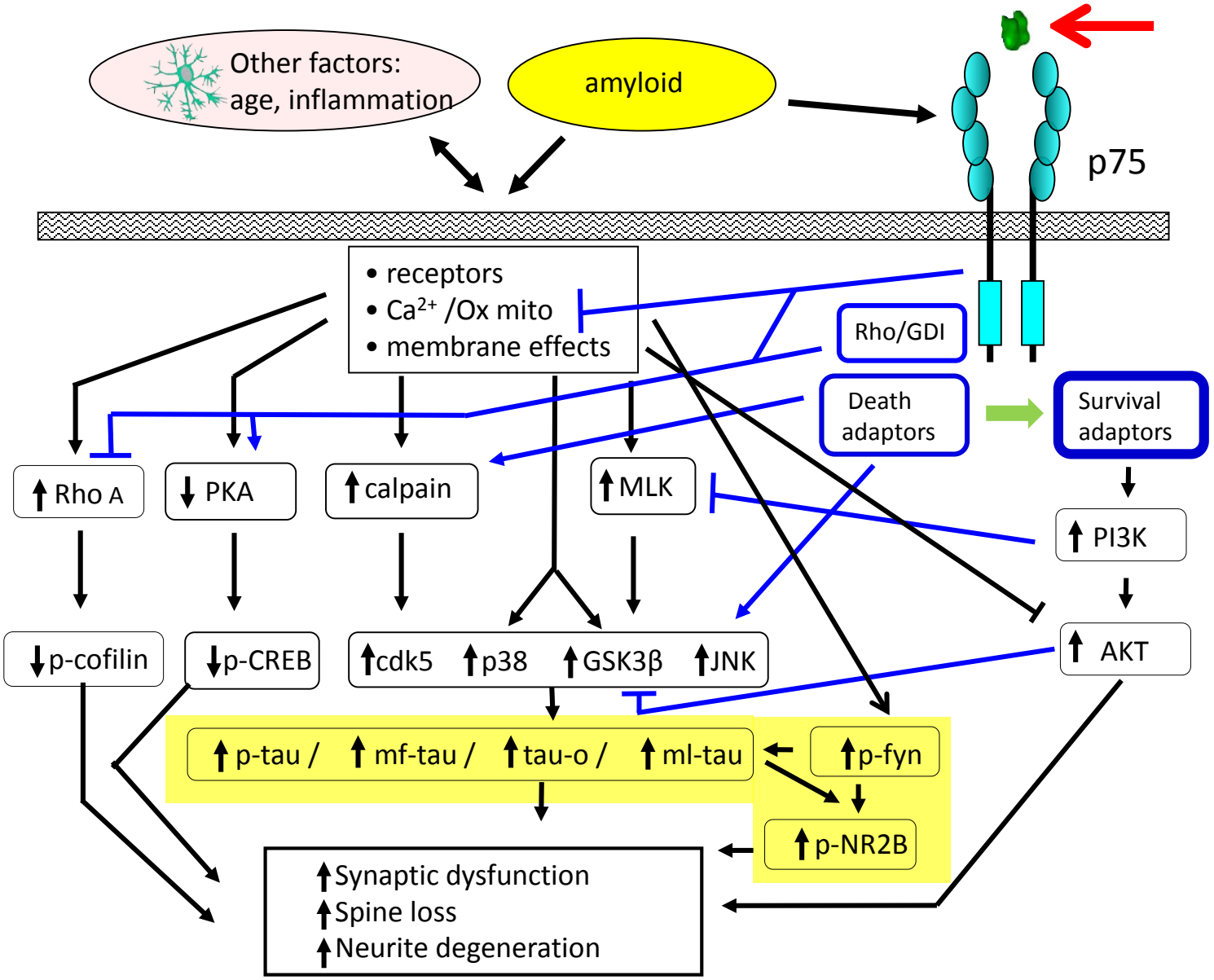


p75 enables Aβ-induced degeneration

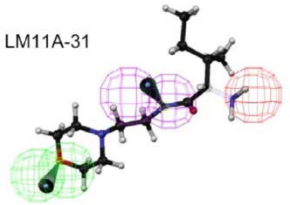
Knowles et al, *J Neurosci* 2009
Coulson Lab 2009
Bartlett Lab 2015


proNGF/NGF
Other factors:
age, inflammation
amyloid
p75
• receptors
• Ca2+ /Ox mito
• membrane effects
Rho/GDI
Death
adaptors
Survival
adaptors
Rho A
PKA
calpain
MLK
PI3K
p-cofilin
p-CREB
cdk5
p38
GSK3β
JNK
AKT
p-tau /
mf-tau /
tau-o /
ml-tau
p-fyn
p-NR2B
Synaptic dysfunction
Spine loss
Neurite degeneration

Signaling effects:



Signaling effects:



Massa et al
J Neurosci 2006

Other factors:
age, inflammation

amyloid

p75

- receptors
- Ca^{2+} /Ox mito
- membrane effects

Rho/GDI

Death adaptors

Survival adaptors

↑Rho A

↓PKA

↑calpain

↑MLK

↑PI3K

↓p-cofilin

↓p-CREB

↑cdk5 ↑p38 ↑GSK3β ↑JNK

↑AKT

↑p-tau / ↑mf-tau / ↑tau-o / ↑ml-tau

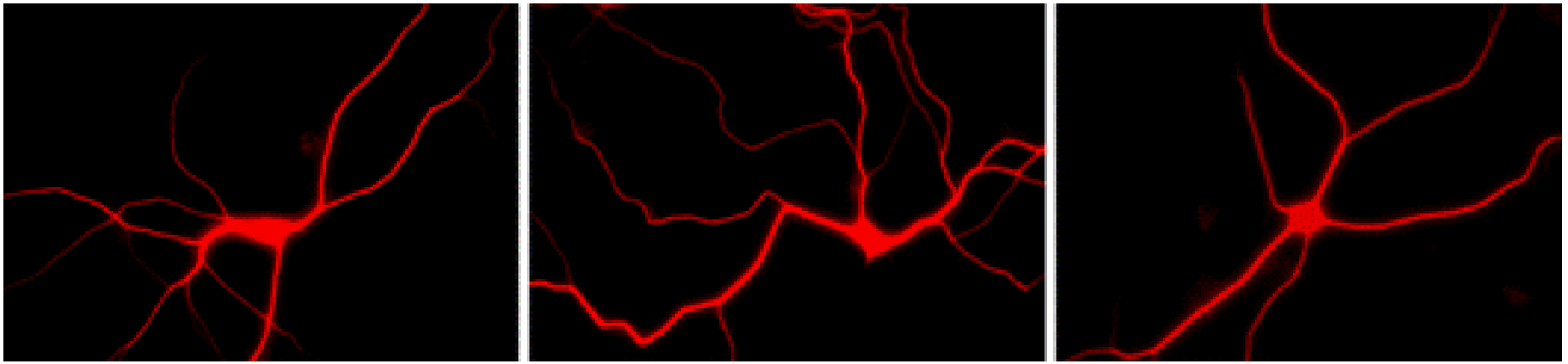
↑p-fyn

↑p-NR2B

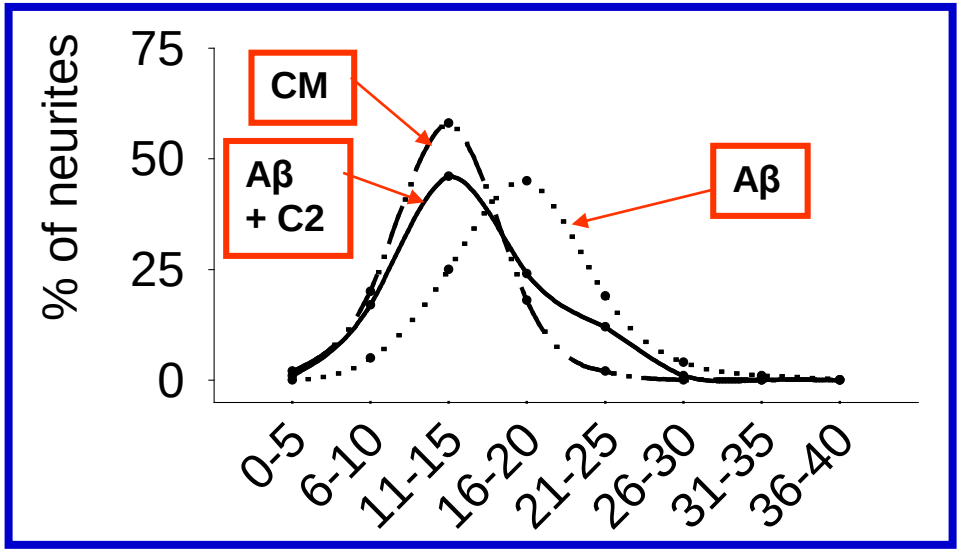
↑Synaptic dysfunction
↑Spine loss
↑Neurite degeneration

LM11A-31 inhibits Aβ-induced dystrophy

CM **$A\beta_{1-42}$** **$A\beta_{1-42}$ + ligand (100 nM)**

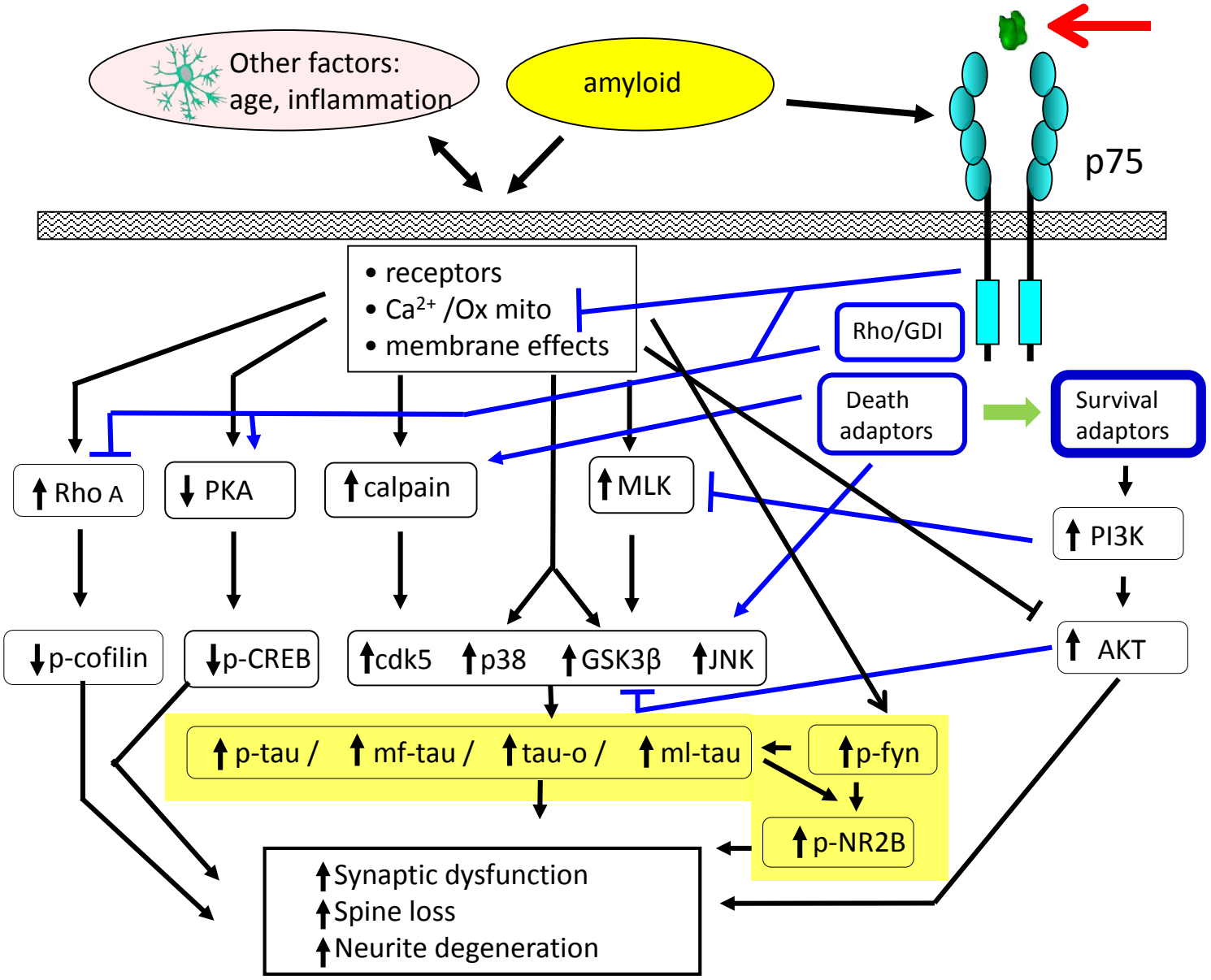


E17 div 21 matured hippocampal neurons

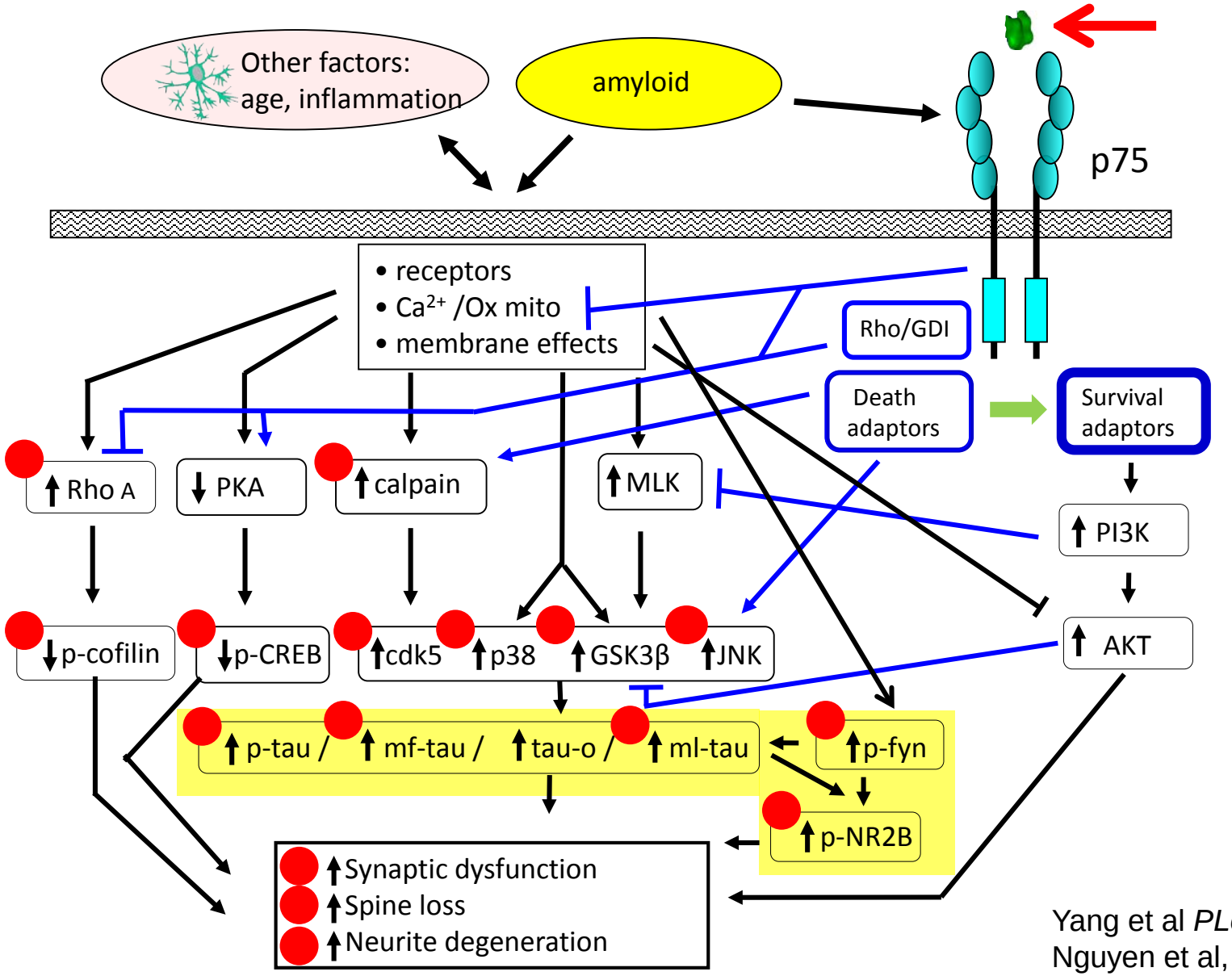


Modified from Yang et al *PLoS One*, 2008

Signaling effects:

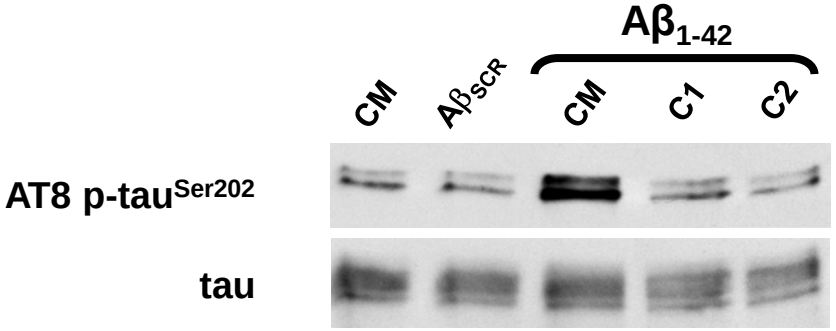


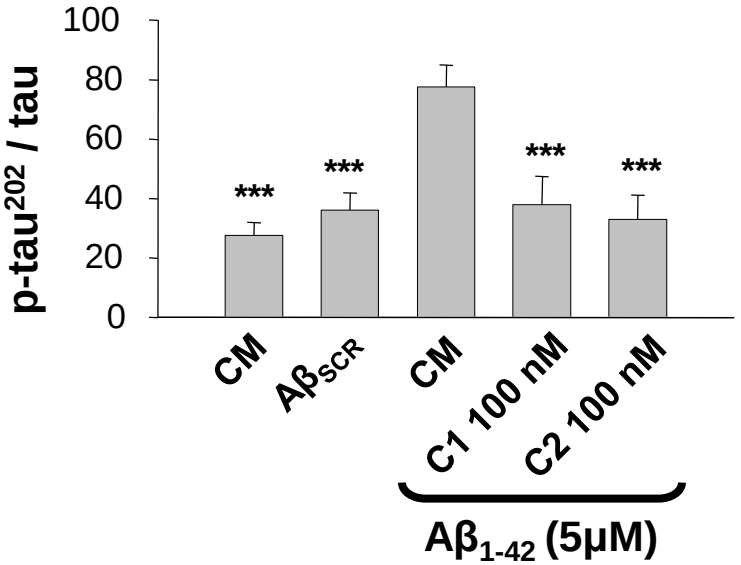
Signaling effects:



Yang et al *PLoS One* 2008
Nguyen et al, *JAD* 2014
Yang et al, *SNS* 2014

p75^{NTR} ligands block Aβ-induced p-tau / AT8 epitope





E17 div 21 hippocampal neurons

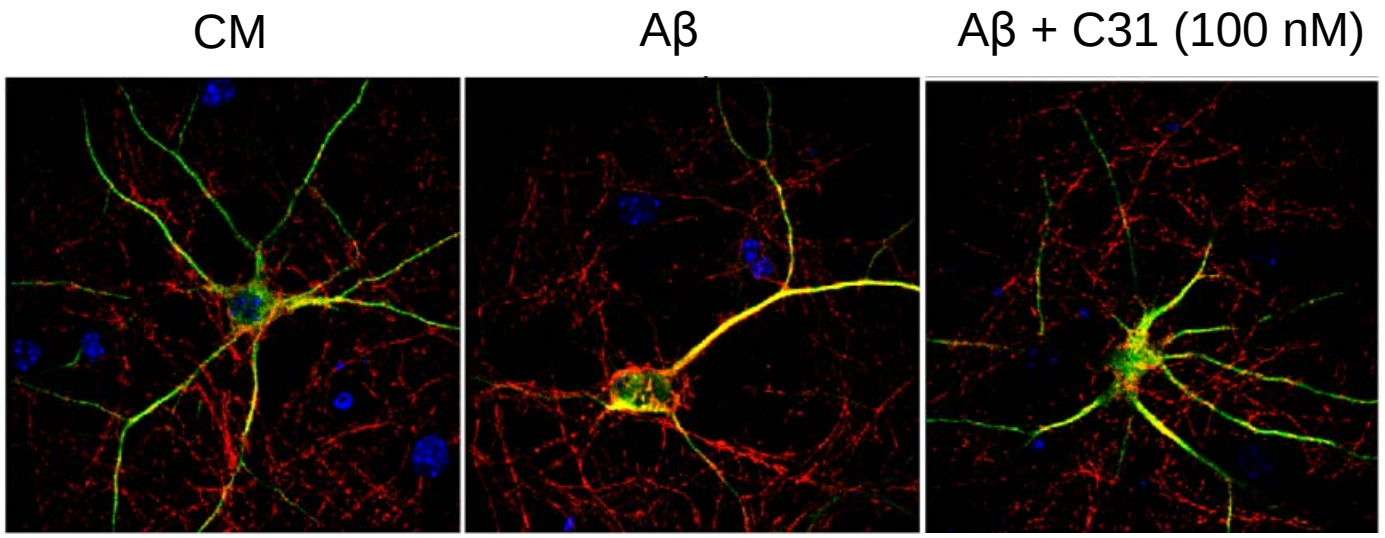
Modified from Yang et al *PLoS One*, 2008

Inhibition of Aβ-induced tau mislocalization

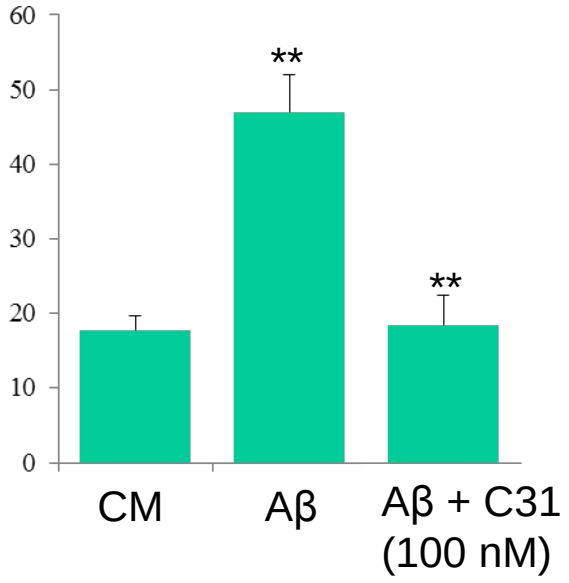
E17 DIV 21 hippocampal neurons

MAP2 (dendrites)

Tau (axons)



yellow µm / 100 µm



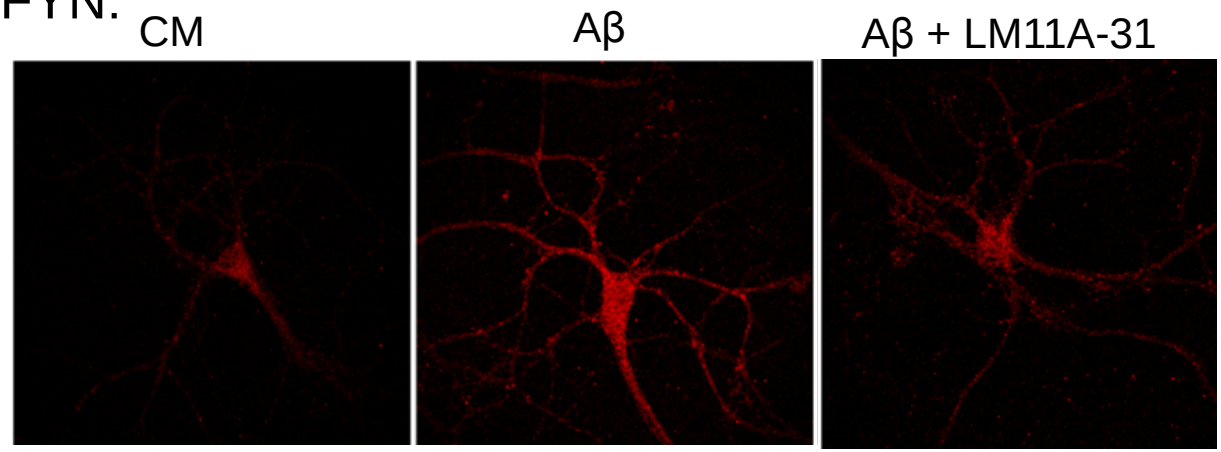
FYN-NR2B activation?

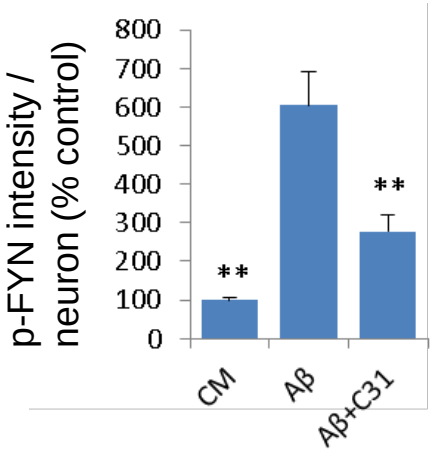
Yang, Longo SNS 2014

Inhibition of Aβ-induced FYN and NR2B activation

21 DIV HC neurons

p-FYN:





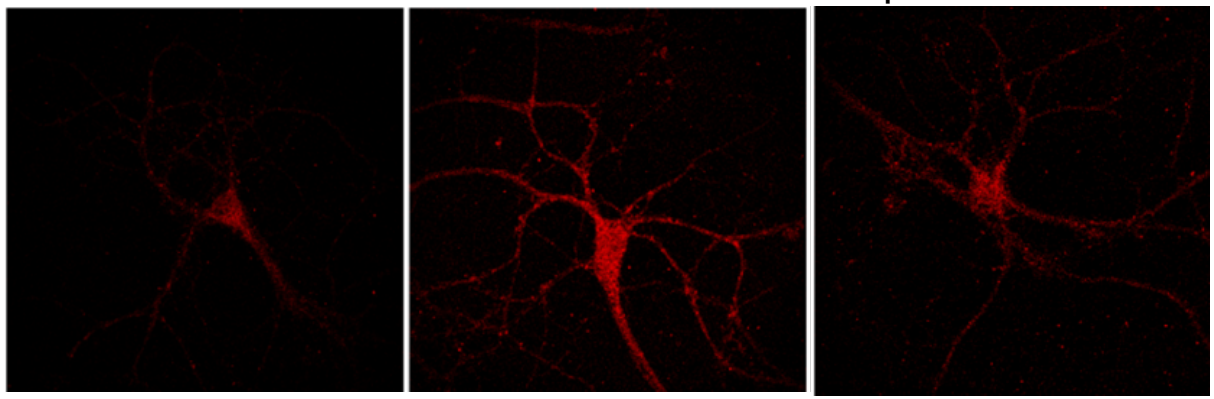
Yang, Longo SNS 2014

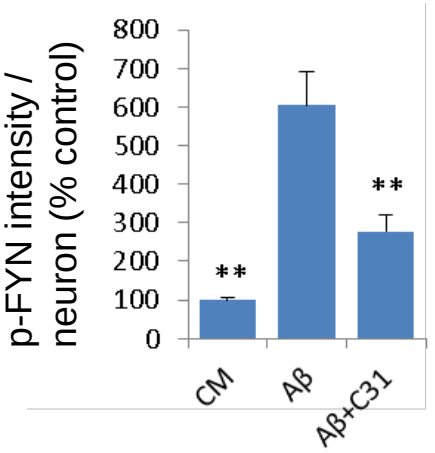
Inhibition of Aβ-induced FYN and NR2B activation

21 DIV HC neurons

p-FYN:

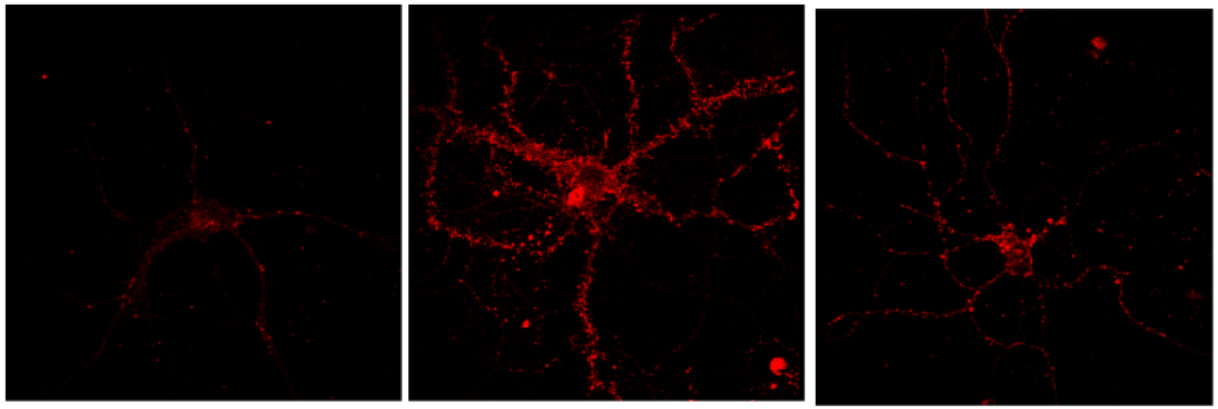
CM | Aβ | Aβ + LM11A-31

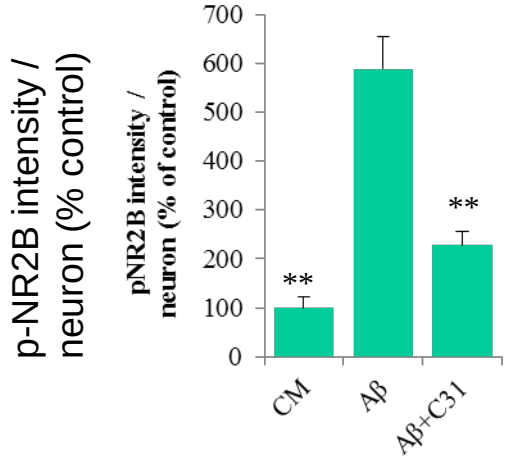




p-NR2B:

CM | Aβ | Aβ + LM11A-31





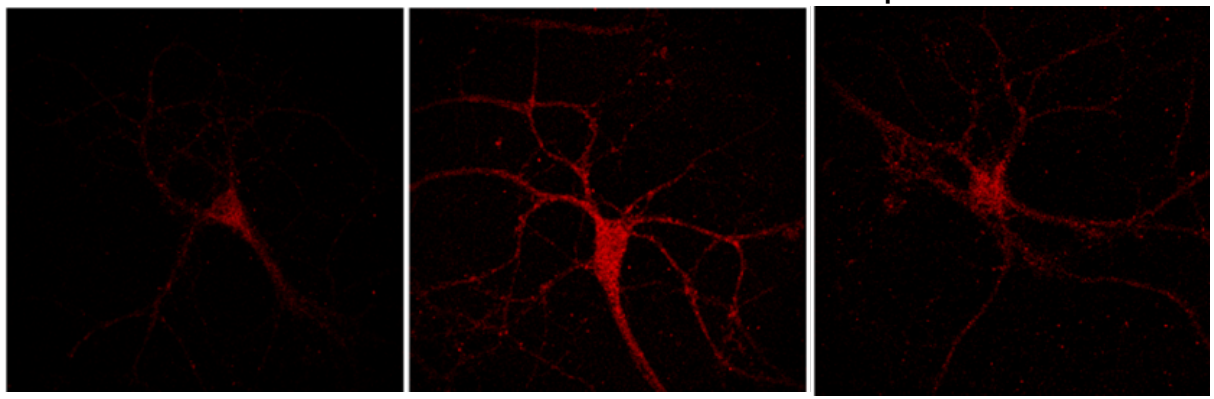
Yang, Longo SNS 2014

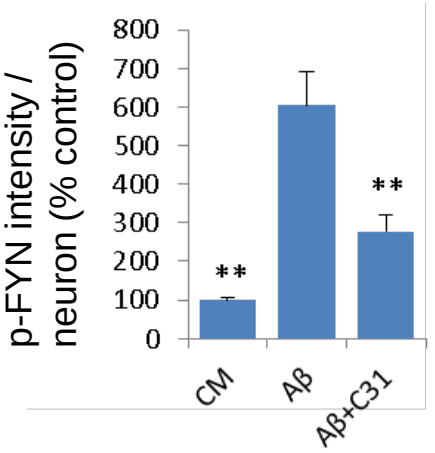
Inhibition of Aβ-induced FYN and NR2B activation

21 DIV HC neurons

p-FYN:

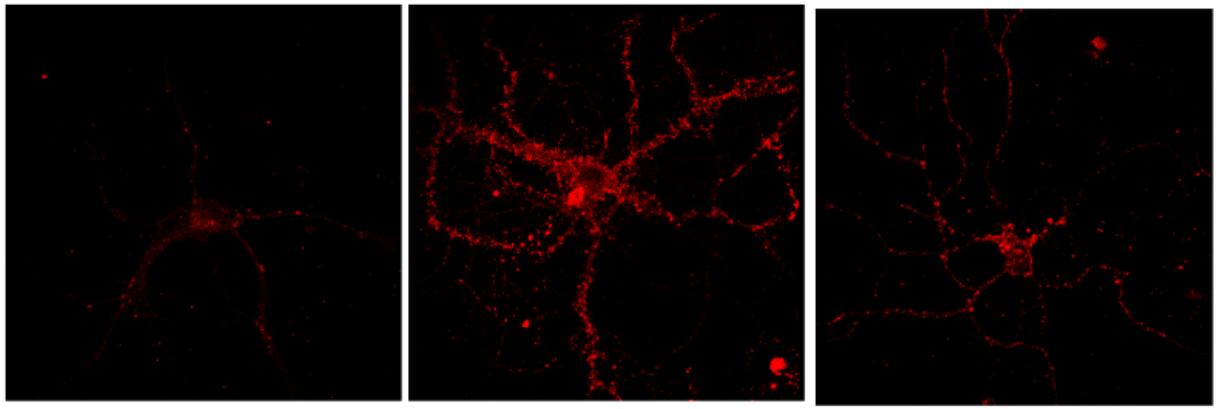
CM | Aβ | Aβ + LM11A-31

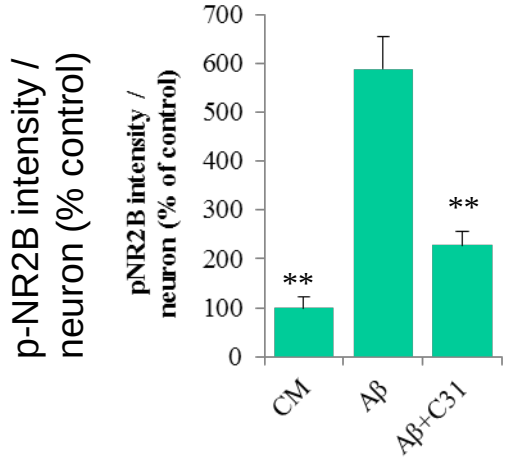




p-NR2B:

CM | Aβ | Aβ + LM11A-31

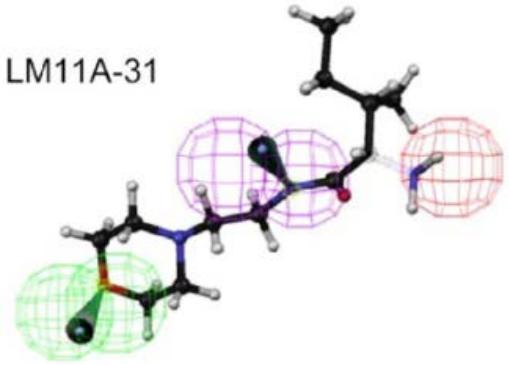




LTP/behavior ?

Yang, Longo SNS 2014

In vivo Studies

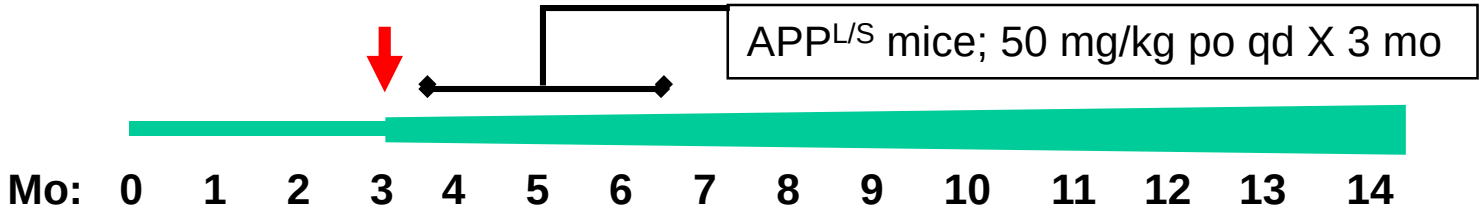


Orally bioavailable CNS
Water soluble, stable
Brain/plasma > 1
Brain T1/2 ~ 1 hr
FDA limit dose 2000 mg/kg non-toxic
AMES / hERG / CYP each clear

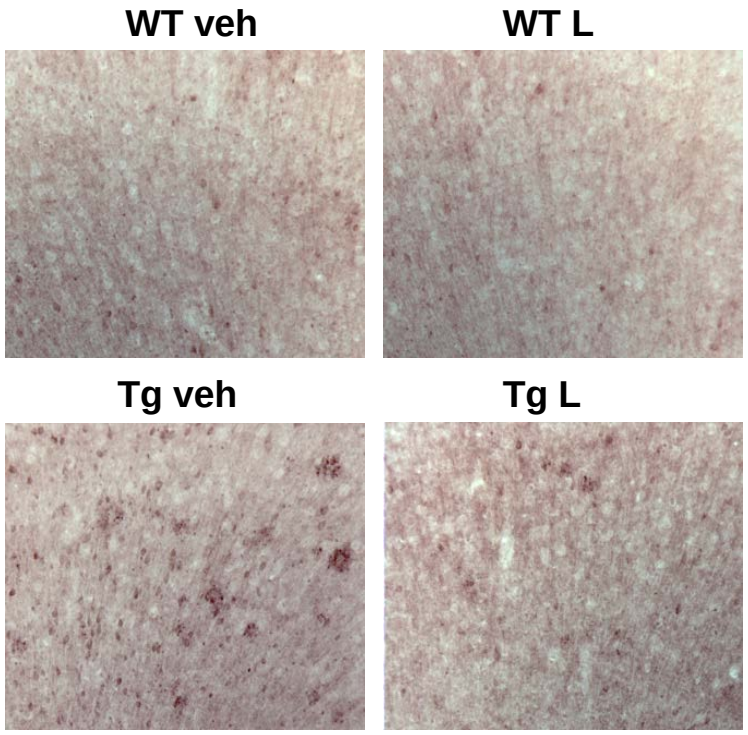
ADMET favorable

CNS target engagement: p75 cleavage

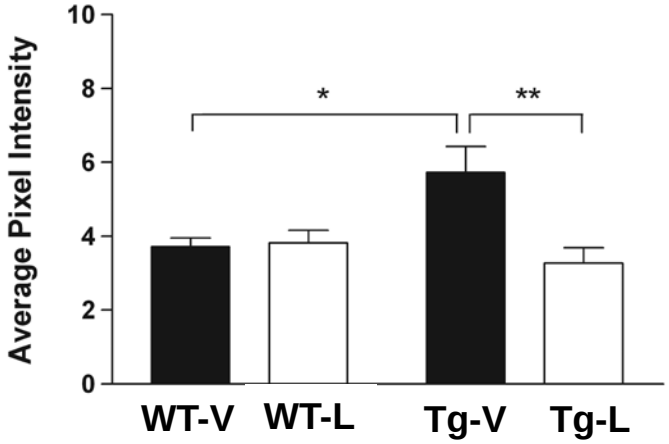
Reduced tau phosphorylation (AT8)



p-tau Ser^{202} (AT8) ctx

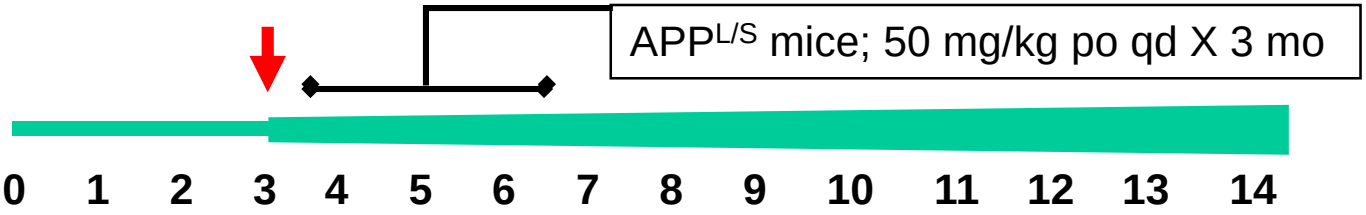


Intraneuronal p-tau

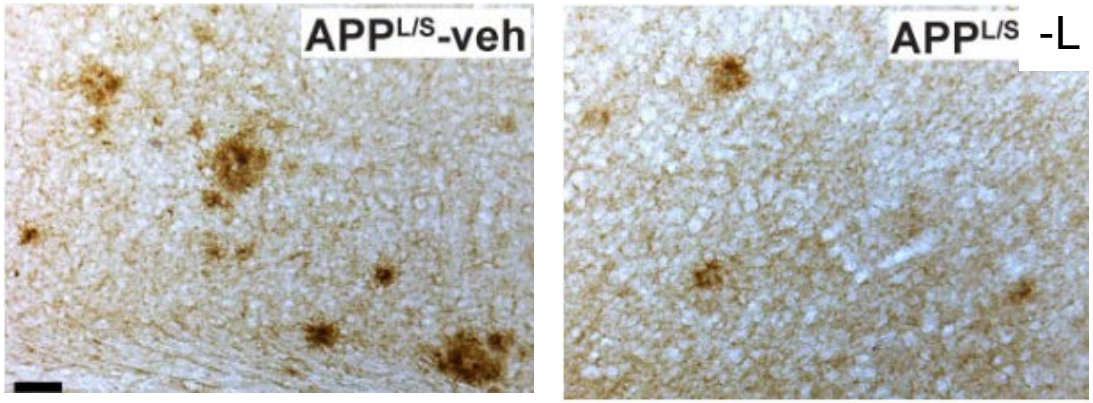


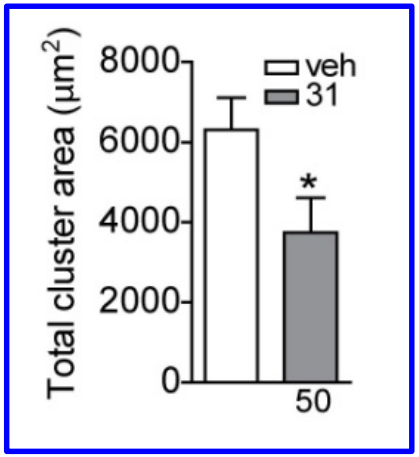
Nguyen et al, *JAD* 2014

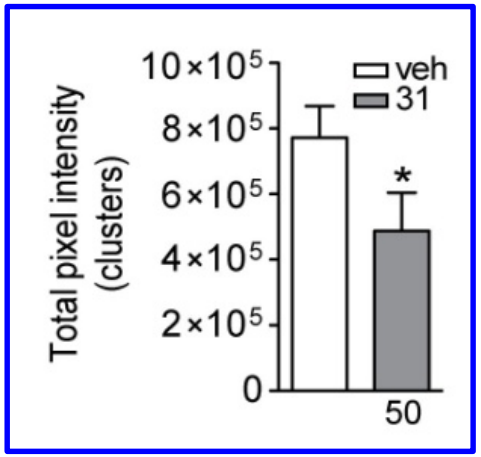
Reduced tau aberrant folding (MC-1)



ctx:

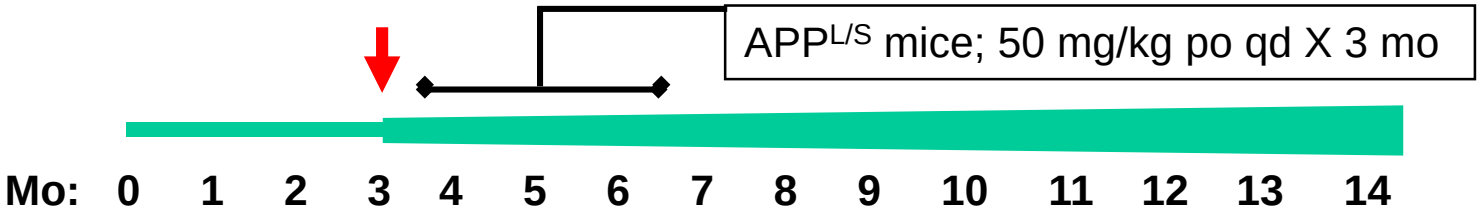


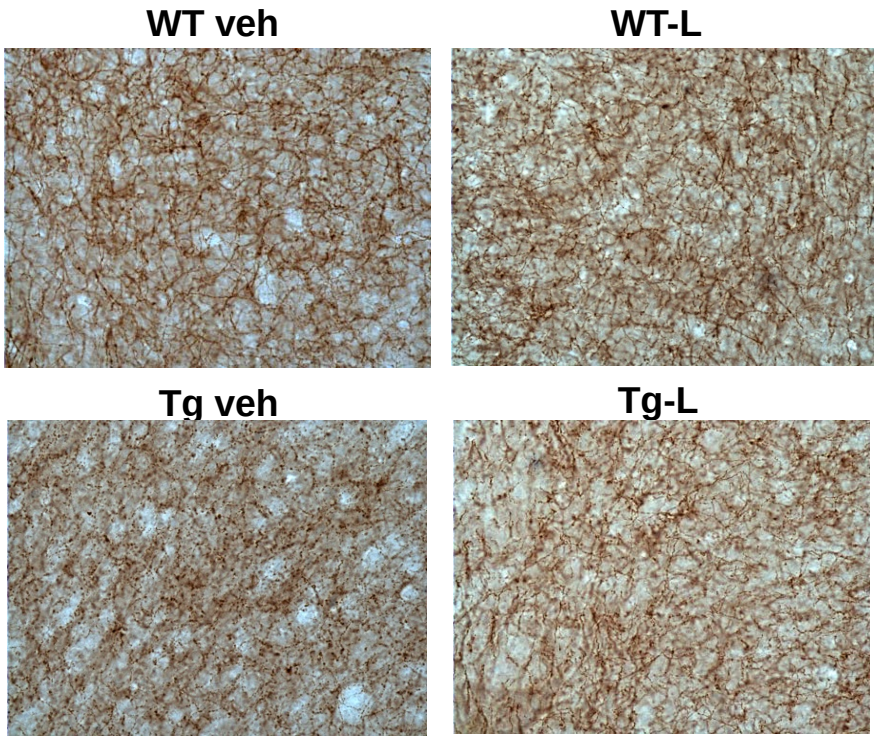


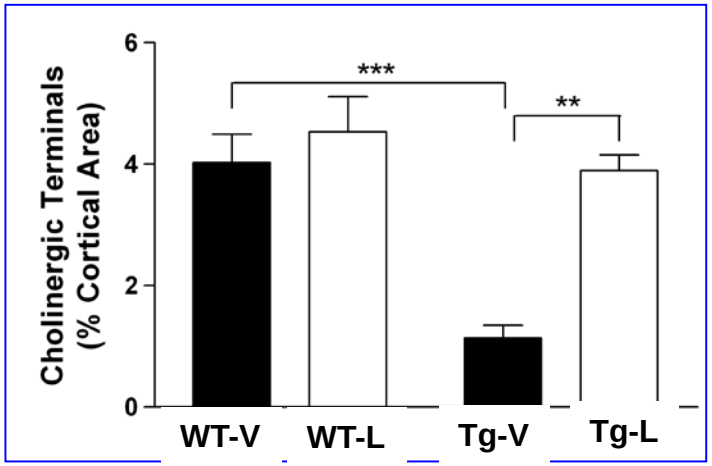


Nguyen et al *JAD* 2014

Reduction of cortex ChAT neurite loss

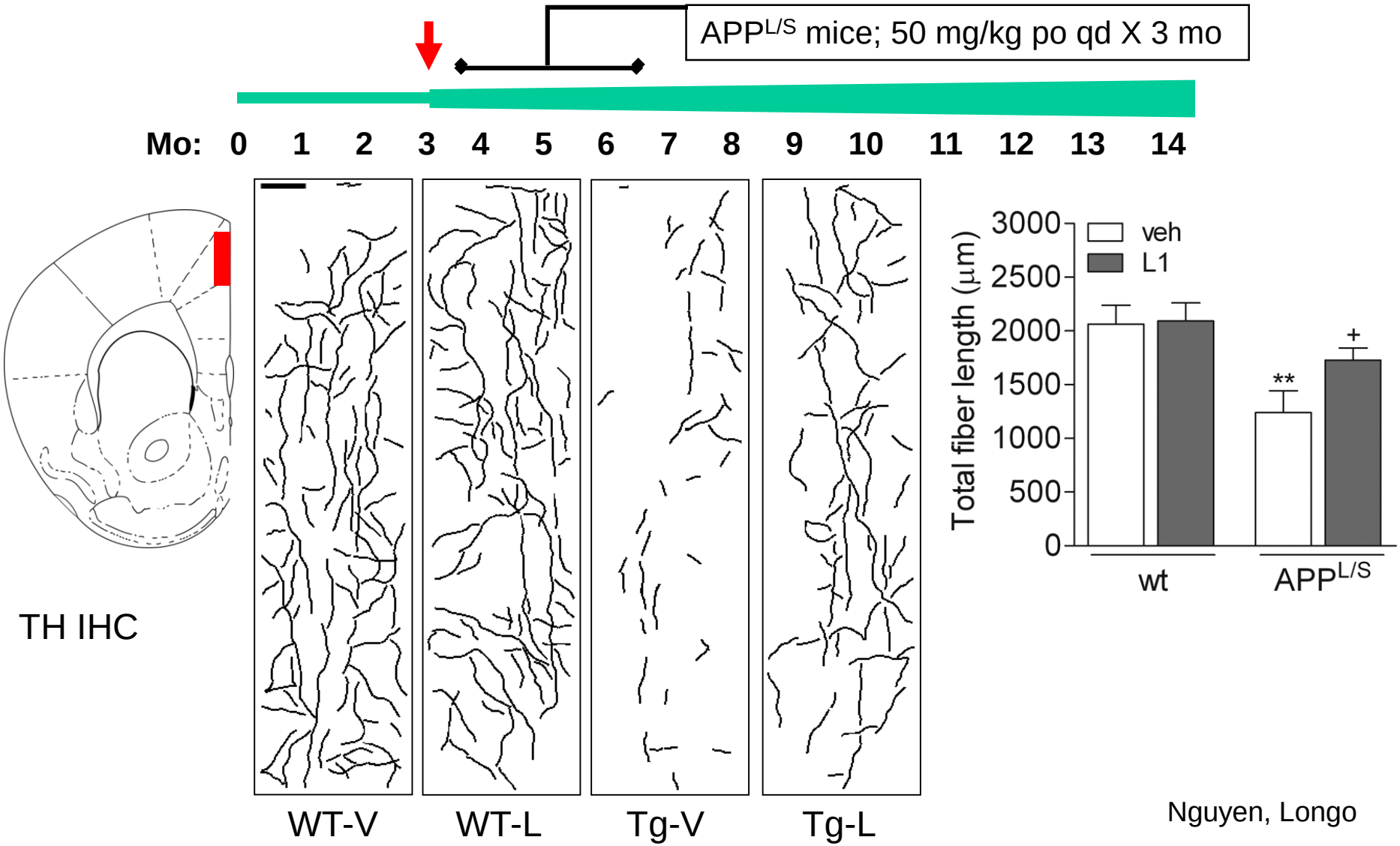






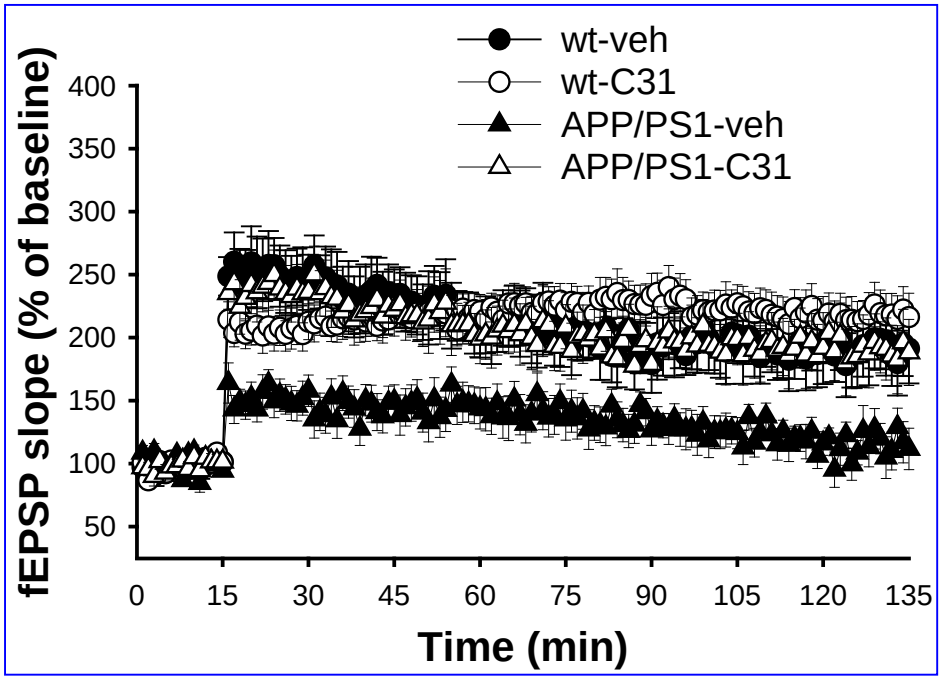
Nguyen et al *JAD* 2014

Reduced loss of LC noradrenergic projection fibers to prefrontal ctx



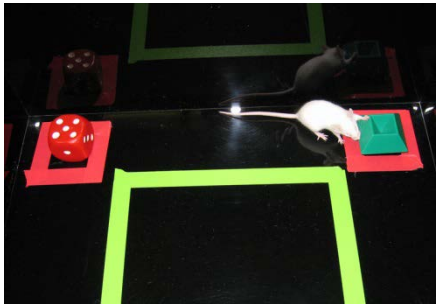
Nguyen, Longo

p75^{NTR} ligands: LTP and behavior

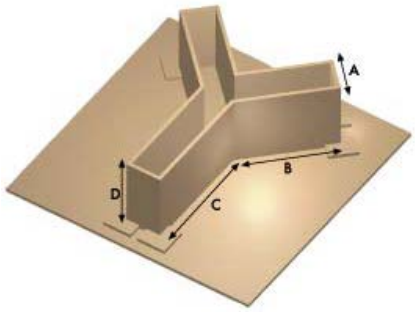


Ottavio Arancio Lab, Columbia
HC slice preparations

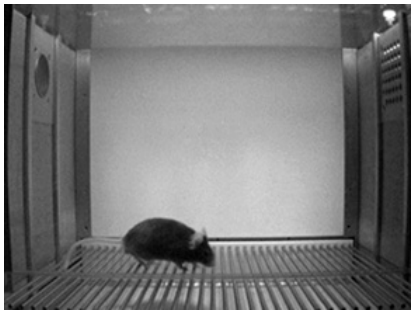
APP-L/S mice 3 mo rx:



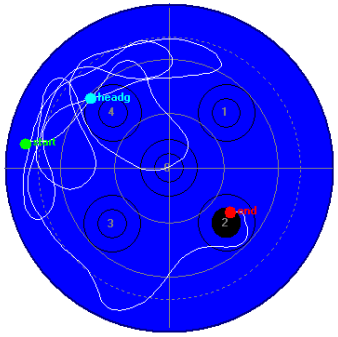
NOR



Y-maze



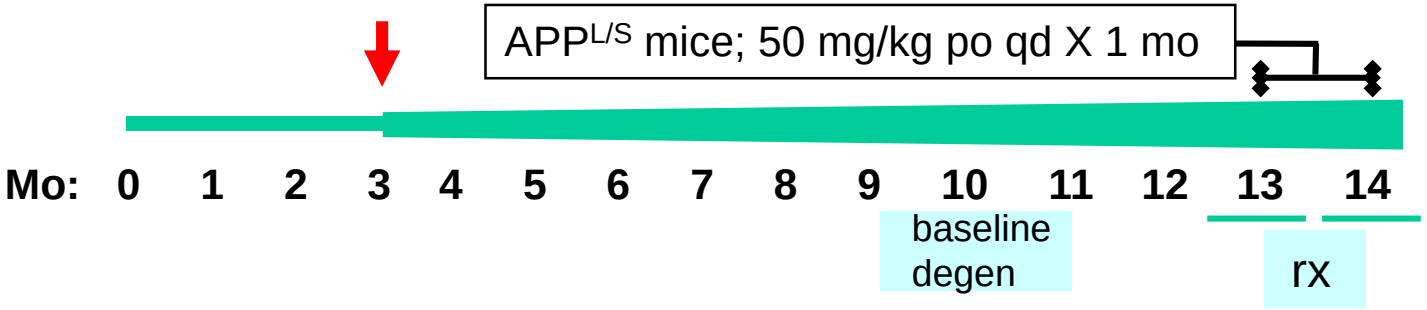
CFC

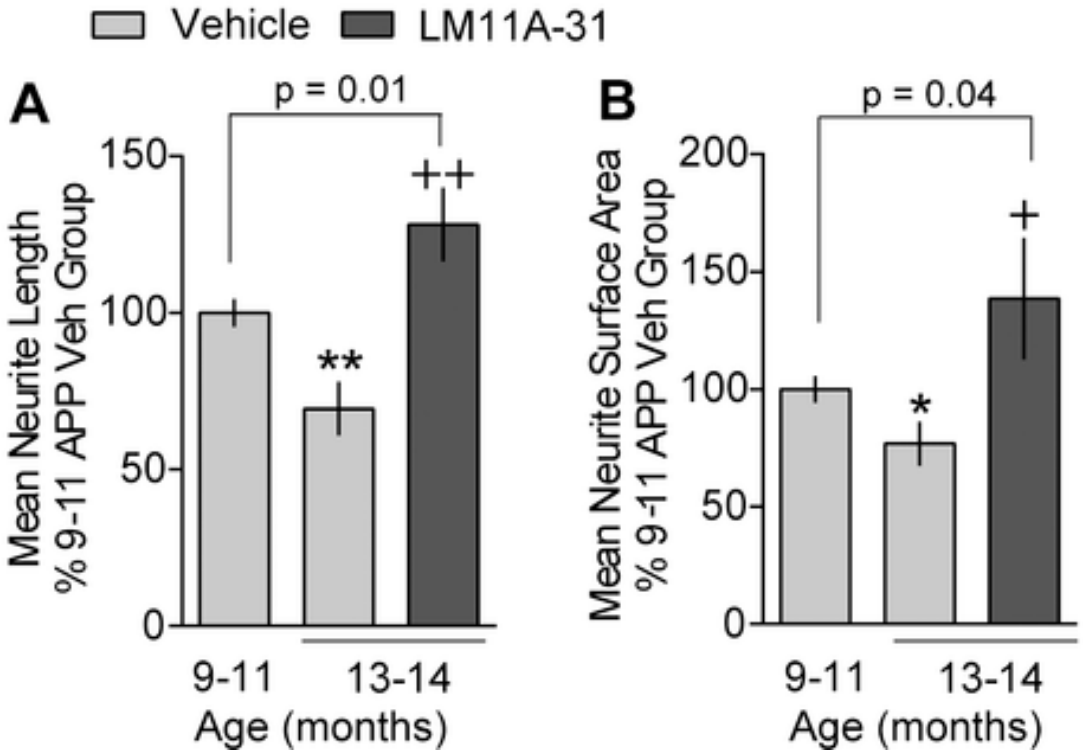


DMP-MWM

Knowles et al *Neurobiol Aging* 2013
Nguyen et al *JAD* 2014

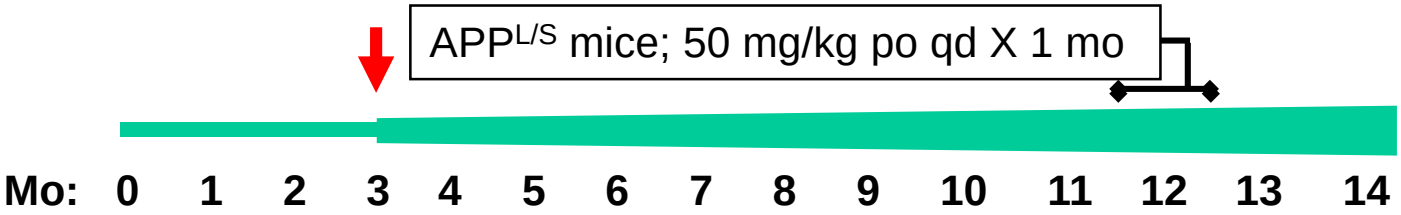
Late stage reversal of BF neurite degeneration



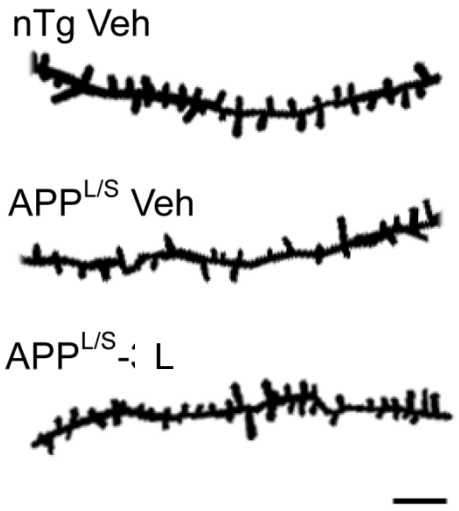


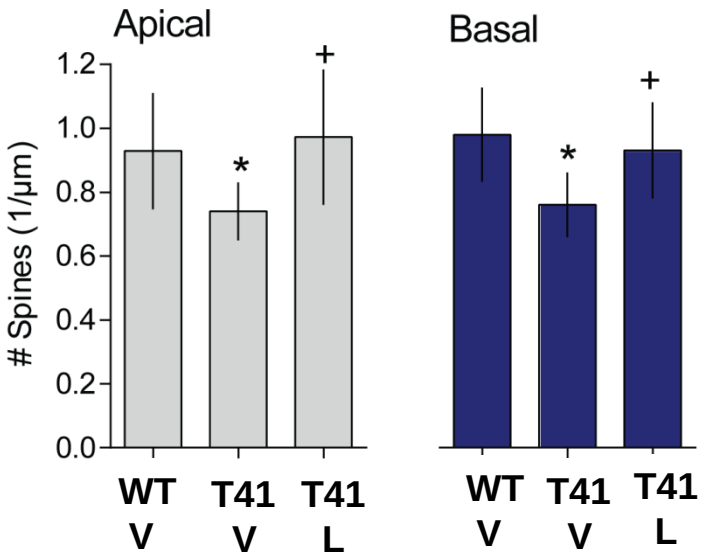
Simmons et al *PLoS One* 2014

Spines: late stage rx with $p75^{NTR}$ ligands



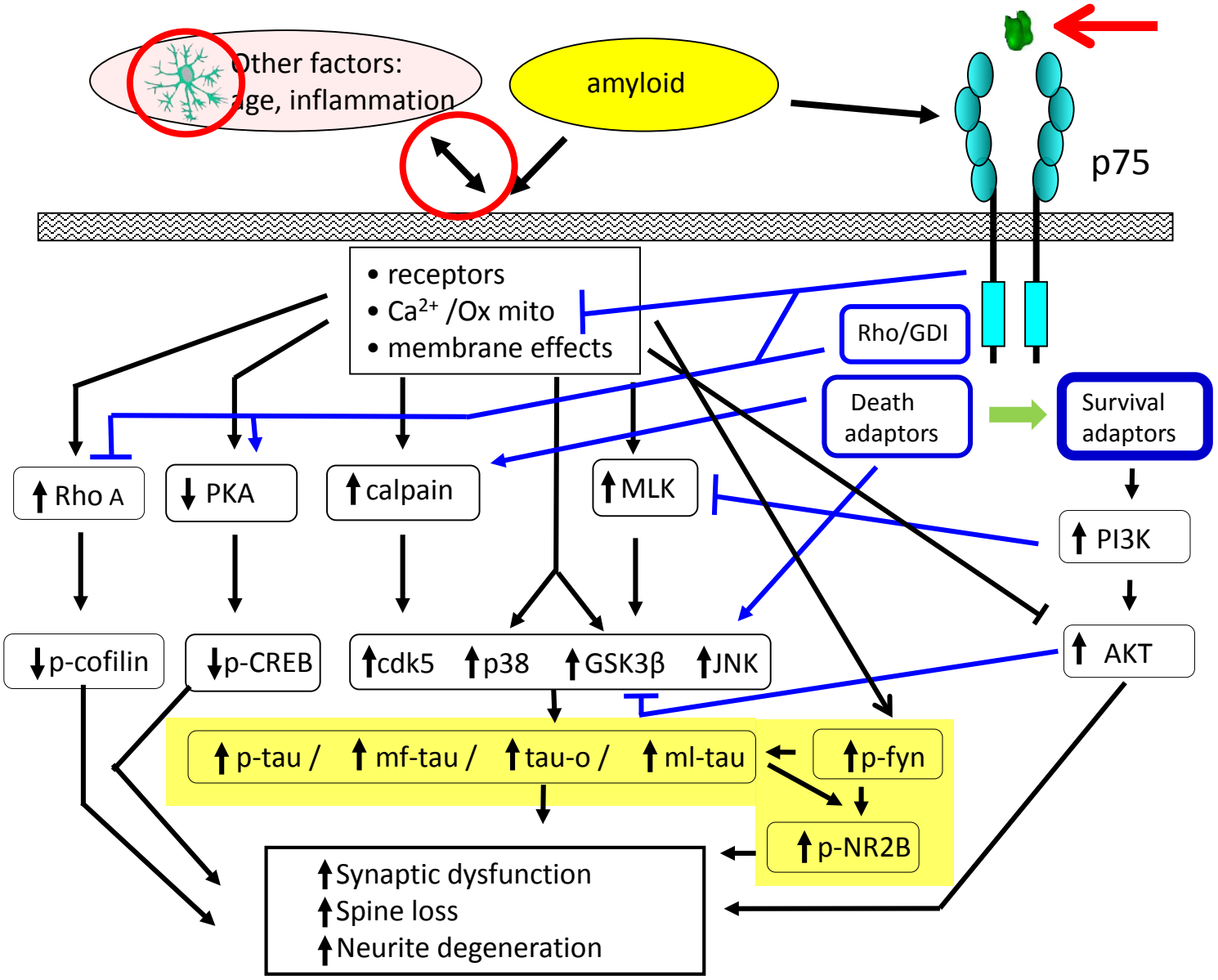
Golgi staining
HC pyramidal



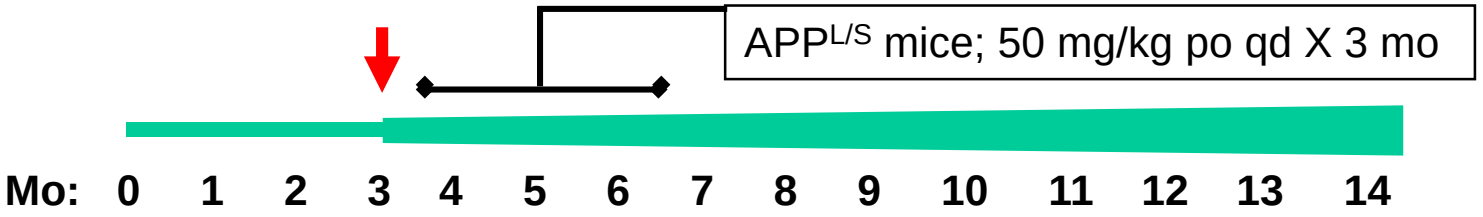


Simmons, Longo

Microglial activation?

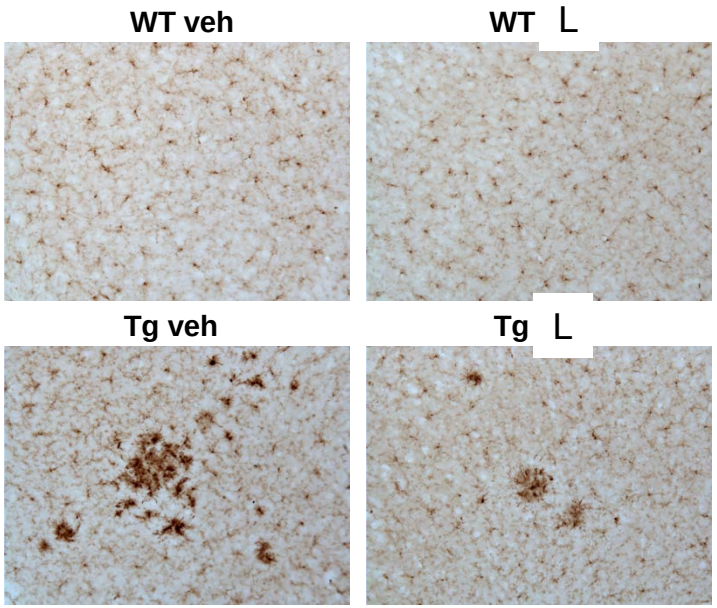


Reduction of microglial activation

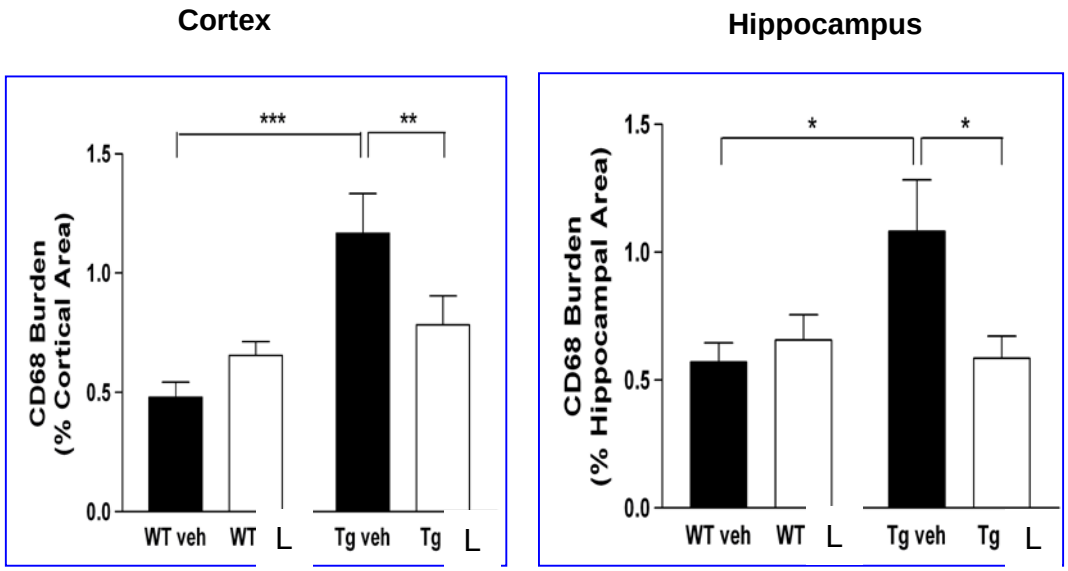


Aberrantly folded tau – MG activation

Zilka et al J Neuroinflammation, 2012



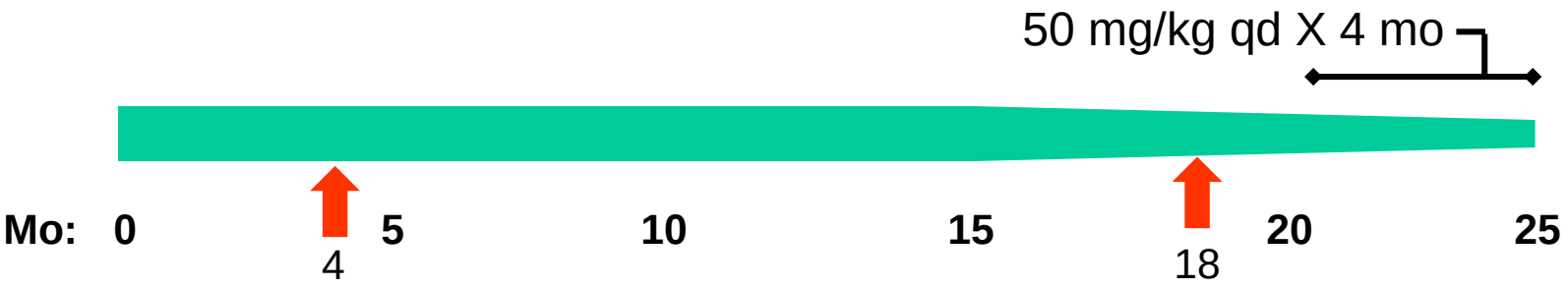
CD68 IHC



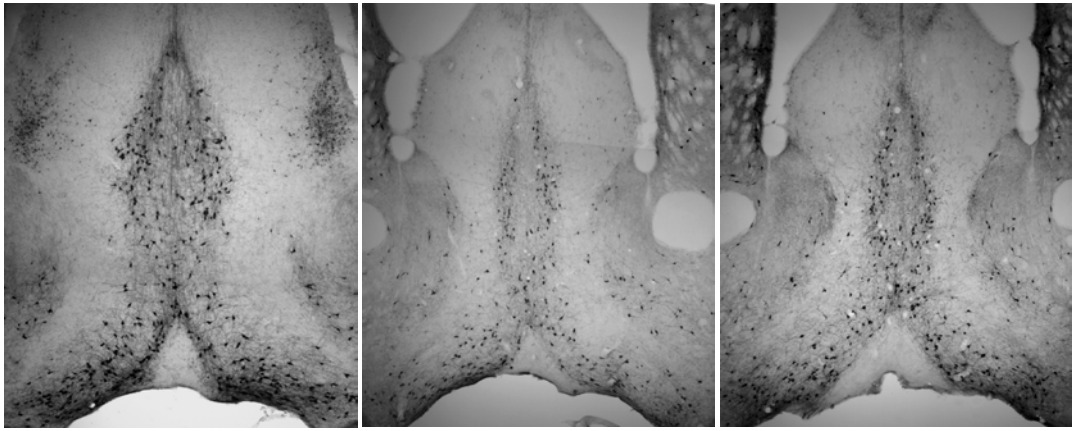
PET imaging ?

Nguyen et al *JAD* 2014

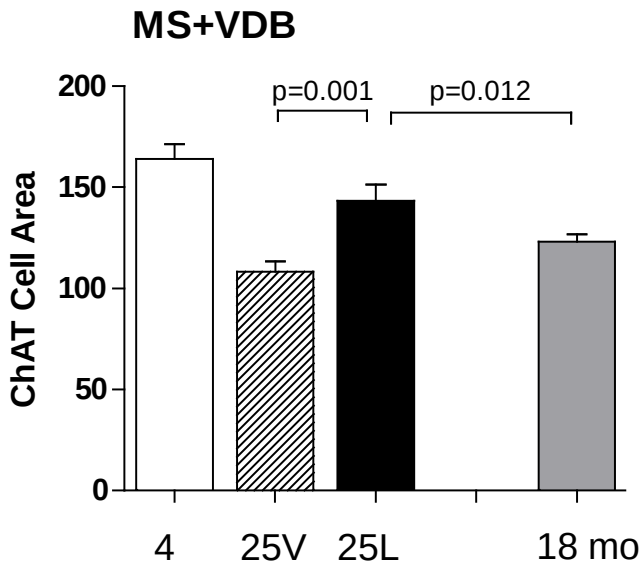
Aged WT mice: reversal of BFCN atrophy



ChAT IHC



4 mo 25 mo V 25 mo L



Xie, Meeker, Longo
UNC-CH

Challenge of mouse to human prediction

Our strategies:

- Many ‘AD-relevant’ mechanisms
- Many *in vivo* endpoints: morphology, behavior
- Multiple ‘AD’ models:
  - APP-L/S (morphology, behavior, mechanisms)
  - Ts65Dn (morphology, behavior)
  - Tg2576 (morphology)
  - PS1-APP(LTP)
- Effects in aged wild-type mice
- Reversal of late-stage effects
- Translatable biomarkers: PET

5 models

Phase 1: LM11A-31-M
Safety and Pharmacokinetics

Single ascending dose (SAD), 6 cohorts:
- Young subjects: D1-4 dose ascending
- Elderly: D4 (fasted and non-fasted)

48 subjects
(36 drug / 12 placebo)

Multiple ascending dose (MAD – 10 days), 2 cohorts:
- Elderly D5 2x/day
- Elderly D6 1x/day

20 subjects
(16 drug / 4 placebo)

No serious Adverse Events (AEs)

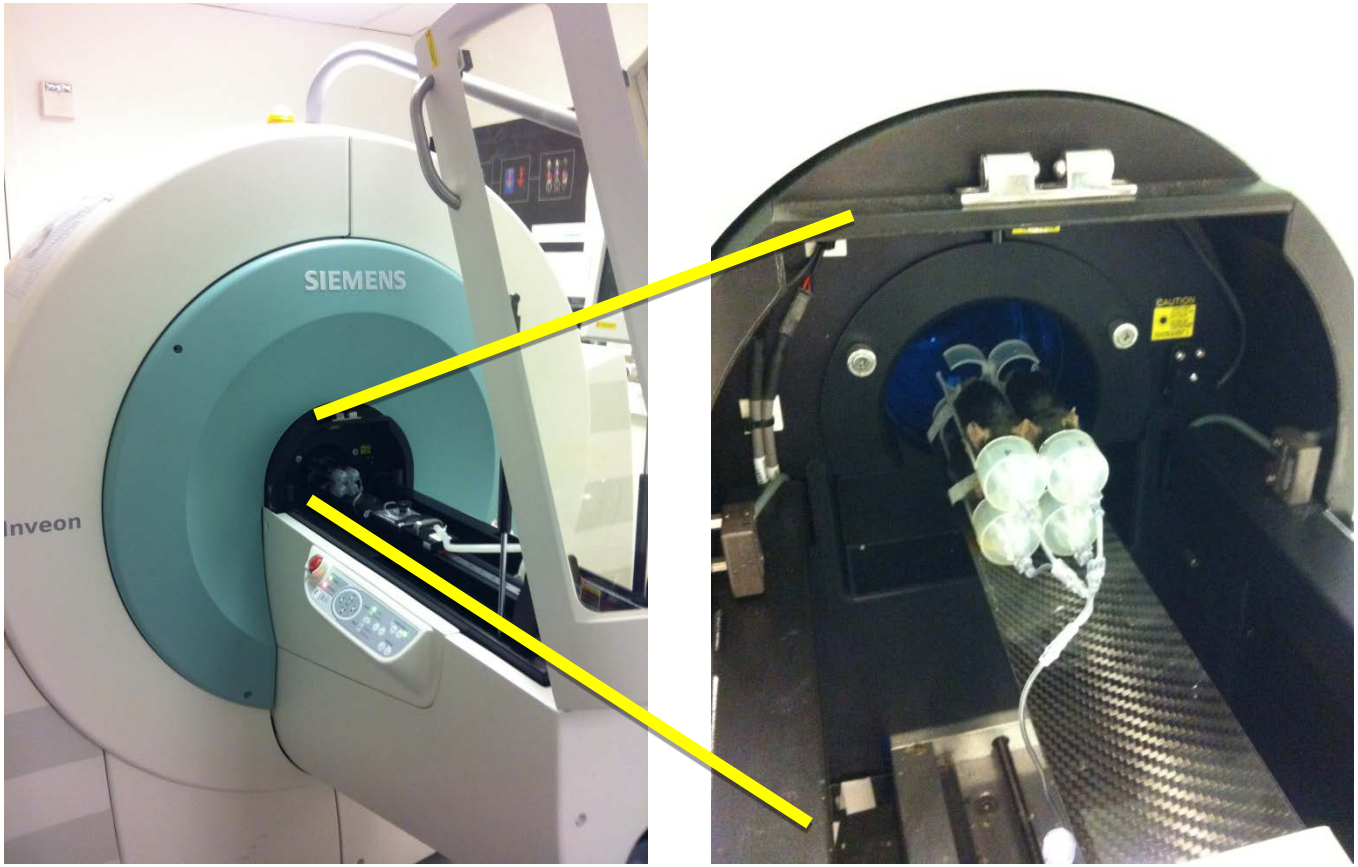
Total: 68 subjects
(52 drug / 16 placebo)

LM11A-31-M is safe and well tolerated in the target elderly population

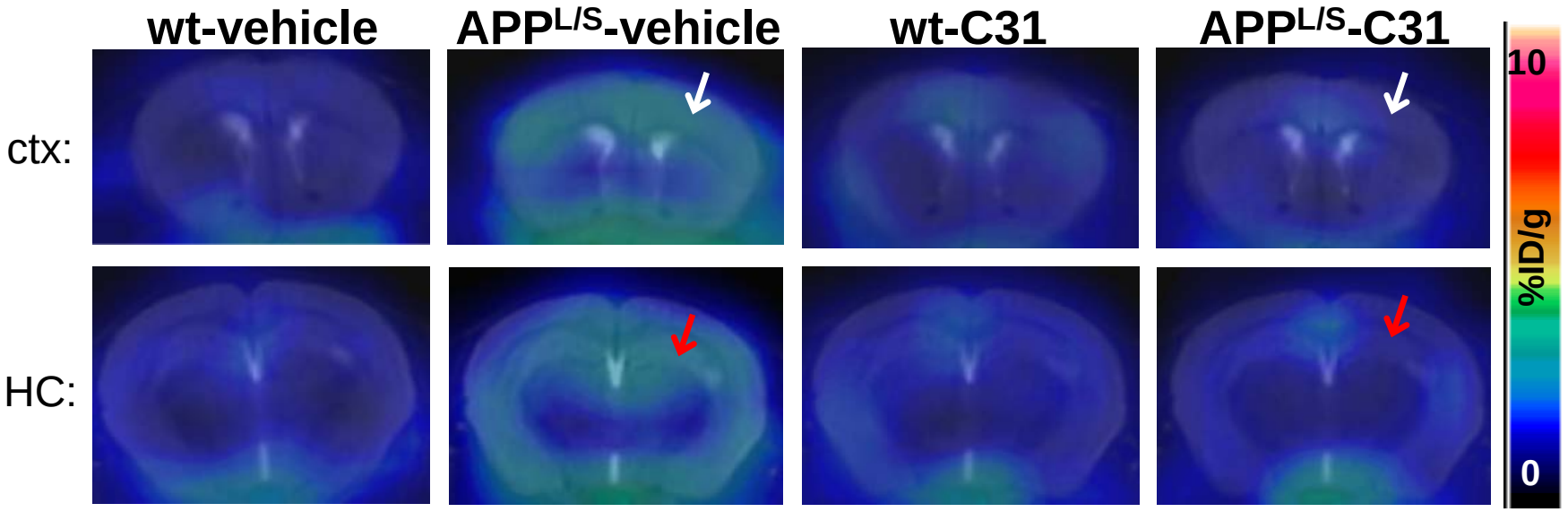
PharmatrophiX

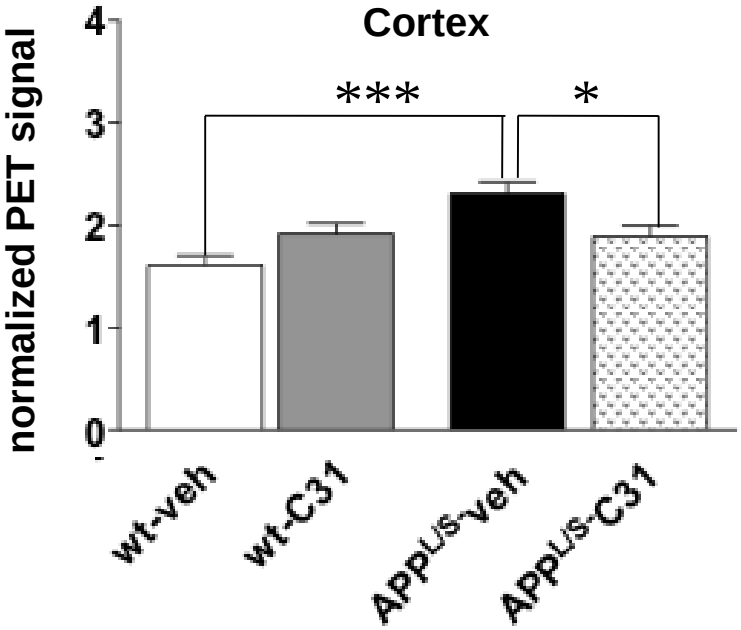
PET/MRI Imaging TSPO ligand: GE-180

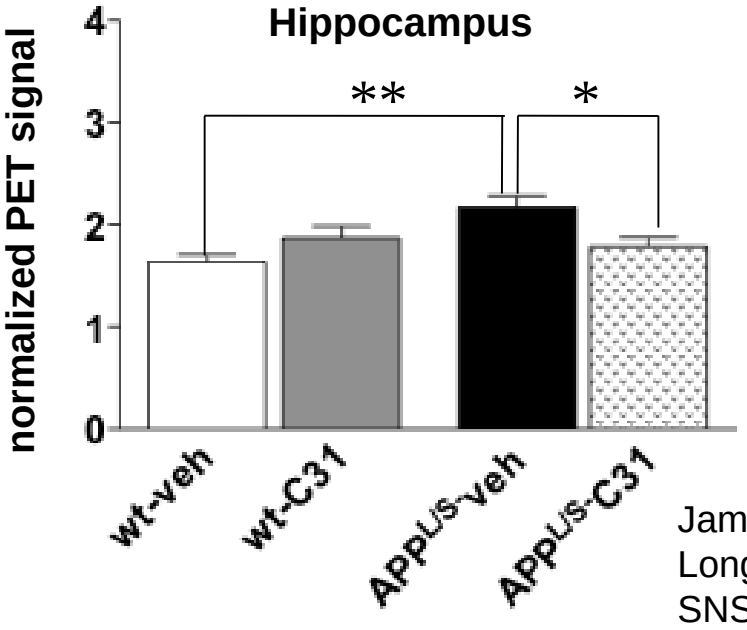
Michelle James & Sam Gambhir, Stanford



GE-180 PET: APP-L/S mice; 3 mo rx (start 5.5-7 mo)







James et al
Longo-Gambhir
SNS 2014

Next: Phase 2a study in mild AD - 2016

- Exploratory endpoint
- 6 mo rx
- Biomarkers: FDG-PET, MRI
  CSF p-tau/tau, Aβ, choline acetyltransferase activity
- Clinical measures: ADAS-Cog-14, NPI, Cogstate