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Attacking Neurodegeneration at its Roots

QR Pharma Inc.

QR Pharma is developing novel drugs for the treatment of neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative conditions

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Challenge of Targeting One Protein

Drug	Class	Company	Phase	Status
AAB-001	*A-beta antibody*	*JNJ/Wyeth/Elan*	*III*	***Failed***
Solanuzumab	*A-beta antibody*	*Eli Lilly*	*III*	***Failed***
LY 450139	*G-secretase inhibitor*	*Eli Lilly*	*III*	***Failed***
BMS 708163	*G-secretase inhibitor*	*Bristol Myers*	*II*	***Failed***
Gammagard	*A-beta antibody*	*Baxter*	*II*	***Failed***
ELND 005	*Ab aggregation inhibitor*	*Elan/Transition*	*II*	***Failed***
Solanuzumab	*A-beta antibody, early*	*Eli Lilly*	*III*	***Failed***
Verubecestat	*B-secretase inhibitor*	*Merck*	*II/III*	***Failed***
Verubecestat	*B-secretase inhibitor, very early*	*Merck*	*III*	***Failed***
Solanuzumab	A-beta antibody, very early	Eli Lilly	III	**May Fail**
Amaranth	B-secretase inhibitor	AstraZeneca/Lilly	III	**May Fail**
Mission AD1	B-secretase inhibitor	Biogen/Esai	III	**May Fail**
CNP520	B-secretase inhibitor	Amgen/Novartis	III	**May Fail**
Aducanumab	A-beta antibody, early	Biogen	III	**May Fail**
Crenezumab	A-beta antibody, early	Genentech/Roche	III	**May Fail**
various	A-beta, tau, other	many	I or preclin	

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The Problem with Neurodegeneration

All disease modifying studies in Alzheimer's and Parkinson's disease to date have failed

WHY?

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End vs. Beginning of Neurodegeneration

In 1906 Alois Alzheimer looked at the brain of a patient that had died with dementia and characterized Alzheimer's disease as

- Plaques
- Tangles
- Brain shrinkage

Today we still define it as plaques, tangles and brain shrinkage

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The Problem with Abeta

Nobody doubts that Abeta is toxic

Why does removing Abeta not result in a solid increase in cognition?

Because the interventions we have studied are

- too little
- too late

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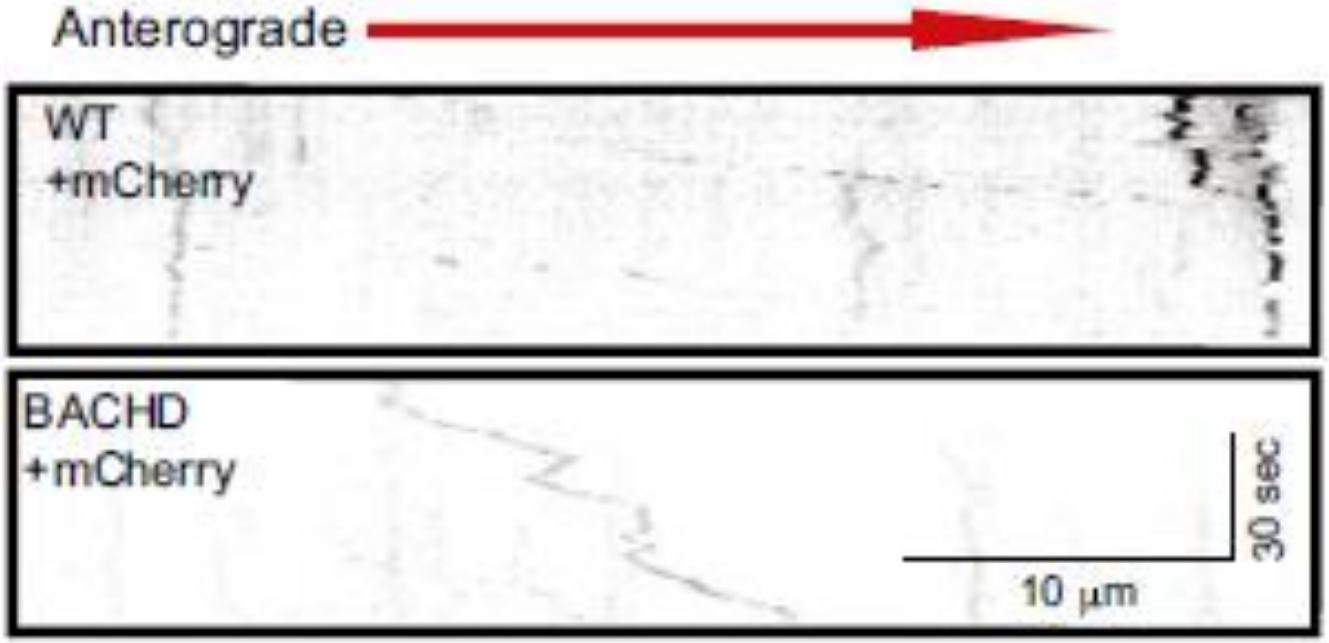
Where Does Neurodegeneration Start?

Neurodegeneration is an axonal transport disease

Anterograde Transport in WT and HD Cells



BACHD mouse has a bacterial artificial chromosome expressing full-length human HTT. The mice exhibit progressive motor deficits and late-onset selective neurodegeneration in cortex and striatum

Shown are kympgraphs of BDNF anterograde transport in the axons of cortical neurons expressing mCherry

Mobley Lab – UCSD, CA; TriC subunits enhance BDNF axonal transport and rescue striatal atrophy in Huntington's disease ; PNAS 2016,1073: 5455

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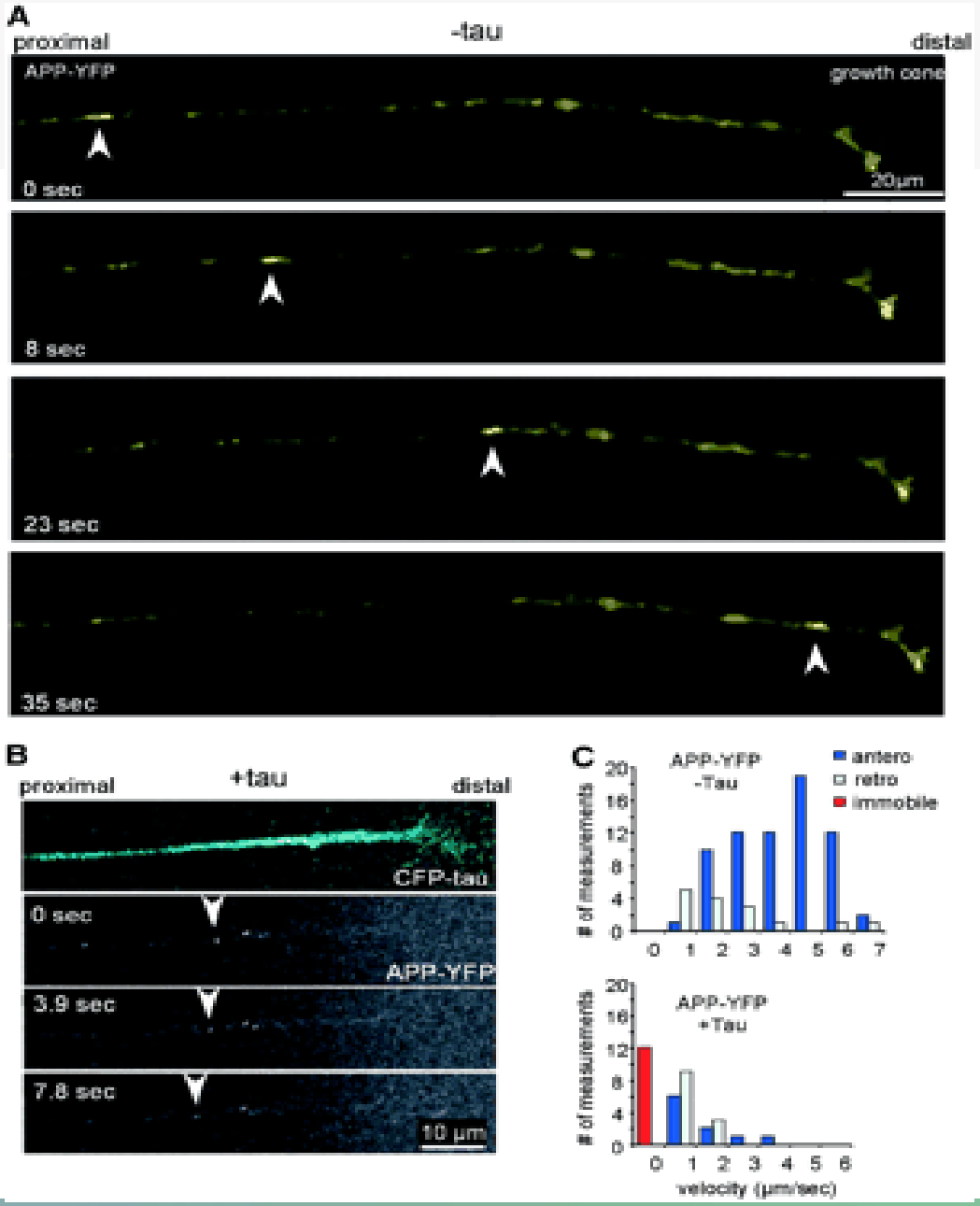
Anterograde and Retrograde Transport of APP -/+ Tau



Time-lapse imaging of APP transport in cultured chick retinal ganglion neurons and inhibition by tau. After transfection with tau, very few vesicles move, many are immobile (red bar), and slow speeds predominate in both directions.

Mandelkow Lab – Max Planck, Hamburg; Tau blocks traffic of organelles, neurofilaments, and APP vesicles; JBC, 2002, 156 (6): 1051

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Neurotoxic Aggregating Proteins that Impair Axonal Transport

- APP, Ab42, C99 – **Mobley**, UCSD;
- Ab42 - **Brady**, NYU Medical Center
- aSYN – **Isacson**, Harvard; **Lee**, U. Penn; **Liang**, U. Montana
- Htt – **Mobley**, UCSD; Buss, U. Cambridge
- Prions – **Sakaguchi**, Tokushima U.
- SOD1 – **Song**, Harvard Medical School; **Horne**, U. Melbourne
- Tau – **Mandelkow**, Hamburg; **Hung**, U. Cambridge; **Berger**, U. Vermont
- TDP43 – **Taylor**, Northwestern

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High Levels of Neurotoxic Aggregating Proteins….

- Cause disturbances in vesicle maturation and transport
- Impair synaptic transmission
  - Lower release of neurotransmitters
  - Lower neurotrophic factor levels
- Cause inflammation
- Eventually kill nerve cells

Evolving Understanding of Neurogenerative Diseases Demands Multi-target Intervention

Disease	Old Knowledge	New Knowledge
AD	Aβ, tau	Aβ, tau, aSYN, prions
PD	aSYN	aSYN, Aβ, tau, prions
DS	Aβ, tau	Aβ, tau, SOD, prions
CJD	Prions	Prions, Aβ
ALS	SOD	SOD, TDP43
HD	Htt	Htt, Aβ, tau
many	tau	present in most neurodegenerative disorders

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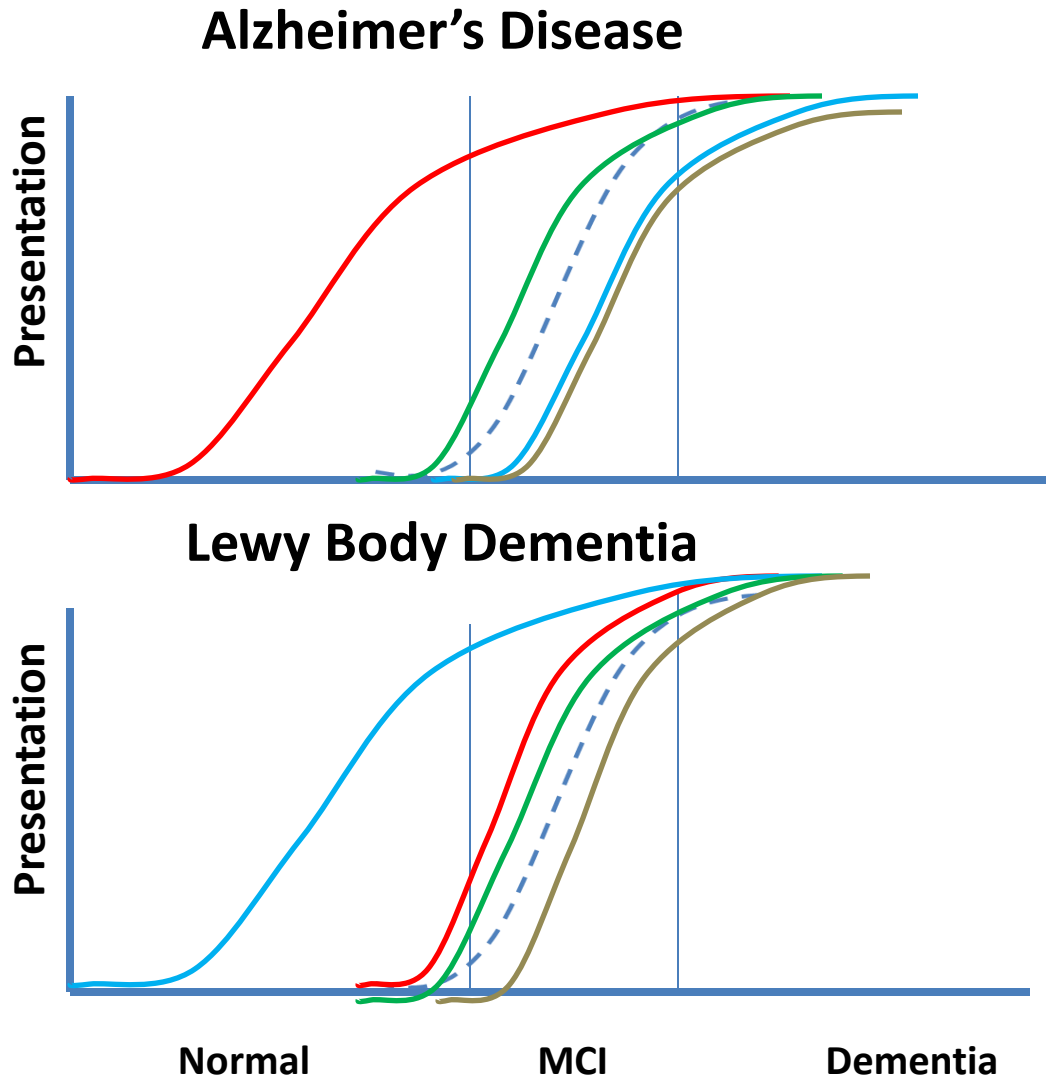
Biomarkers and Disease Progression



Several neurotoxic proteins accumulate at different times during each disease progression

Aβ
Tau
aSyn
Prion

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What Constitutes an Effective Drug?

To show efficacy

an effective drug needs to normalize:

levels of neurotoxic aggregating proteins
leading to normal axonal transport

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AD/PD Require a New Approach

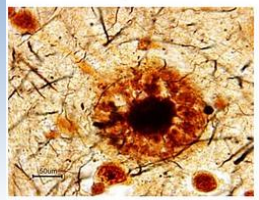
Brain insults lead to neurodegeneration

↓

Increase in aggregating neurotoxic proteins

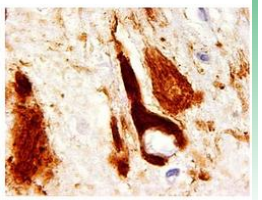
Amyloid β
Alzheimer's
Parkinson's

Aβ Targeting Compounds



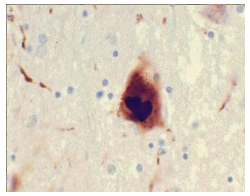
Tau
Tauopathies
Alzheimer's

Tau Targeting Compounds



αSynuclein
Parkinson's
Alzheimer's

PD-specific αSYN Targeting Compounds



Posiphen

Attacking one neurotoxic aggregating protein results in minimal effect;
Posiphen is the only drug to attack multiple neurotoxic proteins

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Commonalities of Neurotoxic Protein Regulation

Neurotoxic aggregating proteins display similar features from gene activation, to protein synthesis to folding, misfolding, toxicity and aggregation:

- Transcription is regulated by Cu/Zn
- **Translation is regulated by Fe**
- At low concentrations they have a normal function
- At high concentrations they form toxic oligomers
- Oligomers can infect other cells in the brain and spread
- They are degraded by the proteasome
- The cell sequesters these toxic oligomers into aggregates to neutralize them

Posiphen Inhibits Translation of Neurotoxic Aggregating Proteins

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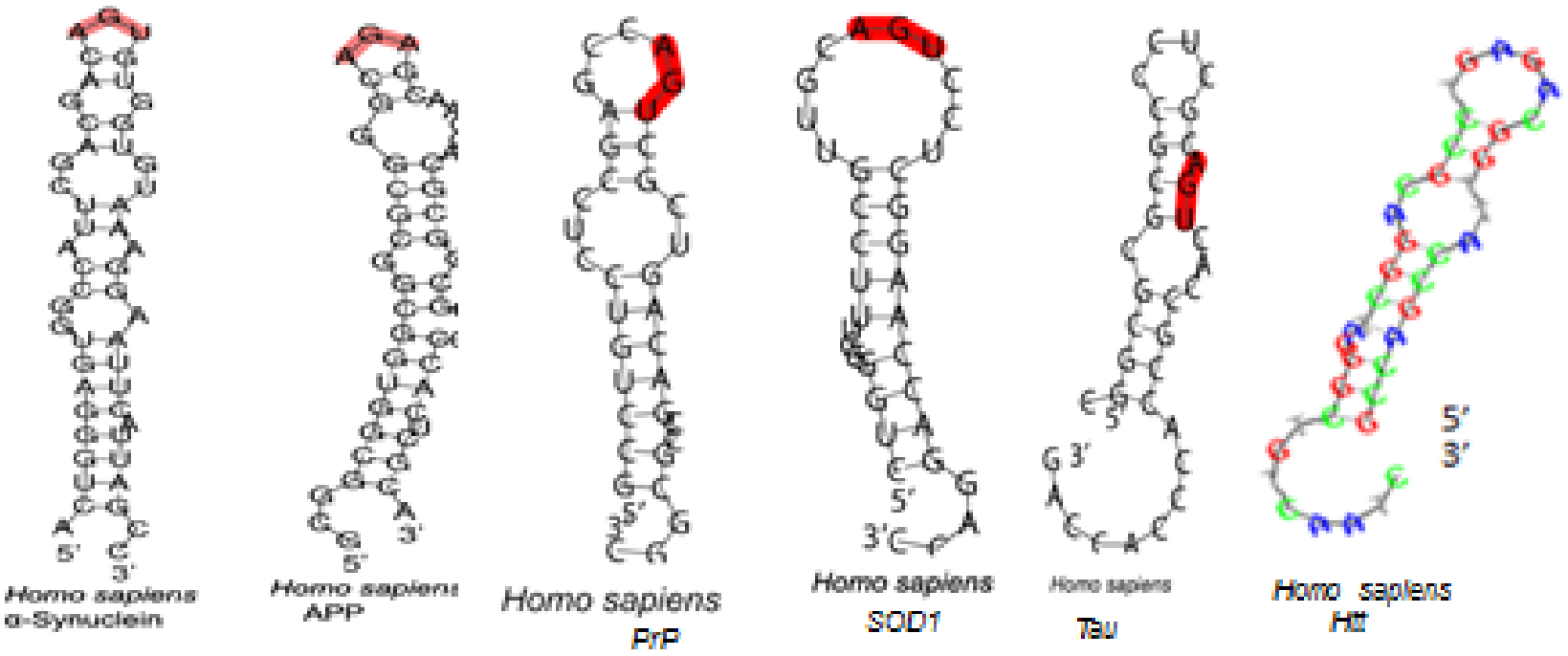
Commonalities in Translational Regulation

mRNAs are always associated with RNA-binding proteins. These proteins influence pre-mRNA processing, transport, localization, translation and stability of mRNAs

Translation of neurotoxic aggregating is regulated by a specific RNA binding protein called iron regulatory protein1 (IRP1)

IRP1 binds the 5'UTR of mRNAs of neurotoxic aggregating proteins

5’ UTR IRE Stem Loop Homology of Neurotoxic Aggregating Protein mRNAs



Highly Preserved Consensus Loop in 5’UTR of Neurotoxic Aggregating Proteins
>50% homology between 5’UTRs of mRNAs

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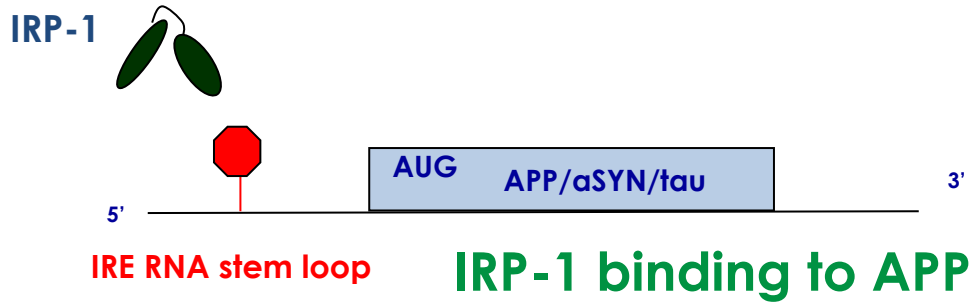
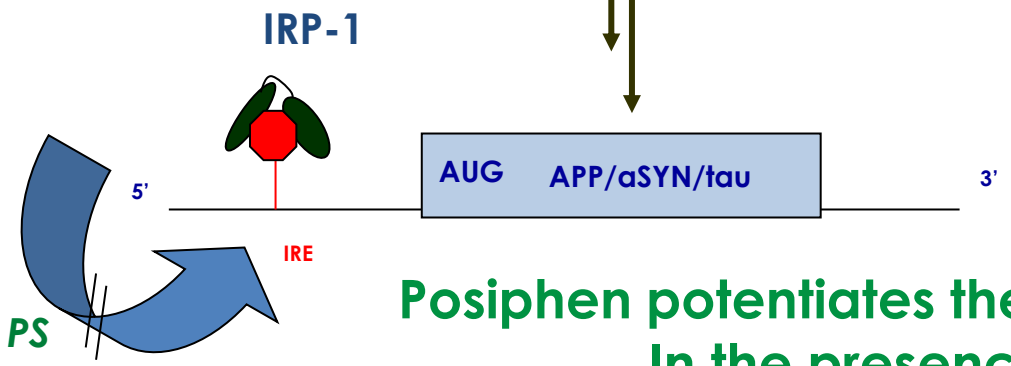
Posiphen Mechanism of Action



IRP-1 binding to APP IRE inhibits APP, tau and aSYN translation

IRE – iron responsive element
IRP – iron binding protein

+ Posiphen (PS)



Posiphen potentiates the binding of IRE to IRP-1 In the presence of high iron
thus further inhibiting translation

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RNA Approaches: mRNA/RBP – antisense RNA - RNAi

Our scientific advisor, Greg Petsko said:

"Posiphen does all the things antisense and RNA interference do, just better and easier"

	Inhibition of Translation	Self - regulation	Manufactu-ring	Stability	Oral Availability	Blood/brain barrier permeability
Drug for mRNA/RBP	yes	yes	easy	very high	yes	yes
RNAi	yes	no	difficult	low	no	no
Antisense RNA	yes	no	difficult	low	no	no

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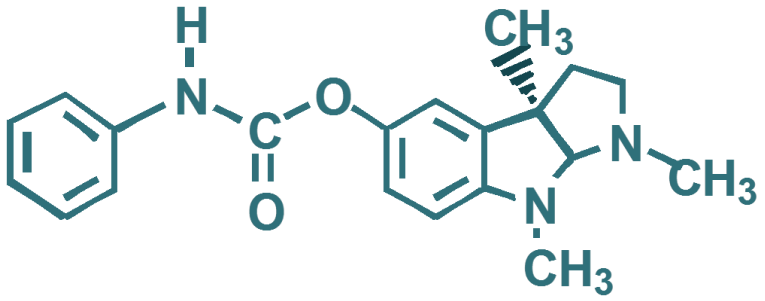
Posiphen is a Compelling NCE

- Orally bioavailable with good blood brain-barrier permeability



- Inhibits several neurotoxic aggregating proteins and protects nerve cells from dying

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Preclinical and Clinical

Pre-clinical:

- Efficacy in AD mouse, PD mouse, TBI rat and glaucoma rat models
- Robust safety data in mice, rats and dogs

Clinical:

- Open IND
- 120 healthy volunteers treated with Posiphen
- PK and MTD established
- **Preliminary proof of concept in 4 MCI patients**
- **Phase II clinical study in early AD patients ongoing**

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Preclinical Data

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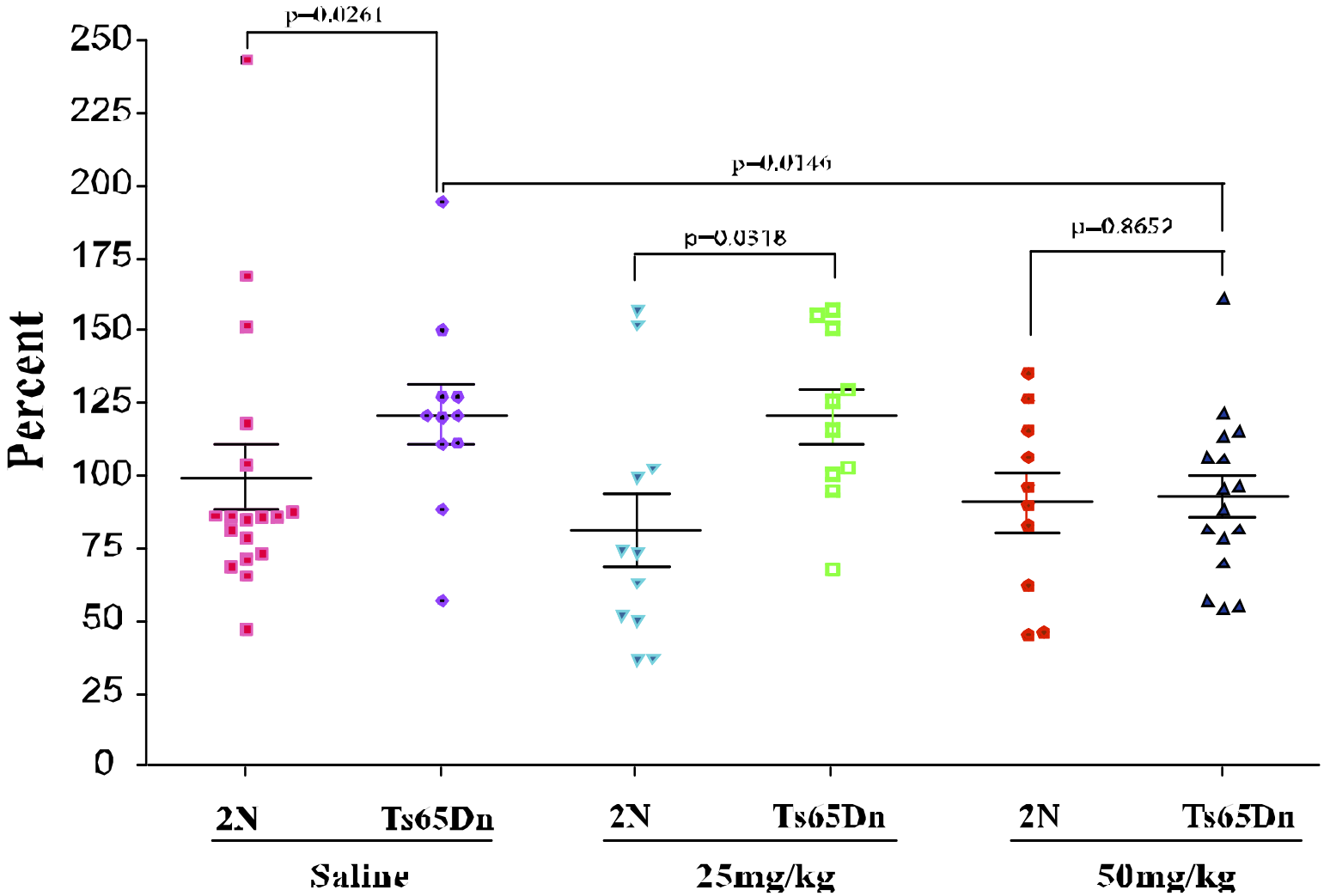
APP Levels in 2N and Ts65Dn Mice: Vehicle vs. Posiphen



1500ng/gm @ 50mg/kg

Salehi et al., 2008

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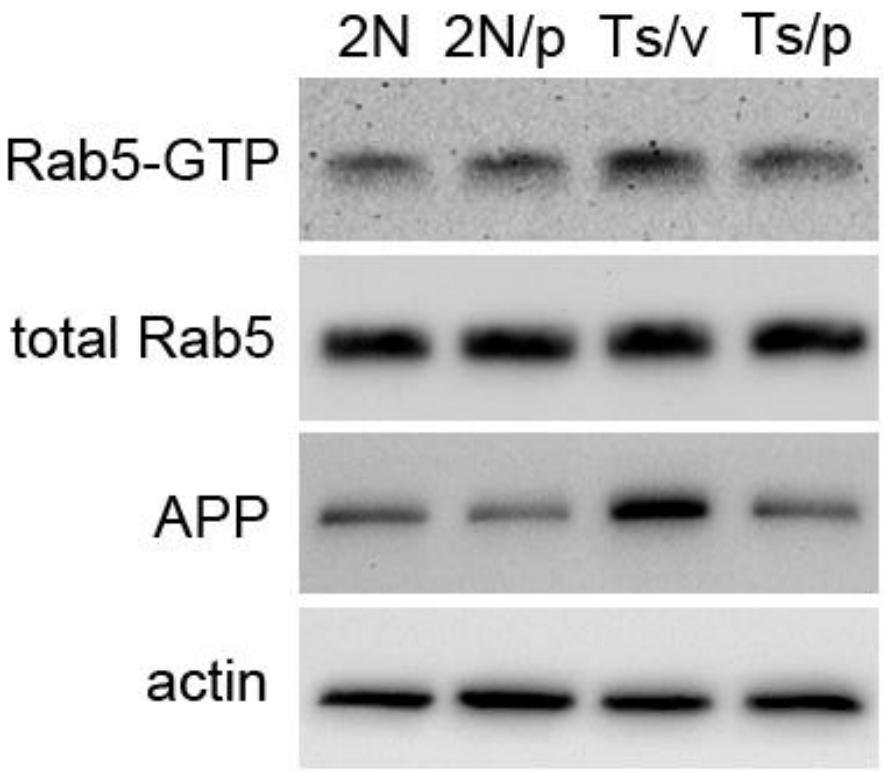
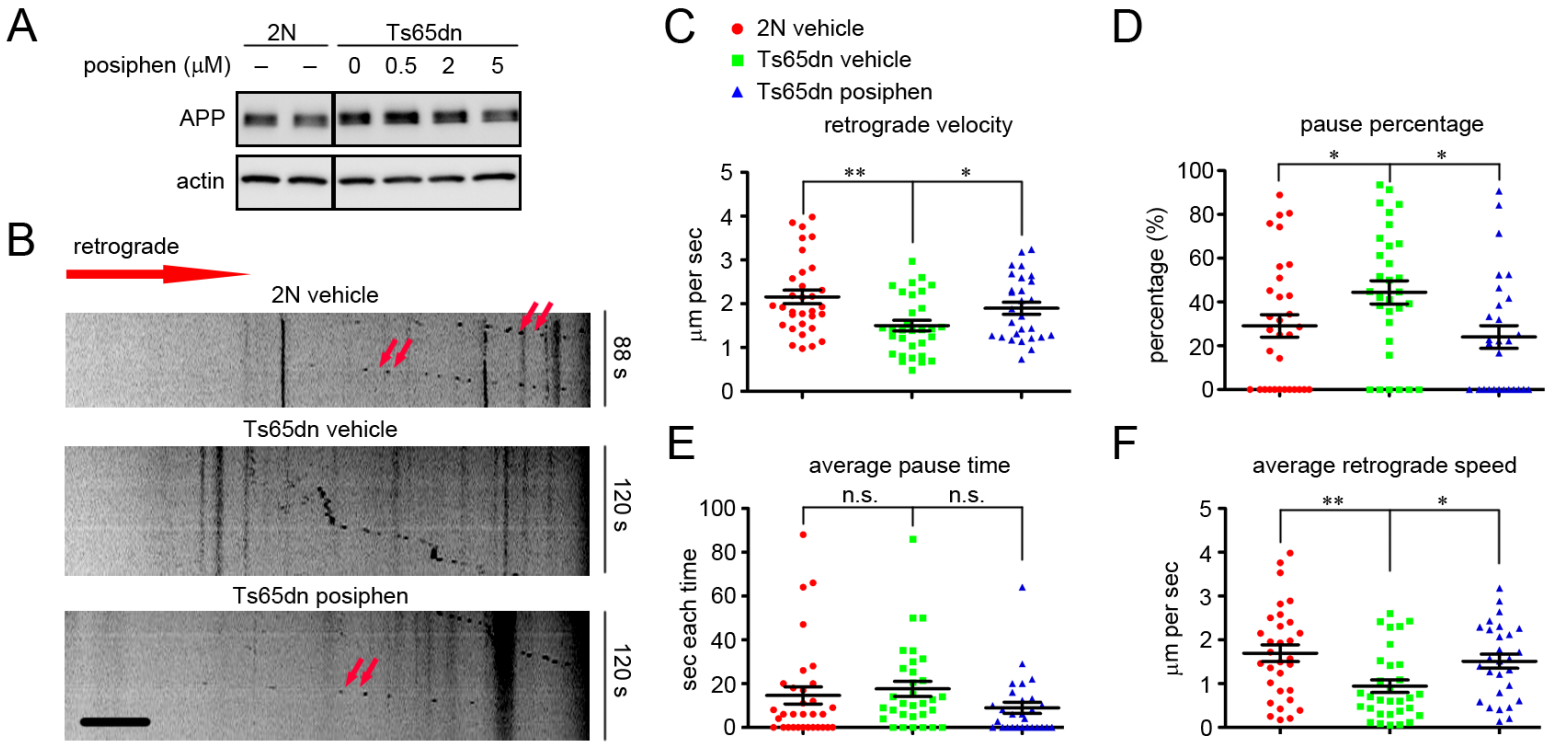
Posiphen Treatment for 48 hrs Reduces APP and Reverses Overactivation of Rab5 in Cortical Ts65DN Neurons



XQ Chen, Mobley Lab, UCSD

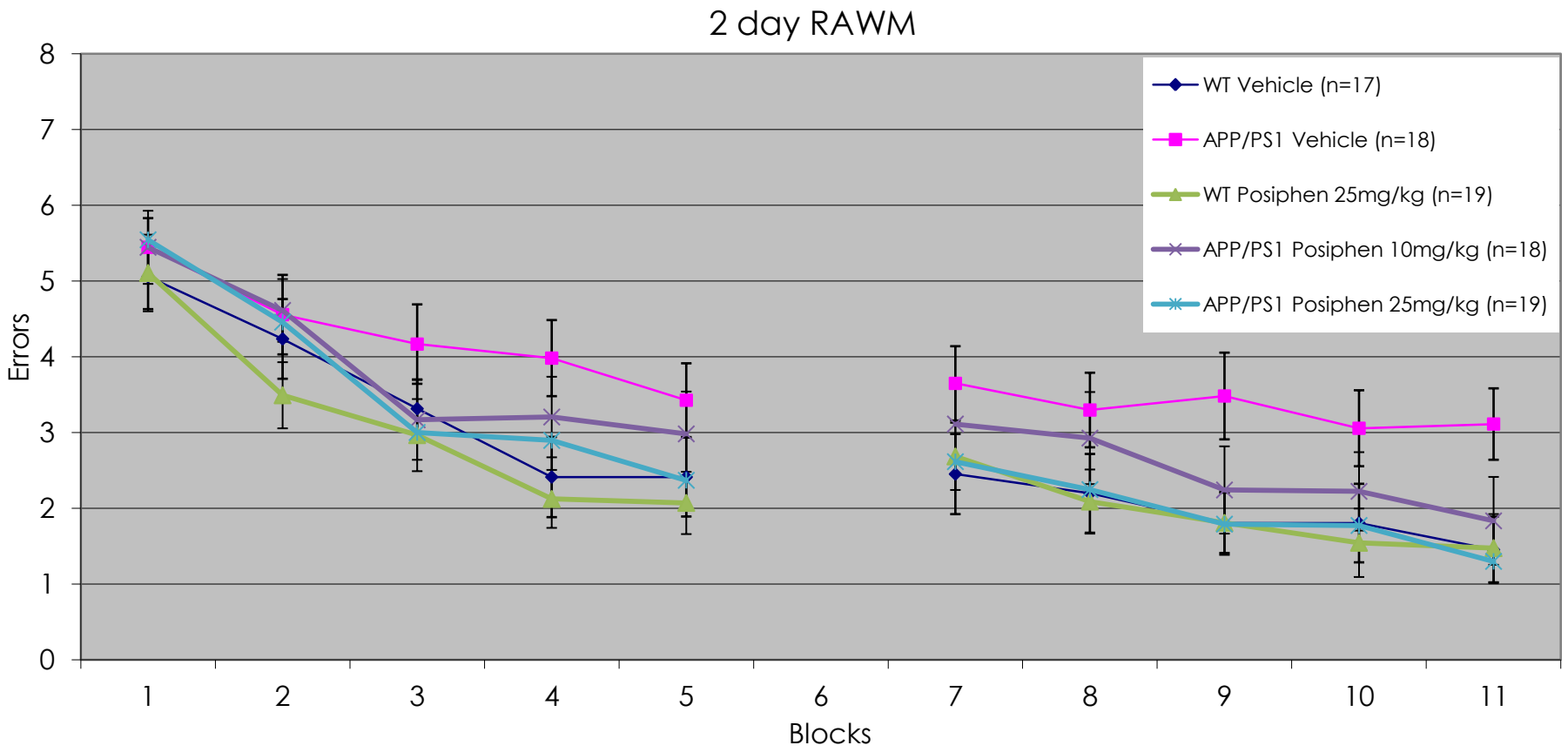
Reduced Axonal BDNF Transport is Reversed by Posiphen



5 uM, 48hr

XQ Chen, Mobley Lab, UCSD

AD: Posiphen Improves Spatial Memory in APPswe/PS1 Mice



Posiphen significantly (p=0.0033) improves spatial memory of double transgenic mice in radial water maze test

Teich et al: Alzheimer's & Dementia: Translational Research & Clinical Interventions; Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and

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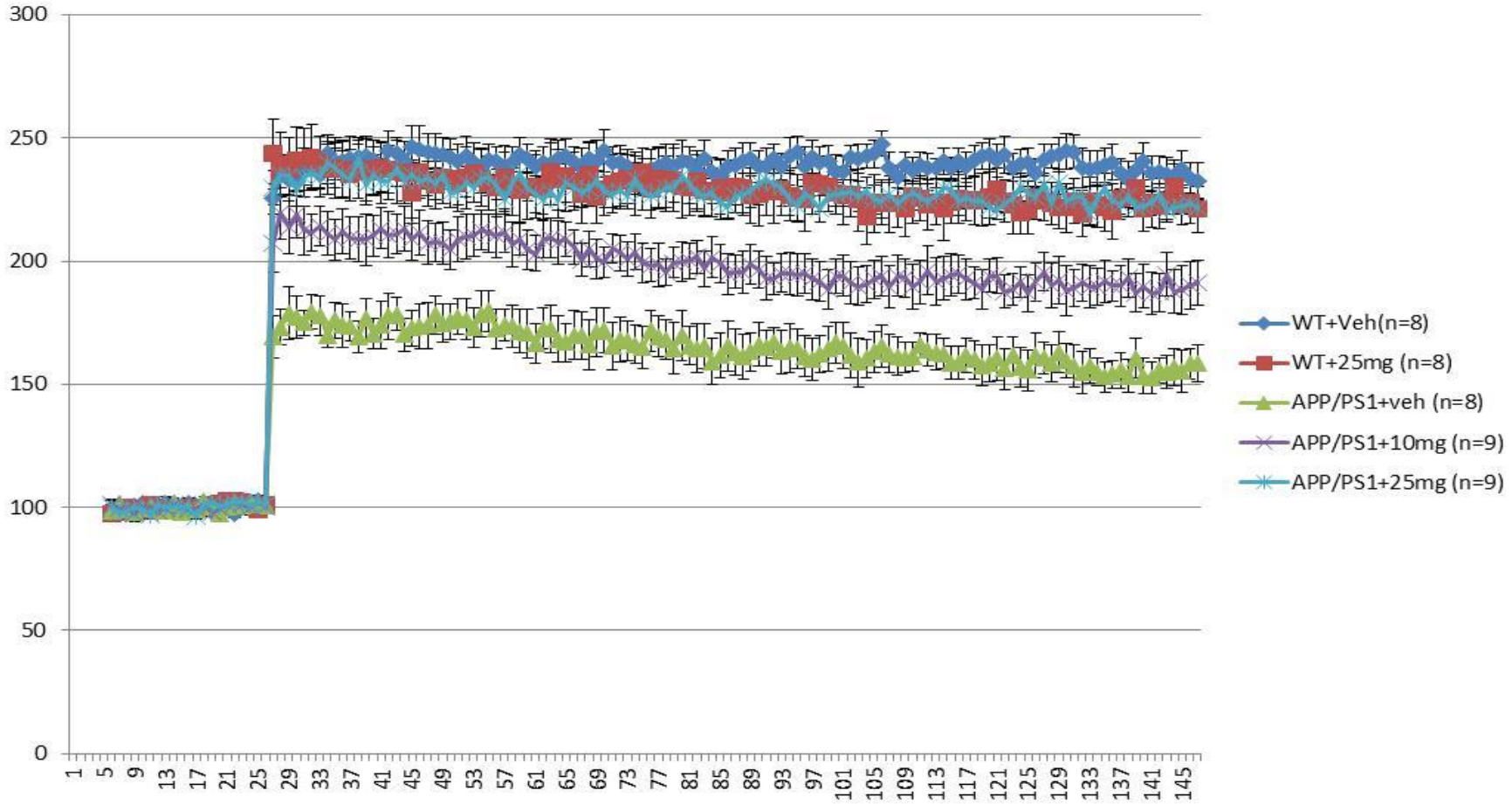
AD: Posiphen Rescues Synaptic Dysfunction (LTP) in Hippocampal Slices from APP/PS1 Mice



Treatment with oral Posiphen rescues long-term potentiation

Teich et al: Alzheimer's & Dementia: Translational Research & Clinical Interventions; Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and pharmacokinetics in the APP/PS1 mouse4 (2018) 37-45

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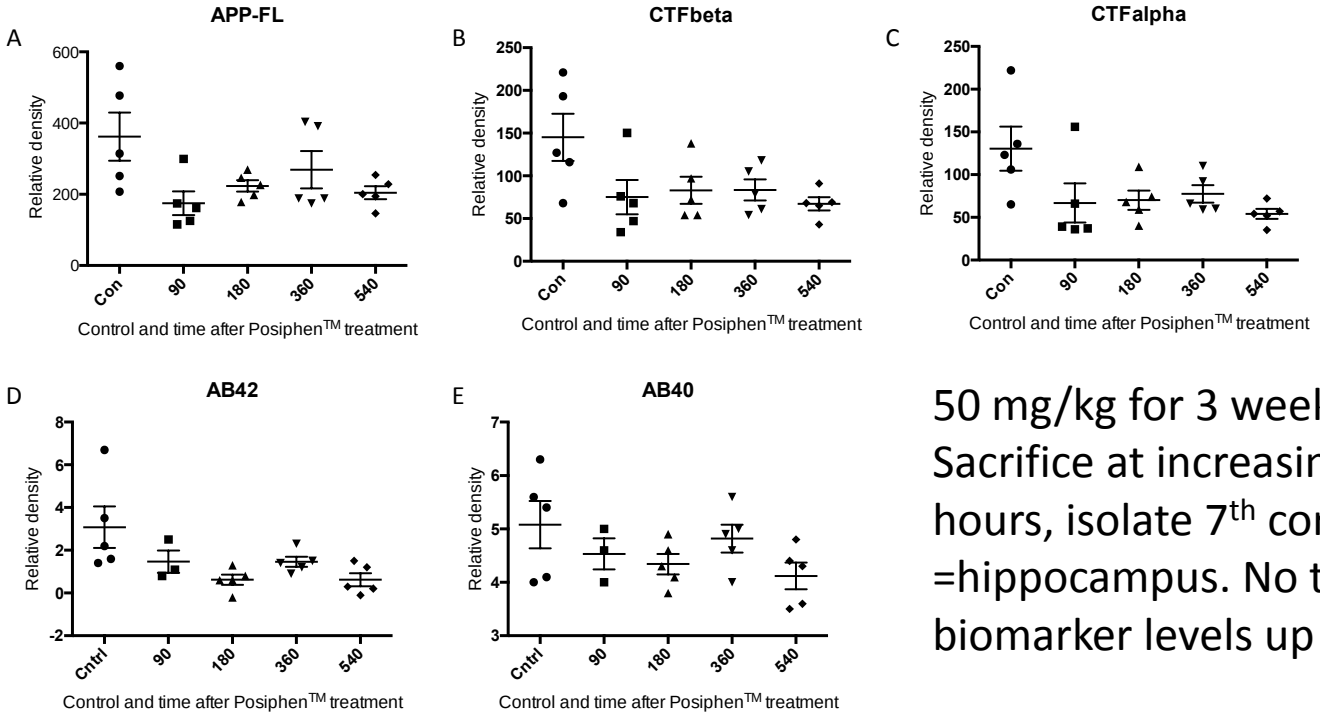
AD: Decrease in APP and APP Fragments in Hippocampus of APP/PS1 Mice



50 mg/kg for 3 weeks
Sacrifice at increasing time-points up to 9 hours, isolate 7th coronal brain slice =hippocampus. No trend for recovery of biomarker levels up to 9 h.

Marker	(%) Drop	p-values
APP	39.8	0.008
CTFβ	46.8	0.0024
CTFα	48.5	0.0031
Aβ42	68	0.0008

Teich et al: Alzheimer's & Dementia: Translational Research & Clinical Interventions; Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and pharmacokinetics in the APP/PS1 mouse4 (2018) 37-45

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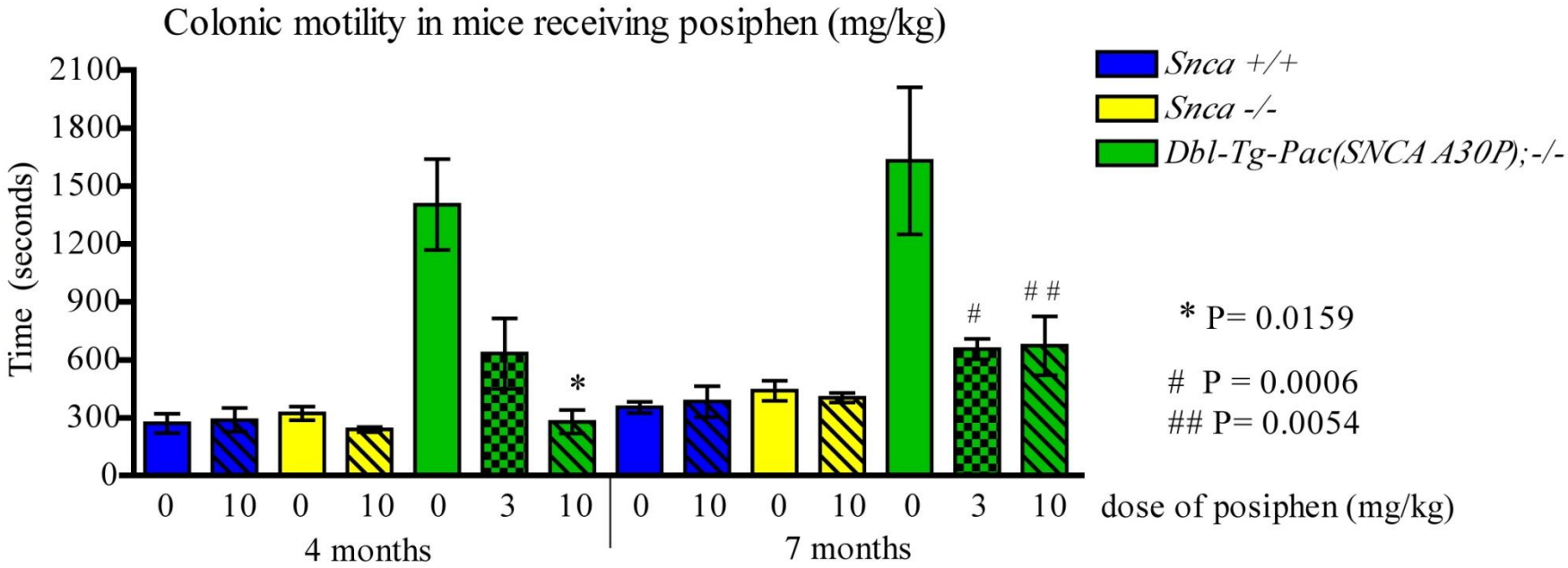
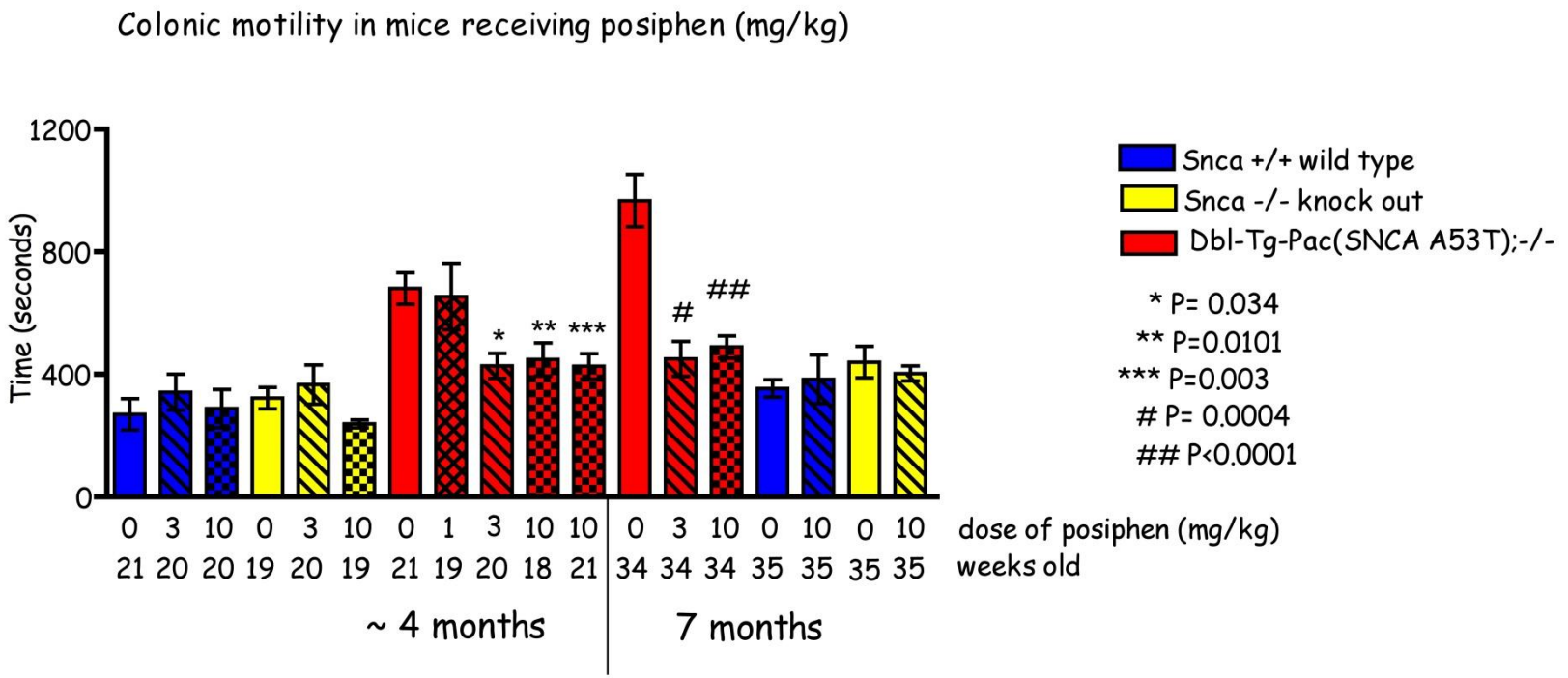
PD: Posiphen Improves Gut Motility in transgenic aSYN A30T Mice



- Dbl-PAC-Tg(*SNCA* ^{A30P}); *Snca* $^{-/-}$ and control mice treated with 0, 3 or 10mg/kg IP daily from 6 to 28 weeks of age
- Colonic motility significantly increased with Posiphen treatment

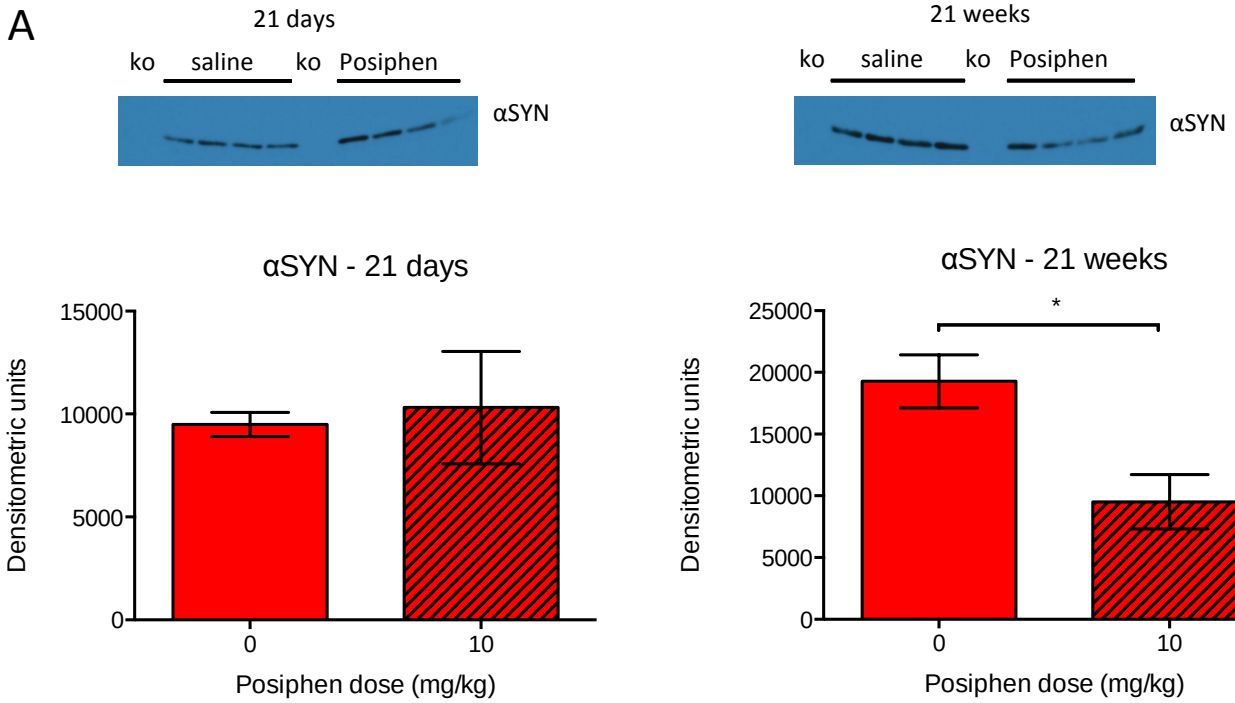
PD: Posiphen Improves Gut Motility in transgenic aSYN A53T Mice

Transgenic PD PAC A53T mice and controls were treated with 10mg/kg ip daily from 2 months to 4 and 7 months of age. Colonic motility was measured and compared to control treated and untreated animals

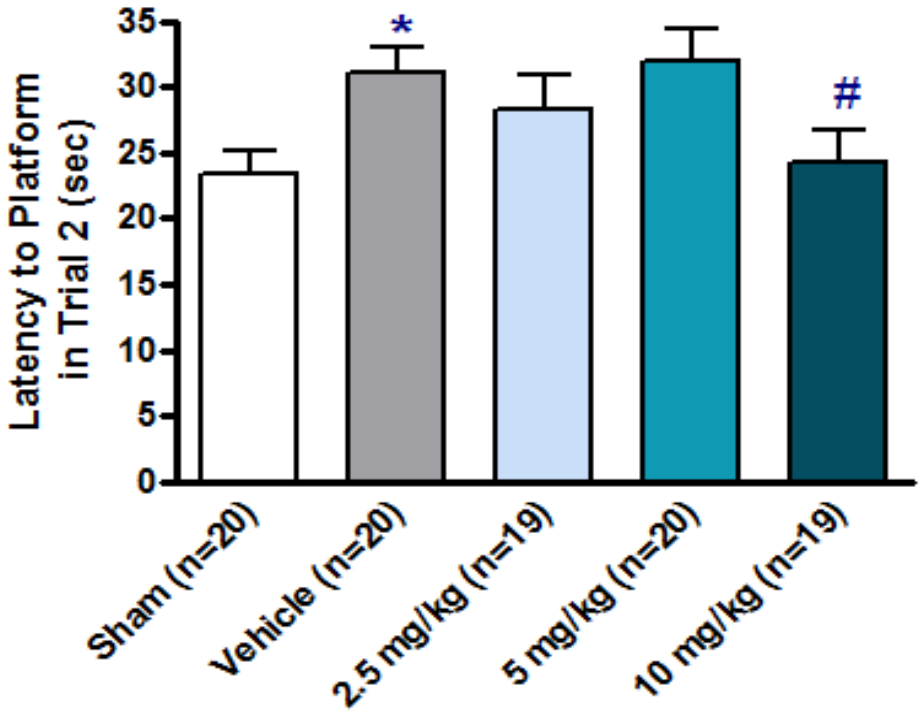


PD: Posiphen Lowers aSYN Levels in Animals with Restored Gut Motility

10 mg/kg of Posiphen treatment of *hSNCA* ^{A53T} mice for 21 weeks statistically significantly reduces the levels of the protein in the gut, as compared to levels in *hSNCA* ^{A53T} mice treated with vehicle. Quantization results were similar with and without normalization.



TBI: Posiphen Rescues Working Memory of Rats in Water Maze



Posiphen significantly improves (p=0.0335) time to find the hidden platform following TBI

UCLA, Marie-Francoise Chesselet, David Hovda

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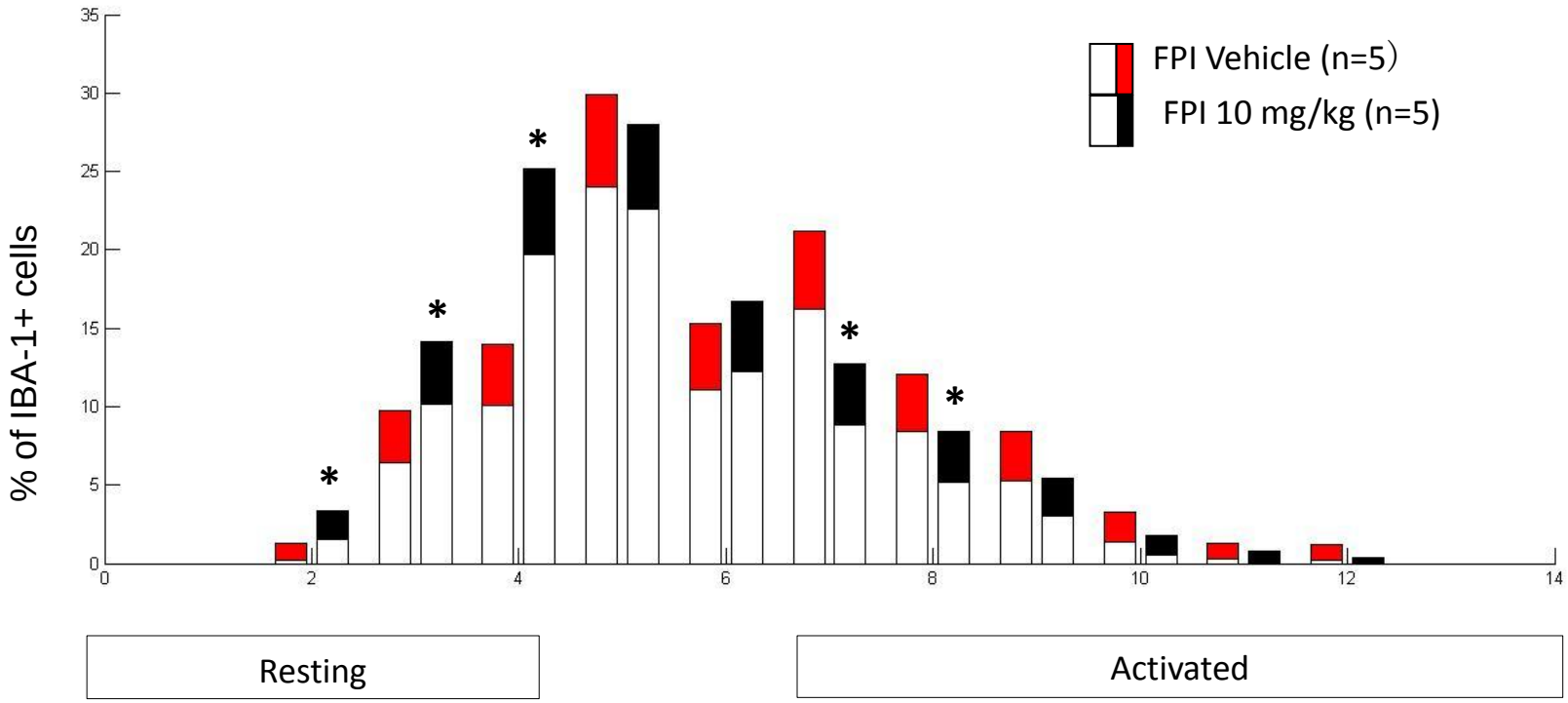
TBI: Posiphen inhibits microglia activation

Data (Mean + 95% CI) analyzed with Bootstrapping method, *p<0.05



Posiphen increases the number of resting microglia and reduces the number of activated microglia – it reduces inflammation

UCLA, Marie-Francoise Chesselet and David Hovda's lab

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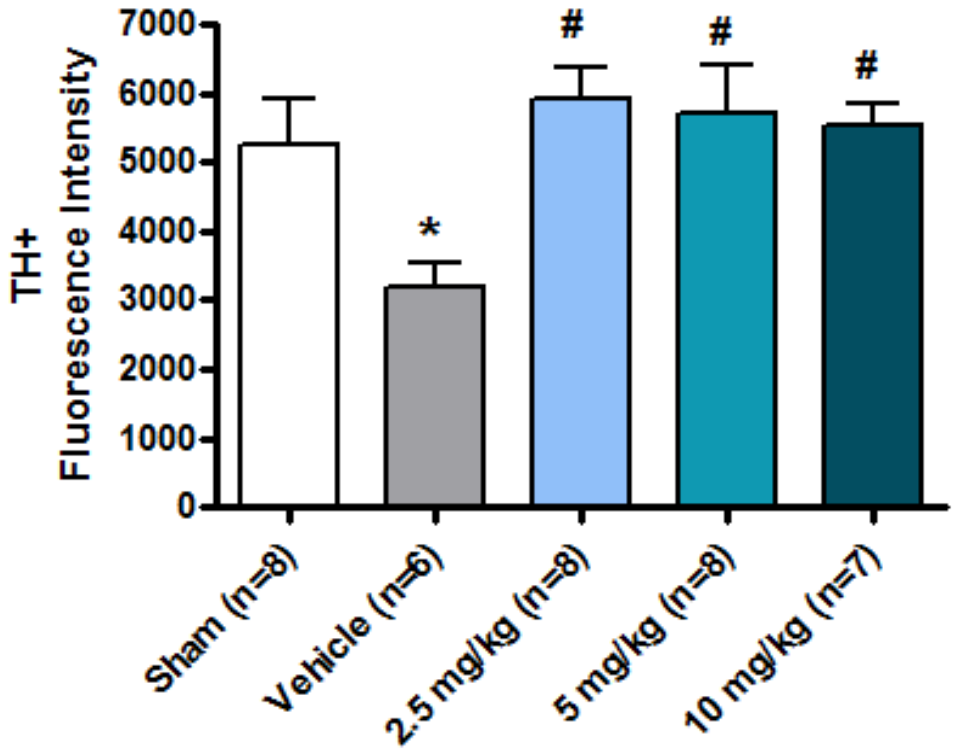
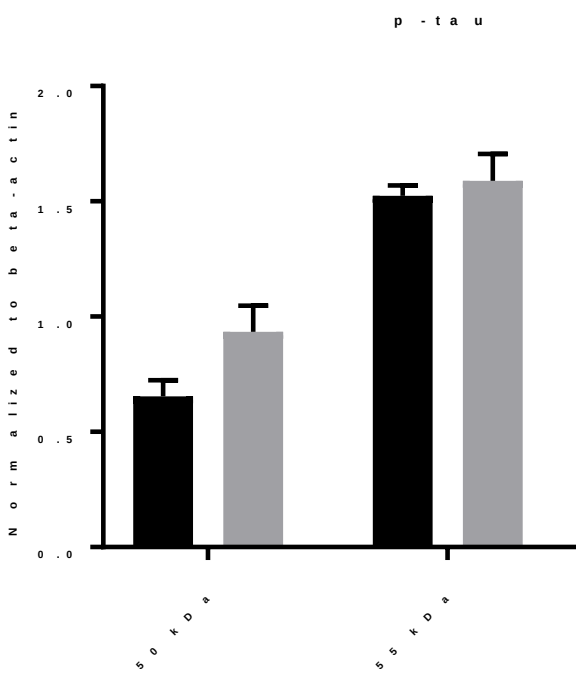
TBI: Posiphen Fully Protects Nerve Cells of Rats in the Striatum



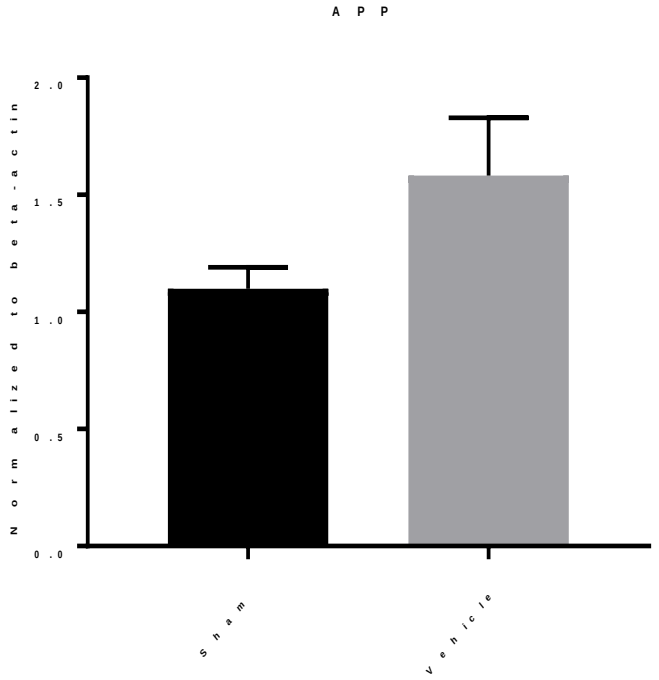
Posiphen protects striatum histology following TBI

TBI: Increase in p-Tau and APP in SN



Data are shown as mean ± SEM (n=6-7)

50 kDa - A Student's t-test revealed an almost significant increase in p-tau in the vehicle group (t=-2.098, p=0.0578).



A Student's t-test between the two groups revealed an increase in APP level in the vehicle group approaching significance (t=-1.840, p=0.0906).

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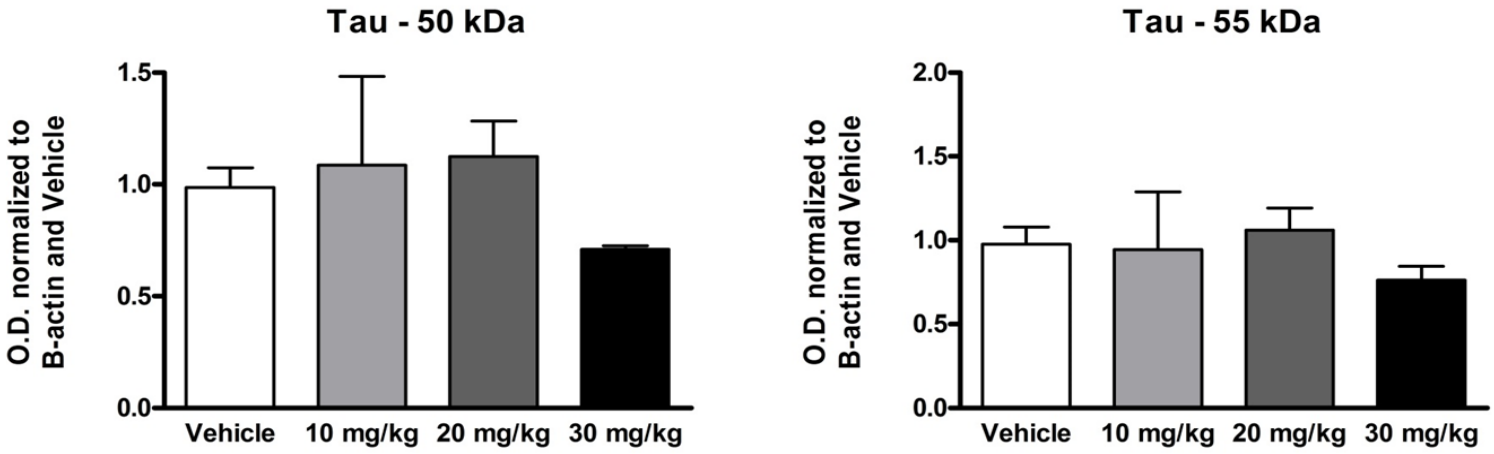
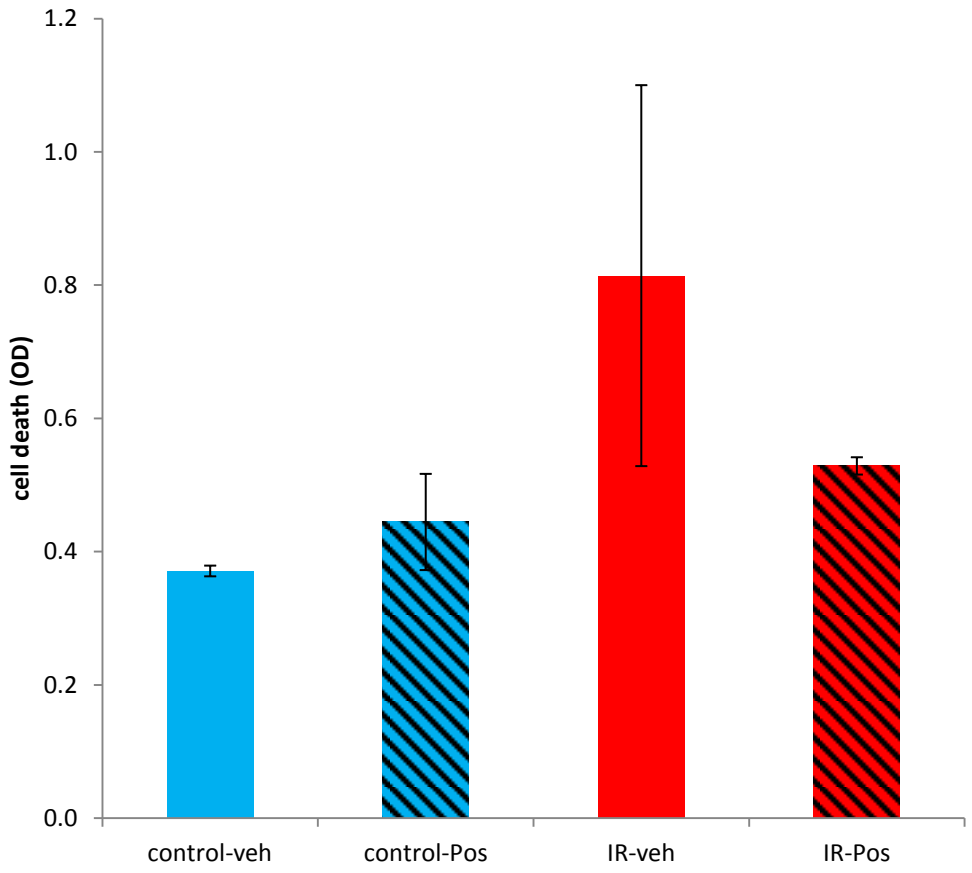
TBI: Posiphen Reduces the Elevated 50kDa Tau Isoform in SN



- **30 mg/kg: 40% decrease from vehicle in 50kDA form:**
  One-way ANOVA (P = 0.021)
- **30 mg/kg: 22% decrease from vehicle in 55kDA form:**
  One-way ANOVA (P = 0.091)

Acute Glaucoma: Posiphen Protects Retinal Cells in Rats



Acute glaucoma is induced by increasing intraocular pressure by micro-injection of saline into the anterior chamber. This induces large amounts of apoptotic cell death in the retina.

There are twice as many dead cells in high pressure retinas of rats treated with vehicle versus control untreated rats.

Posiphen rescues 72% of the retinal neurons.

Hershey Medical Center, Jeff Sundstrom's lab

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Clinical Data

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Three Phase 1 Clinical Studies

- Single oral ascending dose in 60 healthy volunteers vs. placebo control
  - MTD 160 mg

- Multiple oral ascending doses in 48 healthy volunteers vs. placebo control
  - NOAEL 240 mg/day (4x60 mg)
  - PK: C_{max} = 1.5 hrs; $T_{1/2}$ = 5 hrs in plasma

- Proof of mechanism in 5 MCI patients
  - PK: $T_{1/2}$ plasma = 5 hrs; $T_{1/2}$ brain/CSF > 12 hrs
  - Statistically significant reduction of aggregating proteins in CSF
  - Biomarker levels stay depressed for over 12 hrs

Safety in Phase 1 Clinical Trials

AE in Healthy Male and Female Volunteers Single Ascending Dose (n=72)						
Adverse Event	10 mg (n=10)	20 mg (n=20)	40 mg (n=10)	80 mg (n=10)	160 mg (n=10)	Placebo (n=12)
All AEs, mild	2 (20.0)	3 (15.0)	1 (10.0)	3 (30.0)	3 (30.0)	1 (8.3)
All AEs, moderate	0 (0)	2 (10.0)	0 (0)	0 (0)	4 (40.0)	1 (8.3)
All AEs, severe	0 (0)	1 (5.0)	0 (0)	0 (0)	0 (0)	1 (8.3)
Gastrointestial Disorders						
Nausea	0 (0)	2 (10.0)	0 (0)	0 (0)	4 (40.0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	3 (30.0)	0 (0)
Nervous System Disorders						
Dizziness	0 (0)	3 (15.0)	1 (10.0)	3 (30.0)	4 (40.0)	2 (16.7)
Fainting	0 (0)	1 (5.0)	0 (0)	0 (0)	0 (0)	1 (8.3)
General Disorders						
Feeling hot	0 (0)	2 (10.0)	0 (0)	0 (0)	0 (0)	0 (0)
Heart rate increased	2 (20.0)	1 (5.0)	0 (0)	0 (0)	0 (0)	2 (16.7)
Orthostatic hypotension	0 (0)	1 (5.0)	0 (0)	0 (0)	0 (0)	1 (8.3)

AEs in Healthy Male and Female Volunteers Multiple Ascending Dose (n=48)				
Adverse Event	4x20 mg (n=12)	4x40 mg (n=12)	4x60 mg (n=12)	Placebo (n=12)
All AEs, mild	6 (50.0)	3 (25.0)	3 (25.0)	4 (33.3)
All AEs, moderate	2 (16.7)	0 (0)	1 (8.3)	2 (16.7)
All AEs, severe	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal Disorders				
Nausea	1 (8.3)	0 (0)	2 (16.7)	1 (8.3)
Vomiting	0 (0)	0 (0)	2 (16.7)	0 (0)
Nervous System Disorders				
Dizziness	2 (16.7)	2 (16.7)	3 (25.0)	1 (8.3)
General Disorders				
Abdominal pain	1 (8.3)	0 (0)	0 (0)	0 (0)
Headache	2 (16.7)	3 (25.0)	1 (8.3)	2 (16.7)
Other	5 (41.2)	1 (8.3)	1 (8.3)	6 (50.0)

AEs in MCI Patients Multiple Dose (n=5)	
Adverse Event	4x60 mg (n=5)
All AEs, mild	3 (60.0)
All AEs, moderate	0 (0) 1*
All AEs, severe	0 (0)
Gastrointestinal Disorders	
Nausea	1 (20)1*
Vomiting	0 (0) 1*
Nervous System Disorders	
Dizziness	0 (0) 1*
General Disorders	
Leg cramps	0 (0)1*
Headache	4 (80.0) 1*
Other	3 (60.0) 2*

Maccecchini ML, et al. JNNP 2012

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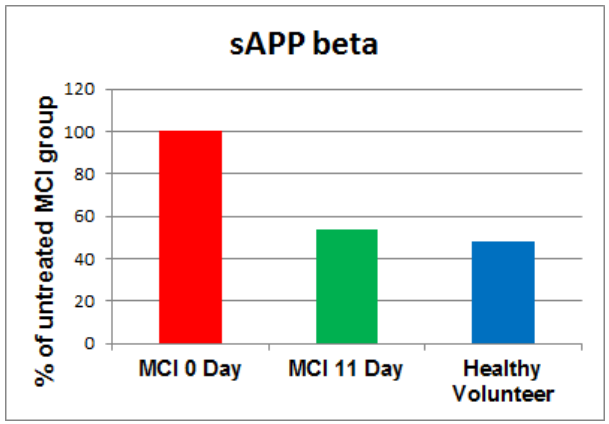
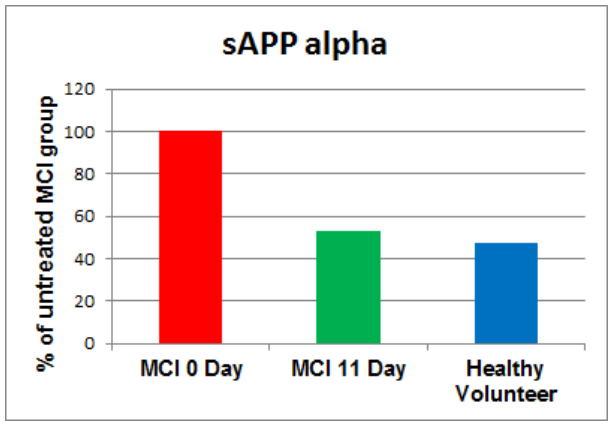
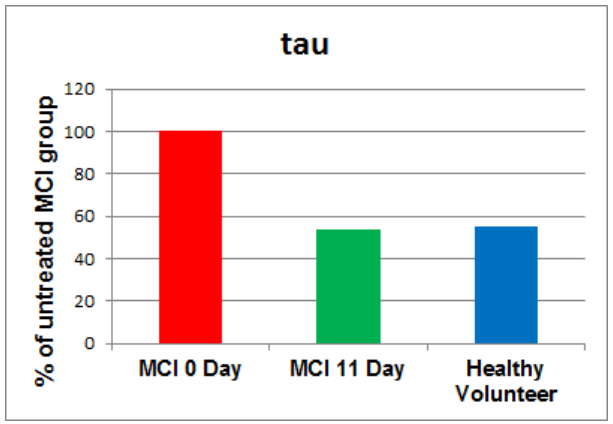
Posiphen Lowers Neurotoxic Proteins in 5 MCI Patients to Levels of Healthy Volunteers







Human Biomarker	CSF % of Time 0	Standard Error	P-Value	Assay
sAPP α	-34.1%	0.659	0.0661	MSD
	-59.9%	0.231	0.0006	AlphaLisa
sAPP β	-34%	1.516	0.0901	MSD
	-57.7%	0.361	0.0001	AlphaLisa
Tau	-46.2%	0.538	0.0020	AlphaLisa
	-74.1%	0.259	0.0150	Innogenetics
pTau	-61%	0.195	0.0039	Innogenetics

Maccecchini ML, et al. JNNP 2012

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Posiphen Inhibits Inflammatory factors in MCI

Human Inflammatory Protein	CSF % of Time 0	Standard Error	p-Value	Assay	Laboratory
Complement C3	-86.9%	0.139	0.0007	Millipore	C. Pan / Inarian
MCP-1	-87.5%	4.813	0.0007	MSD	H. Zetterberg / U.Goteborg
YKL40	-72.7%	2.2	0.0113	R&D Systems	H. Zetterberg / U.Goteborg
sCD14	-26.1%	1.7	0.1159	R&D Systems	H. Zetterberg / U.Goteborg
Factor FH	23.7%	1.237	0.4988	Millipore	C. Pan / Inarian

Maccecchini ML, et al. JNNP 2012

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High Levels of Neurotoxic Aggregating Proteins….

Cause disturbances in vesicle maturation and transport - Posiphen normalizes vesicle transport

- human neuronal cells : Bill Mobley, UCSD

Impair synaptic transmission – Posiphen normalizes it

- rat striatum: Marie-Francoise Chesselet, UCLA
- mouse hippocampus: Ottavio Arancio, Columbia U.

Cause inflammation - Posiphen lowers inflammation in

- human CSF: QR Pharma
- rat brain: Marie-Francoise Chesselet, UCLA

Kill nerve cells - Posiphen protects nerve cells from dying in

- rat substantia nigra: Marie-Francoise Chesselet, UCLA
- rat optic nerve: Jeff Sundstrom, Hershey Medical Center
- mouse enteric nerves: Bob Nussbaum, UCSF

Scientific Advisors

- **Jeff Cummings, MD, Cleveland Clinic**

  Director, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada and Cleveland, Ohio

- **Peter Davies, PhD, Hofstra University**

  Director and Professor, Litwin-Zucker Research Center for the Study of Alzheimer's Disease, The Feinstein Institute for Medical Research

- **Bill Mobley, MD, PhD, UCSD**

  Department Chair , Distinguished Professor and Executive Director of UCSD's Down Syndrome Center and the Florence Riford Chair of Alzheimer Disease Research

- **Greg Petsko, PhD, Weill Cornell**

  Professor of Neurology and Neuroscience and Director, Alzheimer's Disease Research Institute at and adjunct professor of Biomedical Engineering at Cornell University.

- **Sid Strickland, PhD, The Rockefeller University, Chairman**

  Vice President, Dean and Professor, Patricia and John Rosenwald Laboratory of Neurobiology and Genetics

- **Rudy Tanzi, PhD, Massachusetts General Hospital**

  Vice-Chair and Director of Neurology, Genetics and Aging, Joseph and Rose Kennedy Professor of Neurology, Head of CureAD

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Thank You

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Appendix
Preclinical Data

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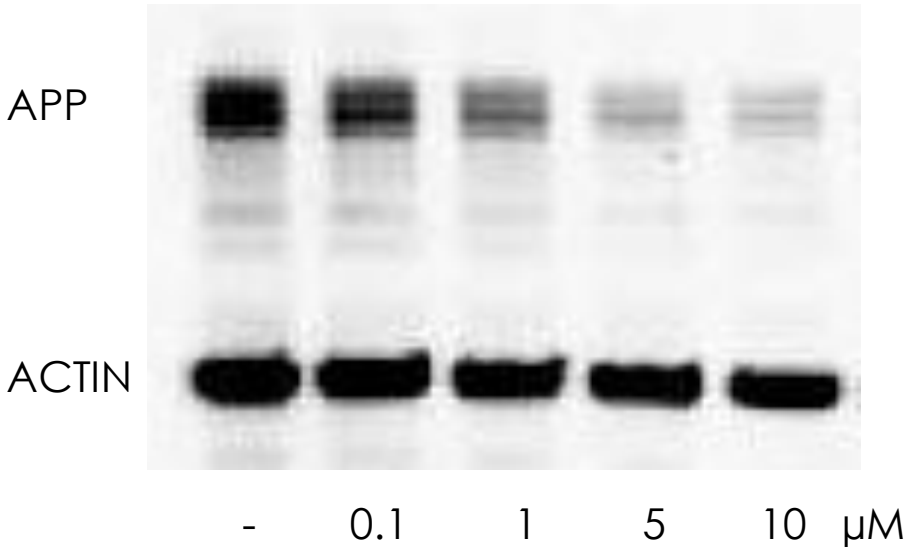
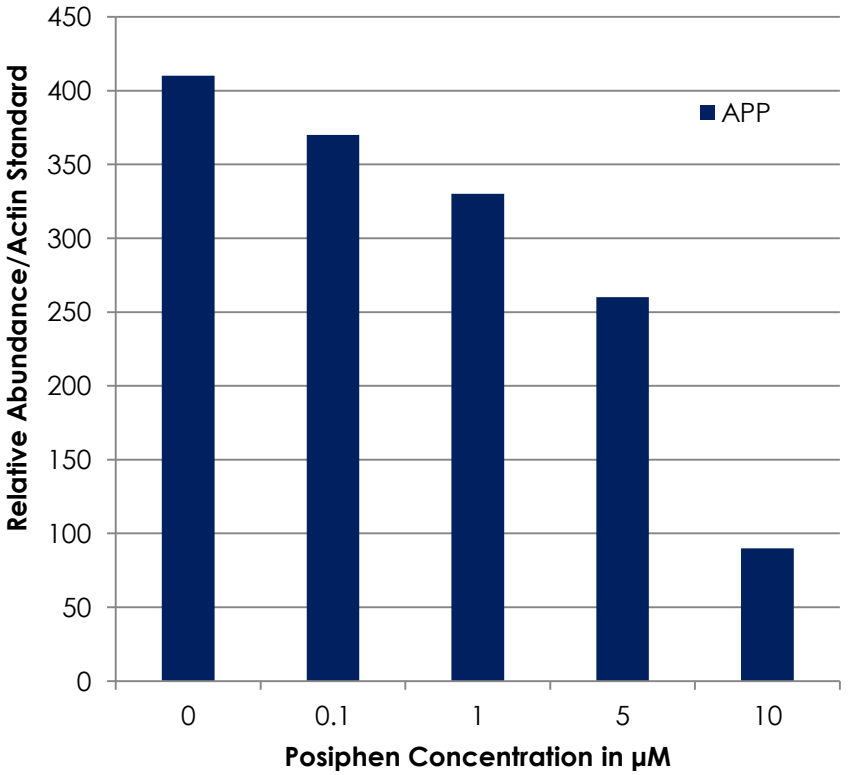
AD - Posiphen Lowers APP In Vitro

Dose-dependent Inhibition of APP in SH-SY-5Y Human Neuroblastoma Cells





Jack Rogers et al. JNT 2010

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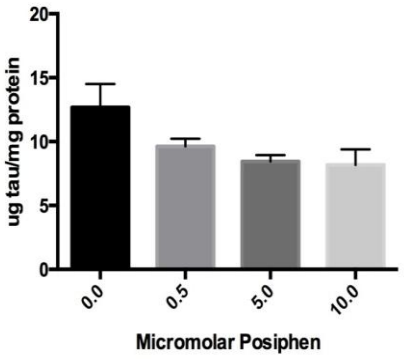
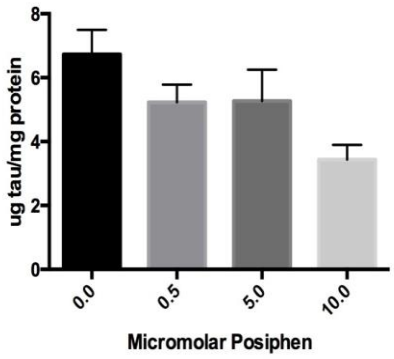
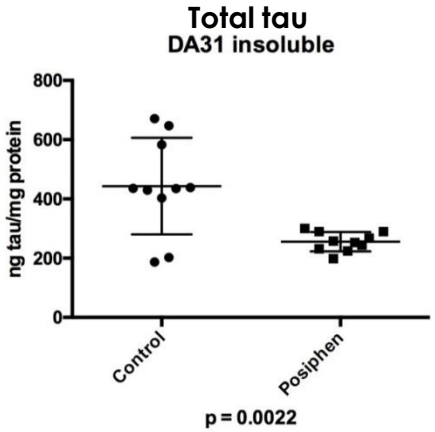
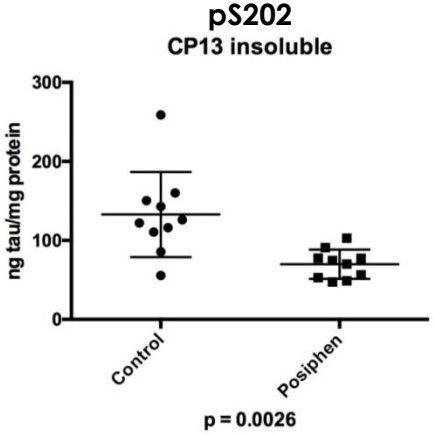
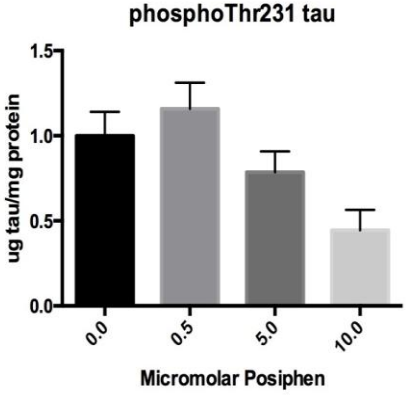
AD - Posiphen Lowers Levels of Aggregated phosphoTau in Tissue Culture and in Brain of P301L Tau Mice

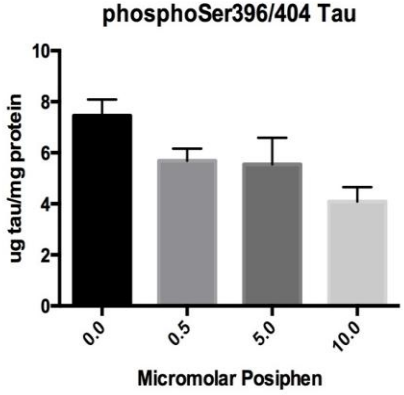


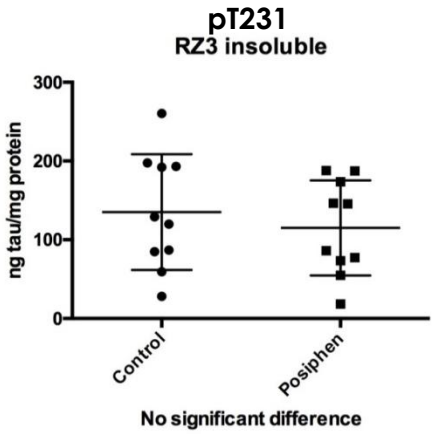


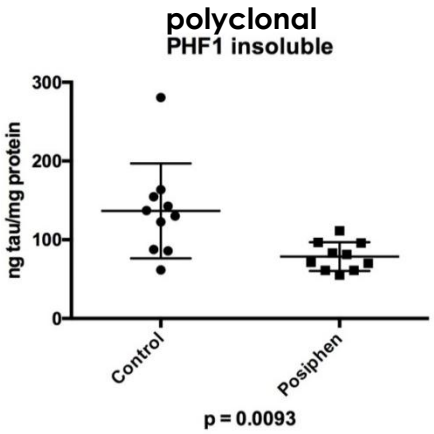












Peter Davies, Hofstra University – Unpublished data

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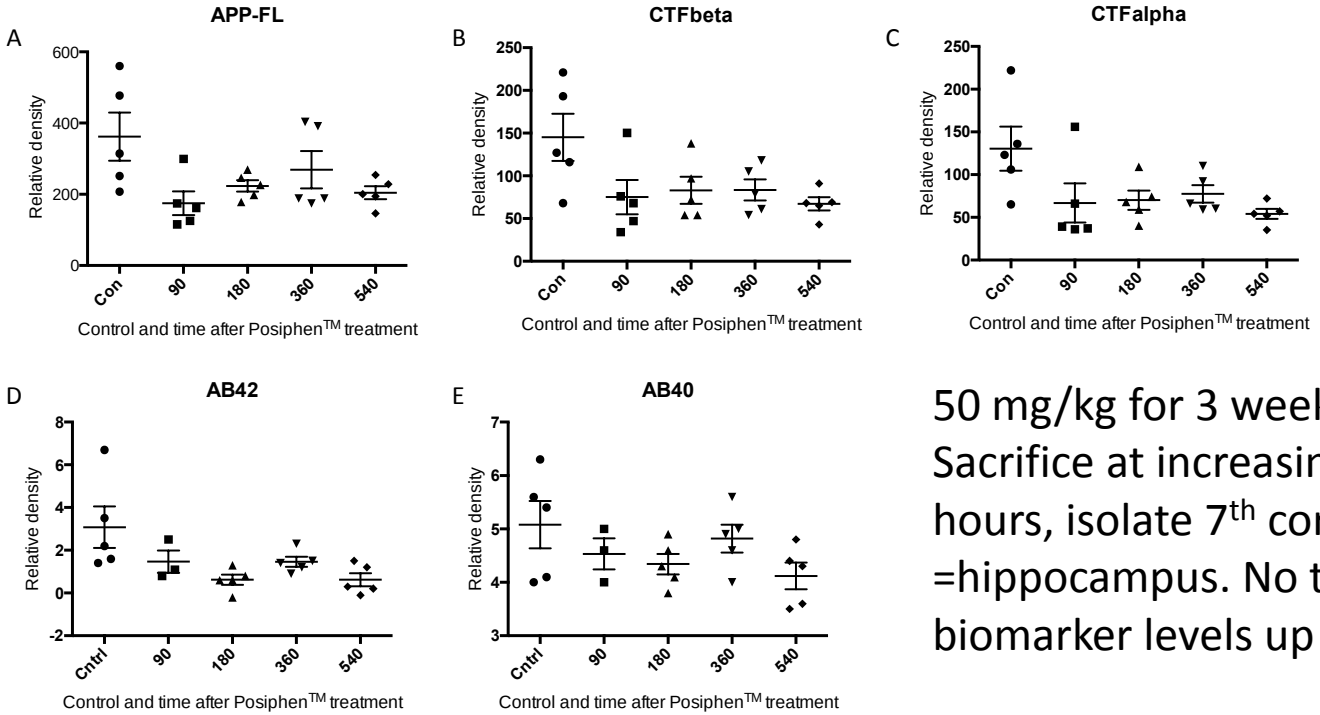
AD-Decrease in APP and APP Fragments in Hippocampus of APP/PS1 Mice



Marker	(%) Drop	p-values
APP	39.8	0.008
CTFβ	46.8	0.0024
CTFα	48.5	0.0031
Aβ42	68	0.0008

50 mg/kg for 3 weeks
Sacrifice at increasing time-points up to 9 hours, isolate 7th coronal brain slice =hippocampus. No trend for recovery of biomarker levels up to 9 h.

Teich et al: Alzheimer's & Dementia: Translational Research & Clinical Interventions; Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and pharmacokinetics in the APP/PS1 mouse4 (2018) 37-45

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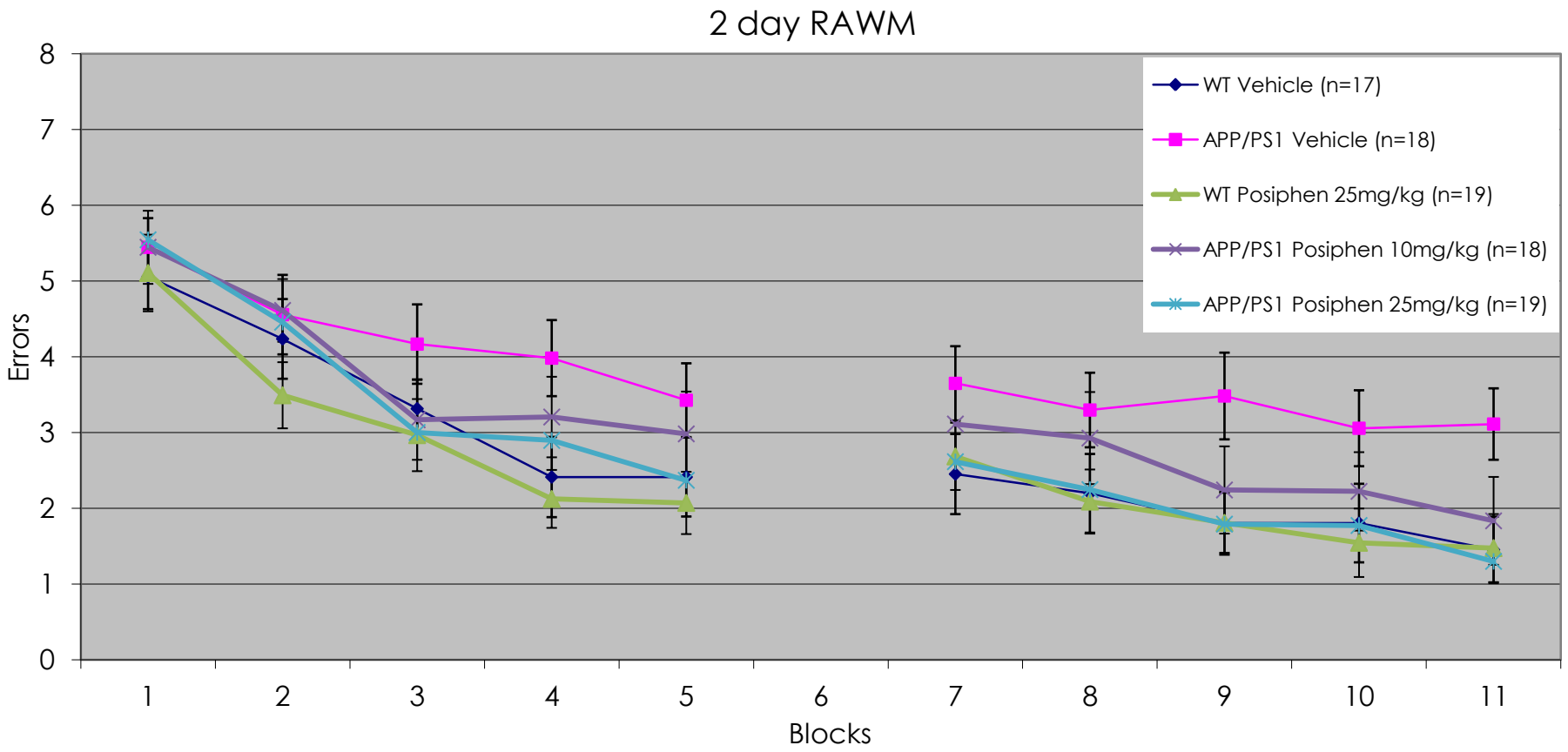
AD - Posiphen Improves Spatial Memory in APPswe/PS1 Mice



Posiphen significantly (p=0.0033) improves spatial memory of double transgenic mice in radial water maze test

Teich et al: Alzheimer's & Dementia: Translational Research & Clinical Interventions; Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and

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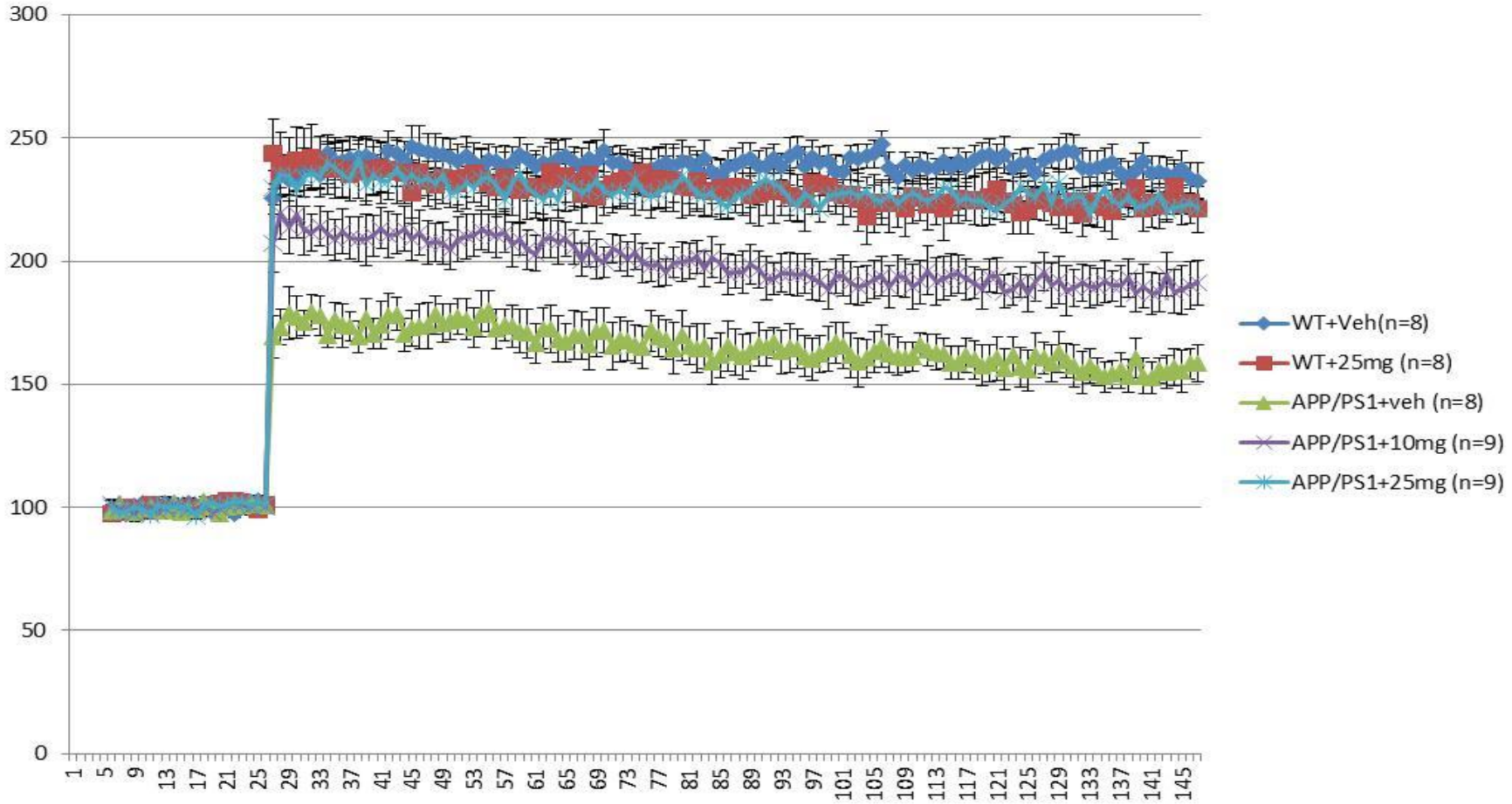
Posiphen Rescues Synaptic Dysfunction (LTP) in Hippocampal Slices from APP/PS1 Mice



Treatment with oral Posiphen rescues long-term potentiation

Teich et al: Alzheimer's & Dementia: Translational Research & Clinical Interventions; Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and pharmacokinetics in the APP/PS1 mouse4 (2018) 37-45

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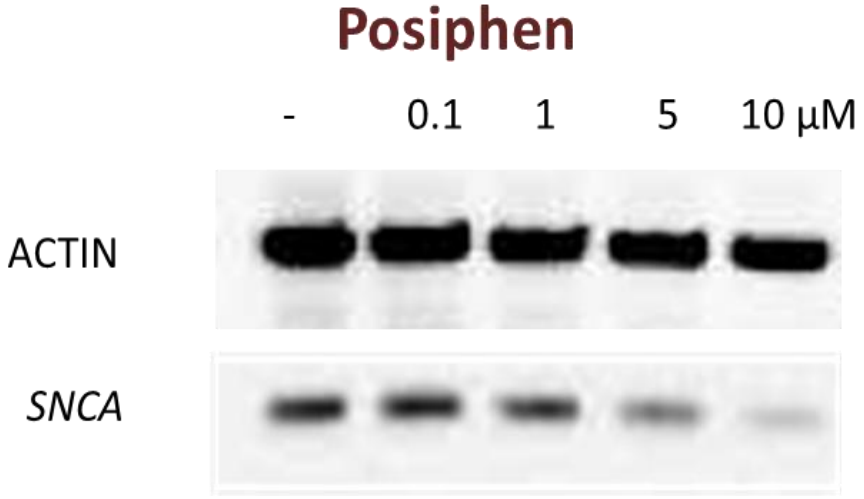
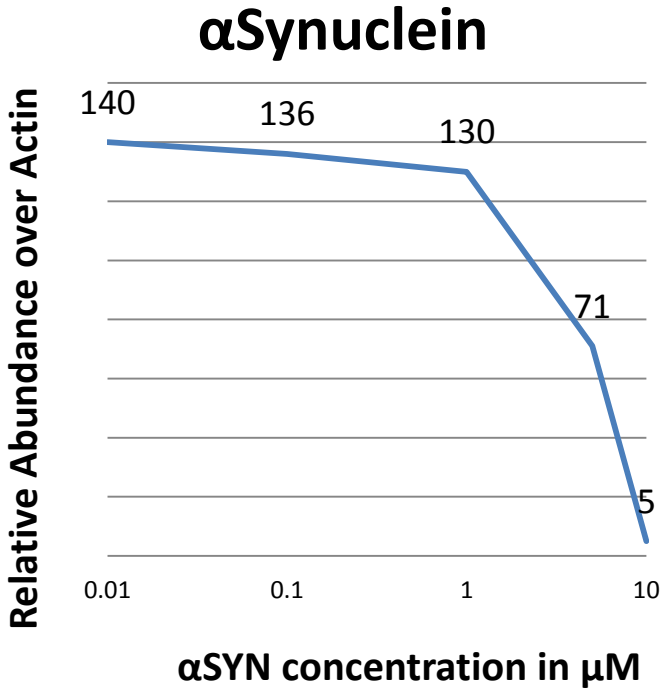
PD - Posiphen Lowers aSYN In Vitro

Dose-dependent Inhibition of aSYN in SH-SY-5Y Human Neuroblastoma Cells

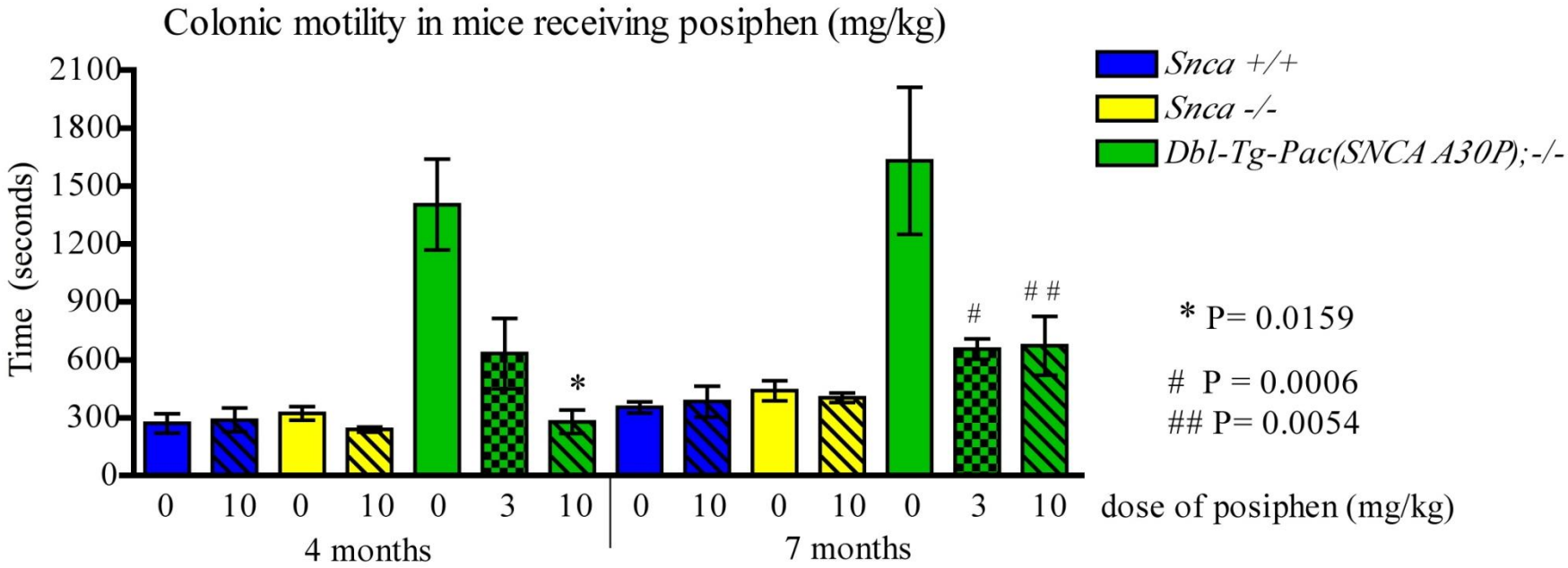




Jack Rogers et al. JNT 2010

QR Pharma

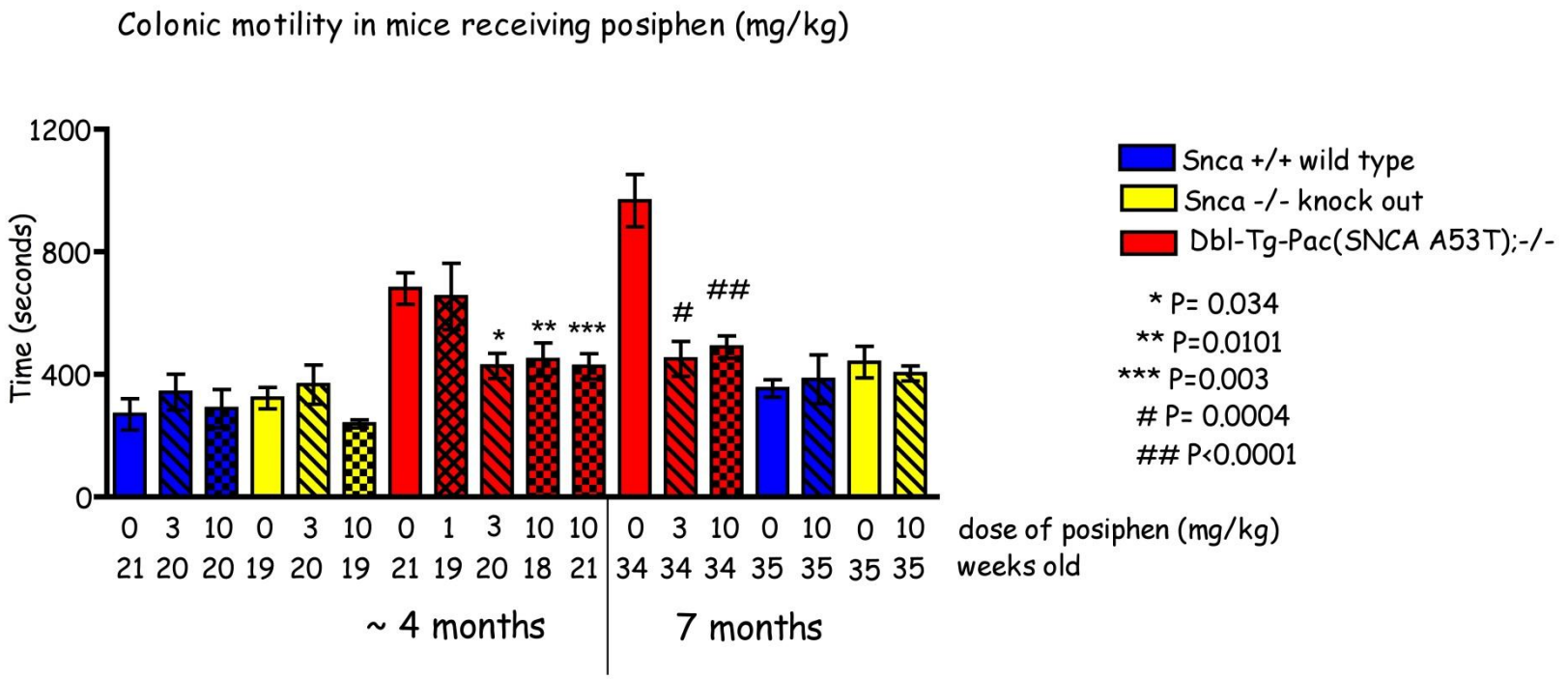
PD: Posiphen Improves Gut Motility in transgenic aSYN A30T Mice



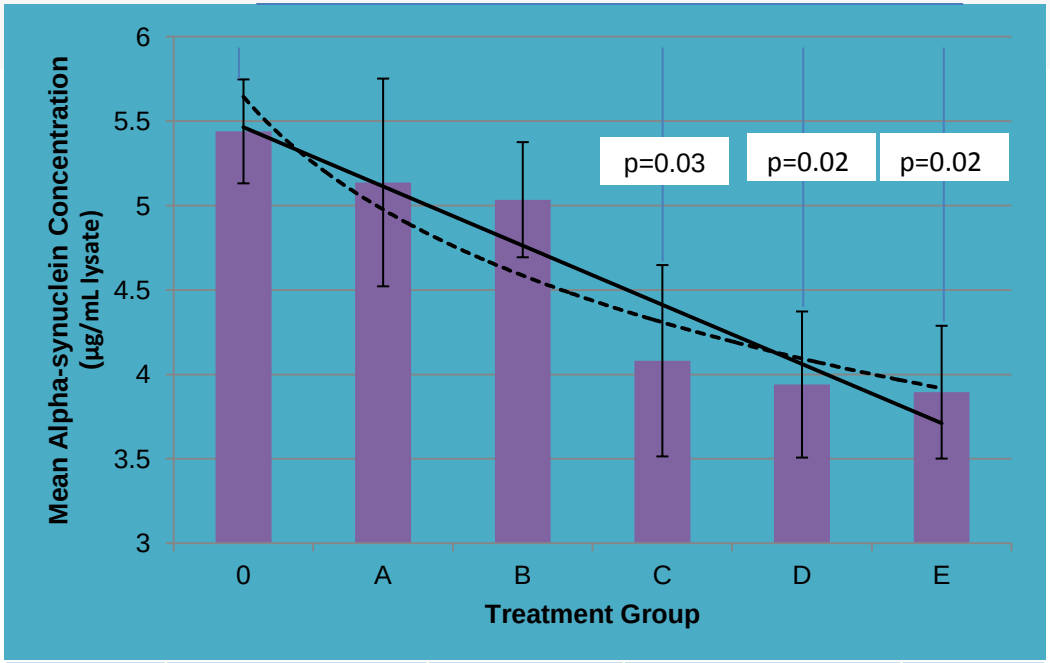
- Dbl-PAC-Tg(*SNCA* ^{A30P}); *Snca* $^{-/-}$ and control mice treated with 0, 3 or 10mg/kg IP daily from 6 to 28 weeks of age
- Colonic motility significantly increased with Posiphen treatment

PD: Posiphen Improves Gut Motility in transgenic aSYN A53T Mice

Transgenic PD PAC A53T mice and controls were treated with 10mg/kg ip daily from 2 months to 4 and 7 months of age. Colonic motility was measured and compared to control treated and untreated animals



Effect of Posiphen by ELISA in Mouse Brain



Group	Posiphen Dose (mg/kg)	Group N	Mean α-syn Concentration	Error
0	0	5	5.44	±0.31
A	5	4*	5.14	±0.62
B	20	5	5.04	±0.34
C	35	5	4.08	±0.57
D	50	5	3.94	±0.39
E	65	5	3.89	±0.41

*One outlier removed from the dataset.

In Jack Rogers Lab aSYN levels drop with increasing doses of Posiphen αSYN A53T mice

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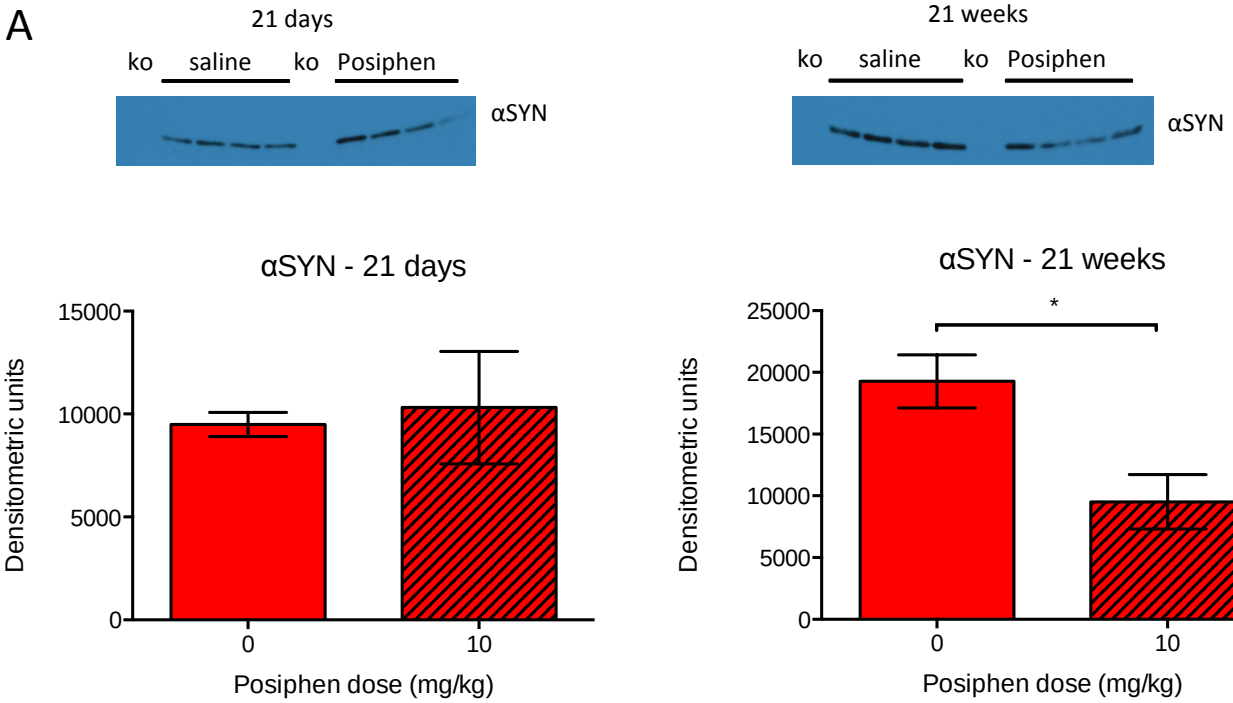
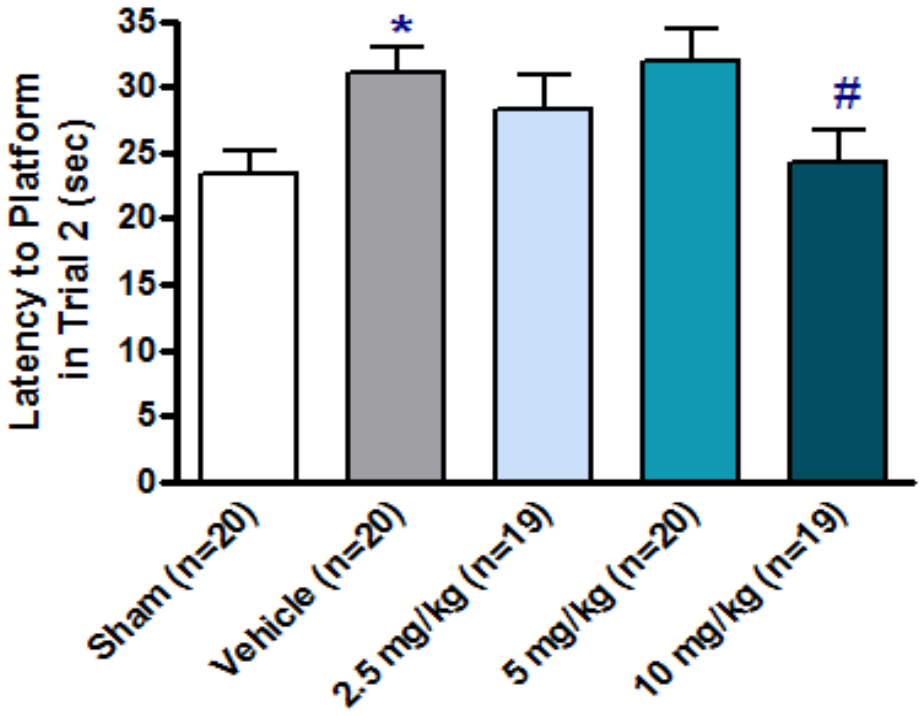
Posiphen Lowers aSYN Levels in Animals with Restored Gut Motility

10 mg/kg of Posiphen treatment of *hSNCA* ^{A53T} mice for 21 weeks statistically significantly reduces the levels of the protein in the gut, as compared to levels in *hSNCA* ^{A53T} mice treated with vehicle. Quantization results were similar with and without normalization.



TBI- Posiphen Rescues Working Memory of Rats in Water Maze



Posiphen significantly improves (p=0.0335) time to find the hidden platform following TBI

UCLA, Marie-Francoise Chesselet, David Hovda

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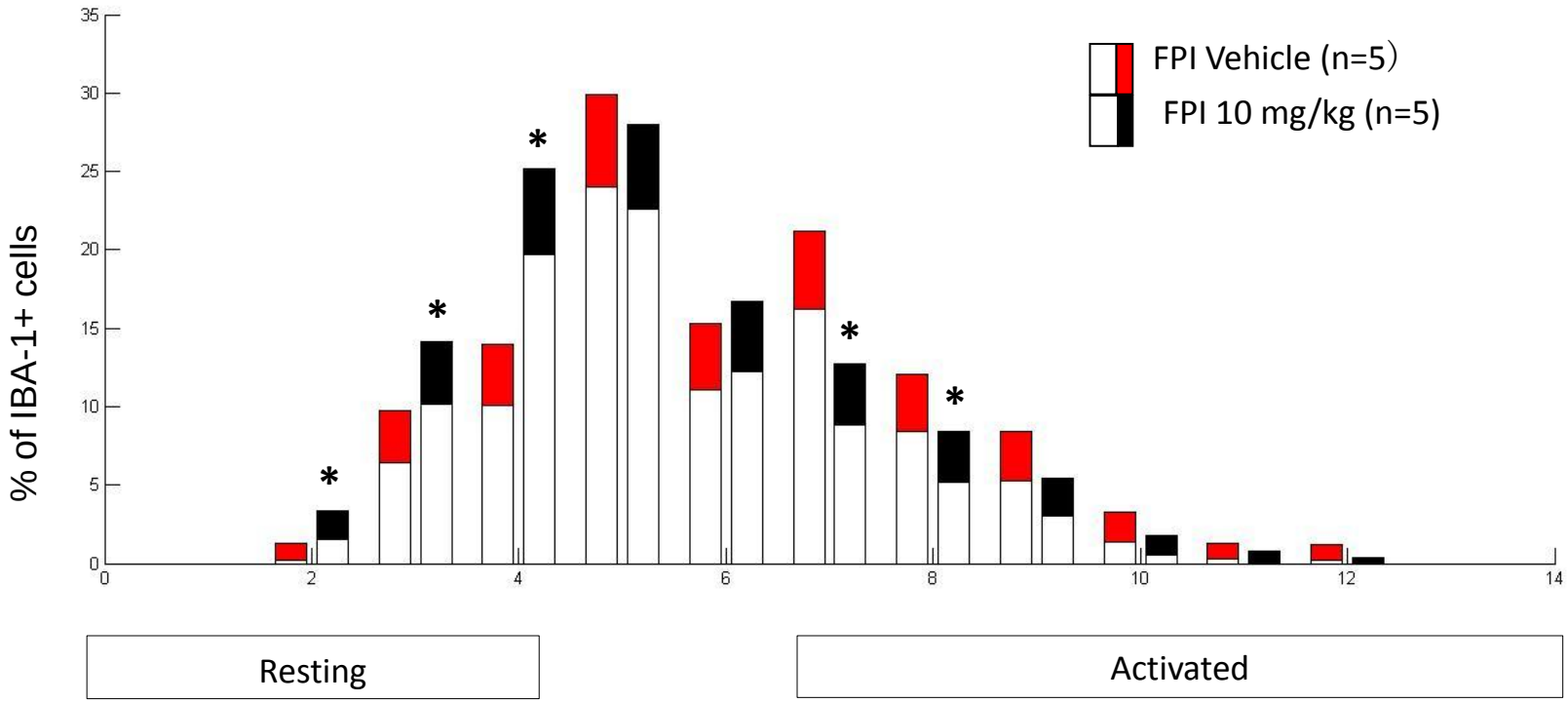
TBI: Posiphen inhibits microglia activation

Data (Mean + 95% CI) analyzed with Bootstrapping method, *p<0.05



Posiphen increases the number of resting microglia and reduces the number of activated microglia – it reduces inflammation

UCLA, Marie-Francoise Chesselet and David Hovda's lab

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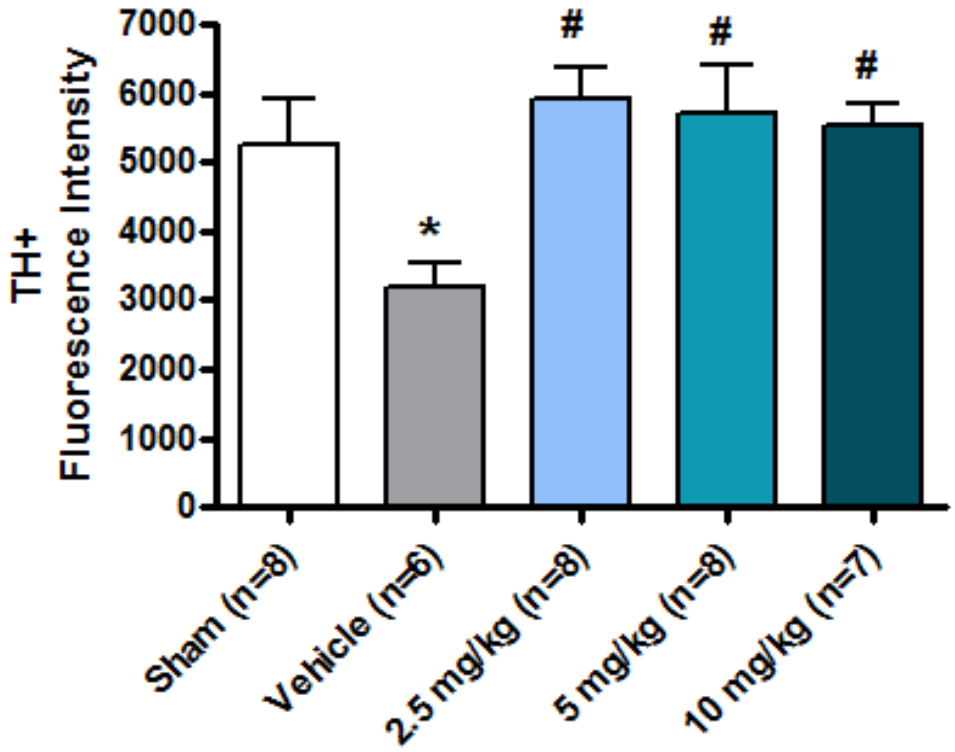
TBI: Posiphen Fully Protects Nerve Cells of Rats in the Striatum



Posiphen protects striatum histology following TBI

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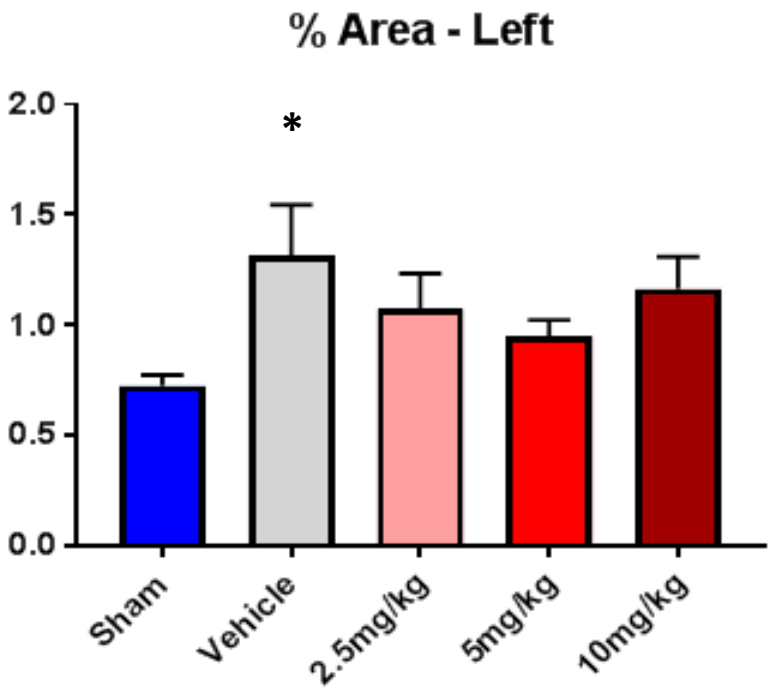
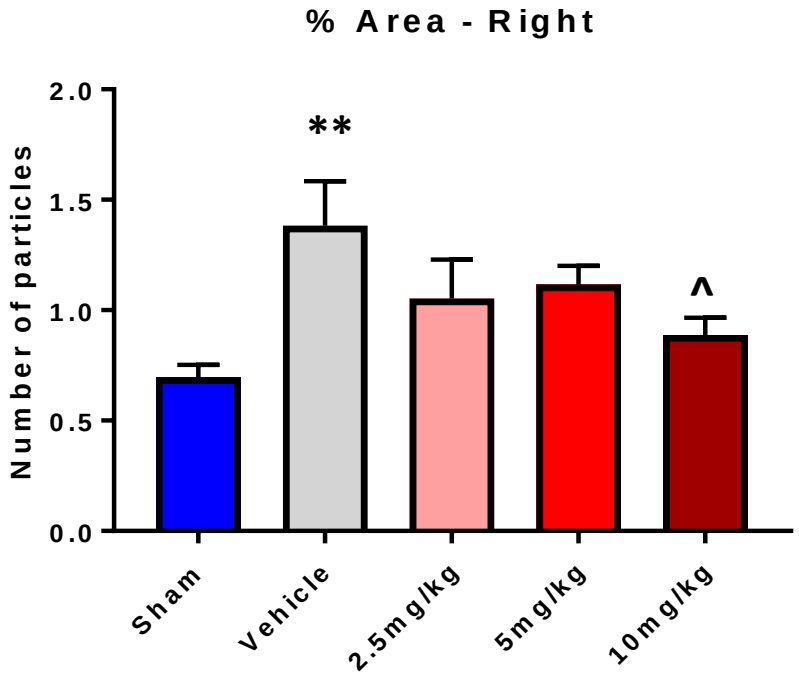
TBI: Comparison of Posiphen and Vehicle Treated Groups in Injured Substantia nigra

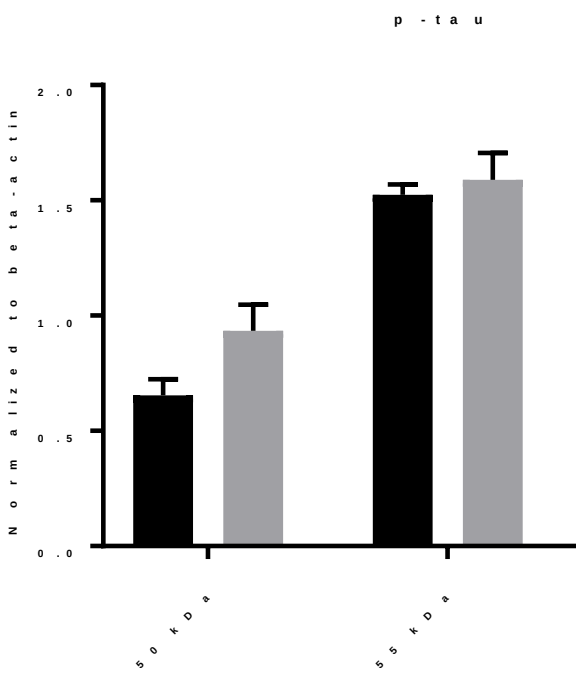


Data are presented as means ± SEMs (N=10 per group). A Mann-Whitney Rank Sum Test on the Sham and Vehicle groups revealed a significant increase in % area of iron staining in the Vehicle group (U=20.000, ***P=0.045 vs. Sham**). A one-way ANOVA on ranks revealed no significant effect of Posiphen treatment



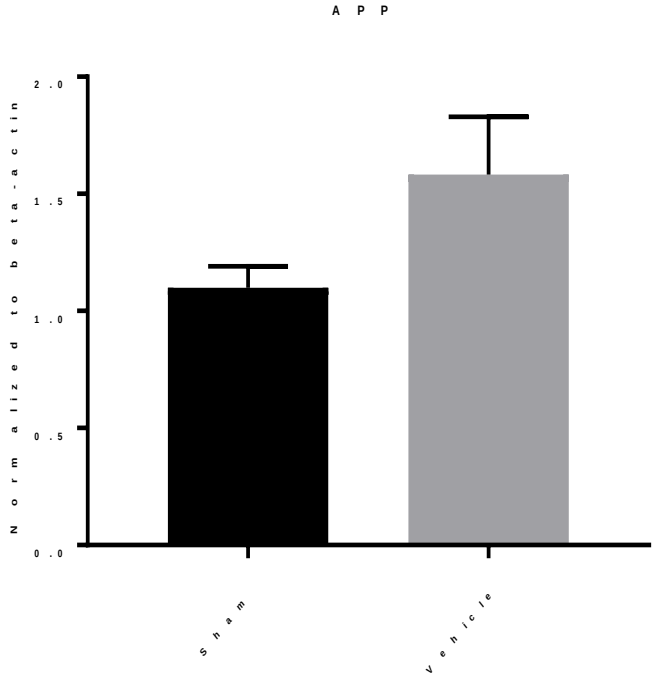
Data are presented as means ± SEMs (N=10 per group). A Mann-Whitney Rank Sum Test on the Sham and Vehicle groups revealed a significant increase in % area of iron staining in the Vehicle group (U=13.000, ****P=0.006 vs. Sham**). While there was no significant decrease in the 2.5 and 5 mg/kg group, a Student's t-test between the 10 mg/kg and Vehicle revealed a significant decrease in % area of iron staining (t=2.299, **^p=0.0337 vs. Vehicle**).

Increase in p-Tau and APP in substantia nigra



Data are shown as mean ± SEM (n=6-7)

50 kDa - A Student's t-test revealed an almost significant increase in p-tau in the vehicle group (t=-2.098, p=0.0578).



A Student's t-test between the two groups revealed an increase in APP level in the vehicle group approaching significance (t=-1.840, p=0.0906).

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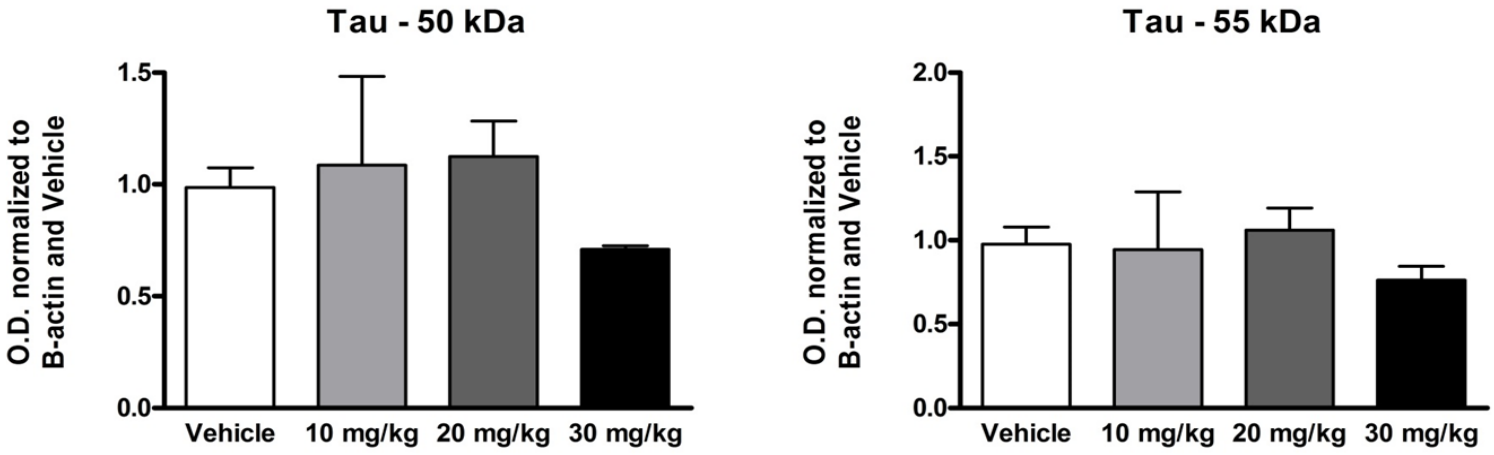
Posiphen reduces the elevated 50kDa Tau Isoform



- **30 mg/kg: 40% decrease from vehicle in 50kDA form:**
  One-way ANOVA (P = 0.021)
- **30 mg/kg: 22% decrease from vehicle in 55kDA form:**
  One-way ANOVA (P = 0.091)

Asa Hatami, UCLA

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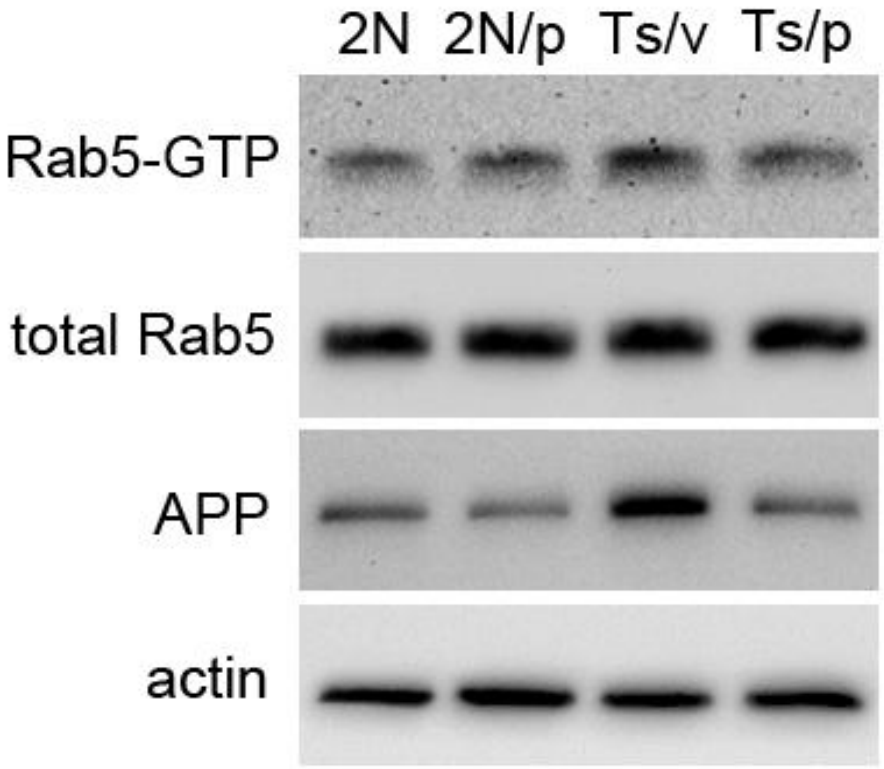
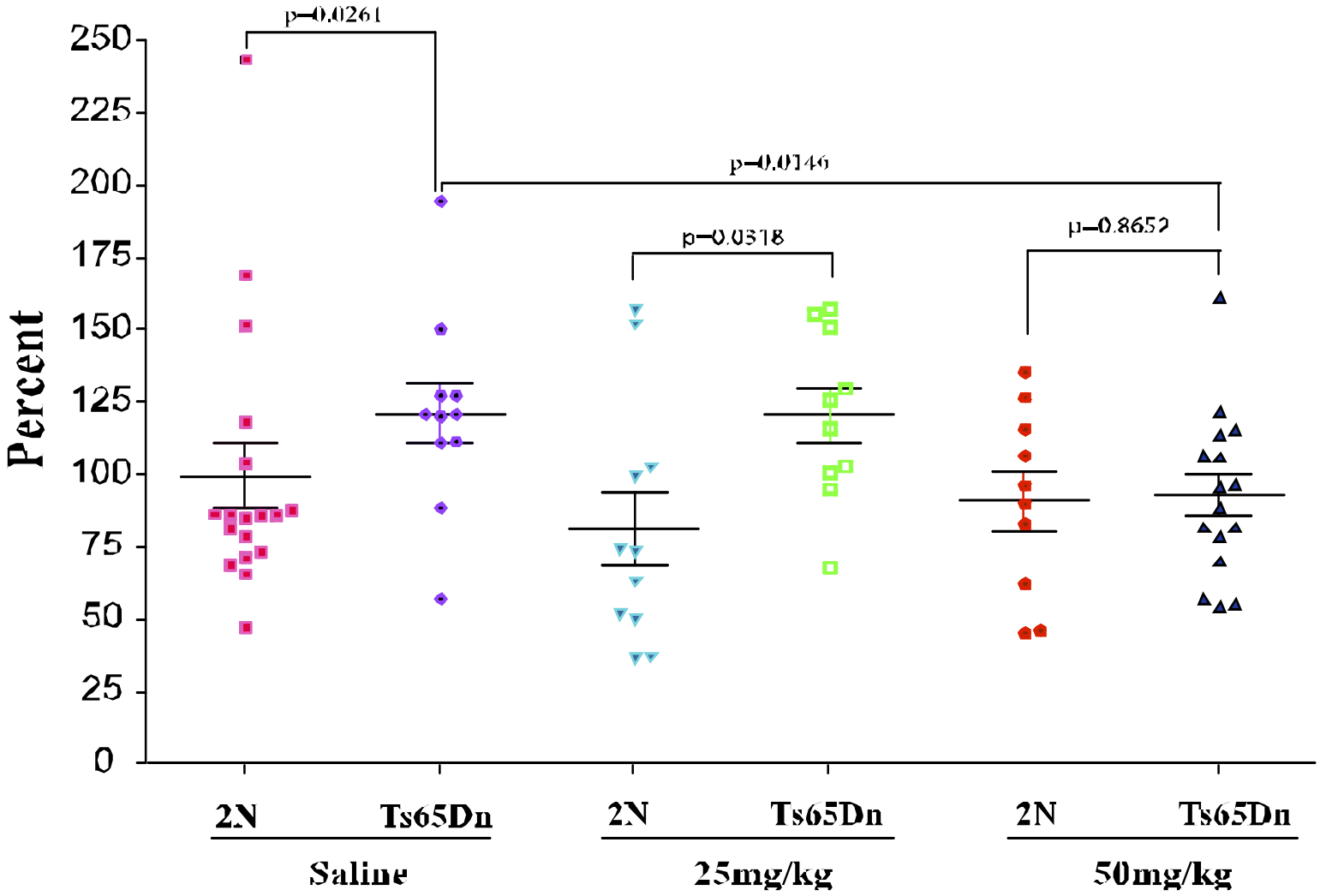
Posiphen Treatment for 48 hrs Reduces APP and Reverses Overactivation of Rab5 in Cortical Ts65DN Neurons



XQ Chen, Mobley Lab, UCSD

APP Levels in 2N and Ts65Dn Mice: Vehicle vs. Posiphen



1500ng/gm @ 50mg/kg

Salehi et al., 2008

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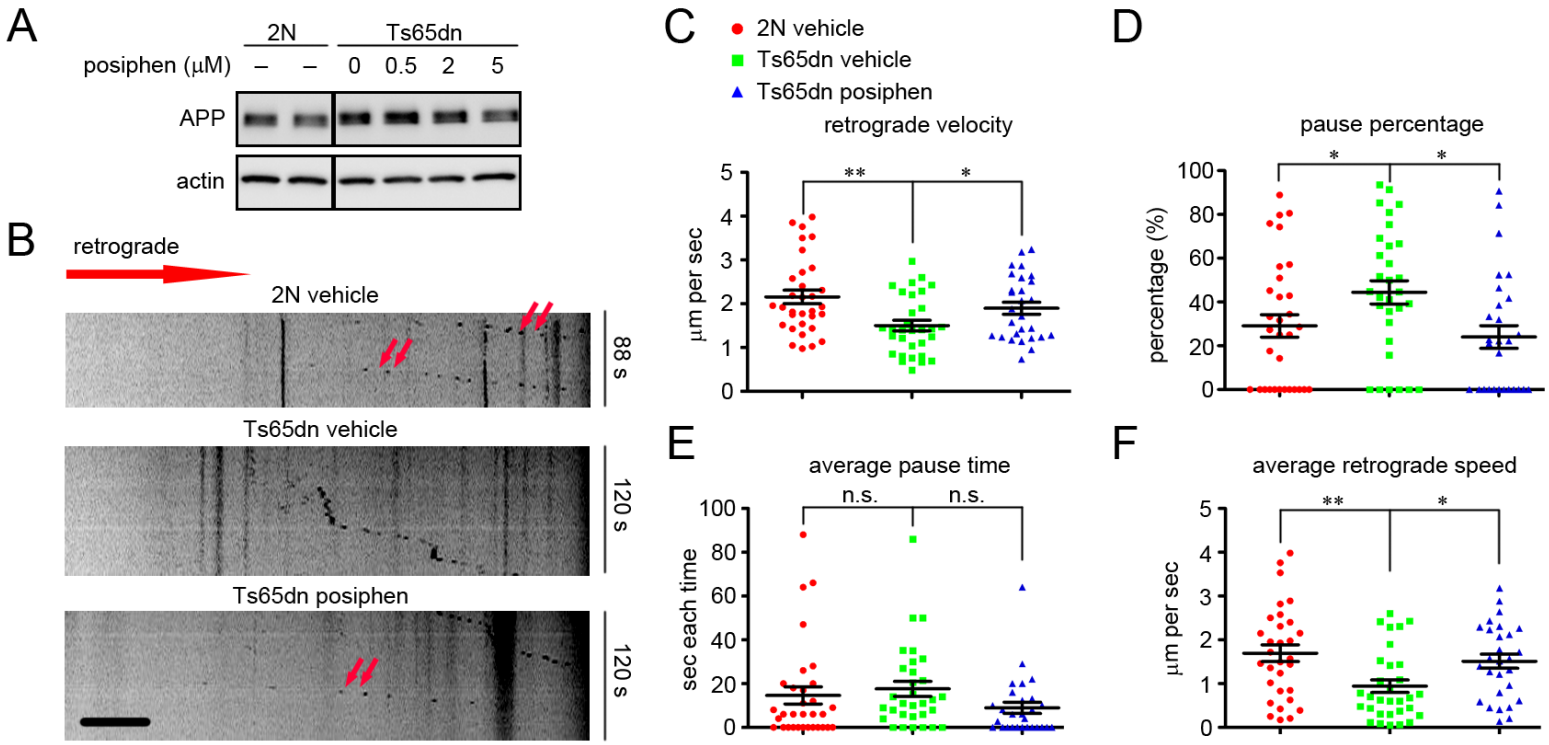
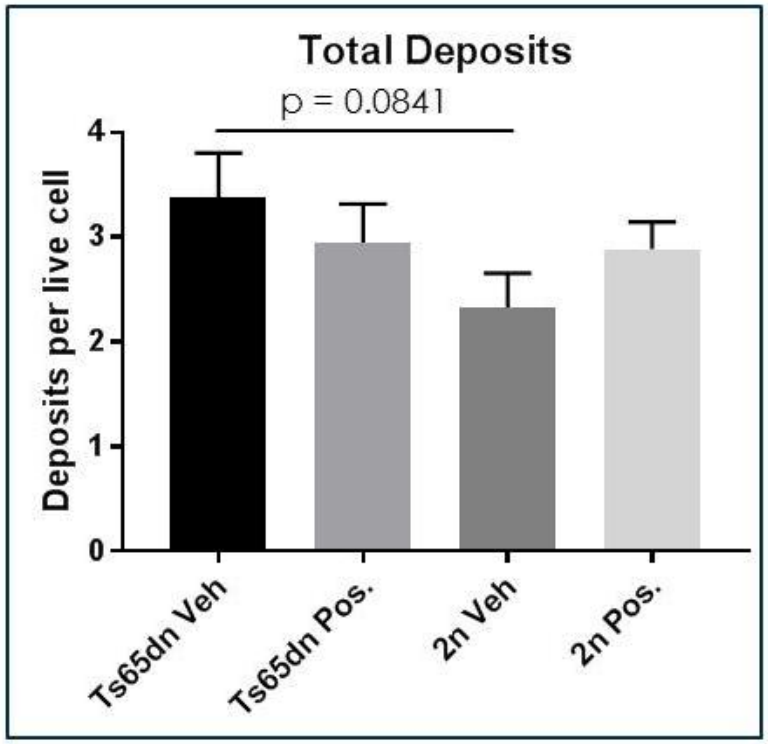
Reduced Axonal BDNF Transport is Reversed by Posiphen



5 uM, 48hr

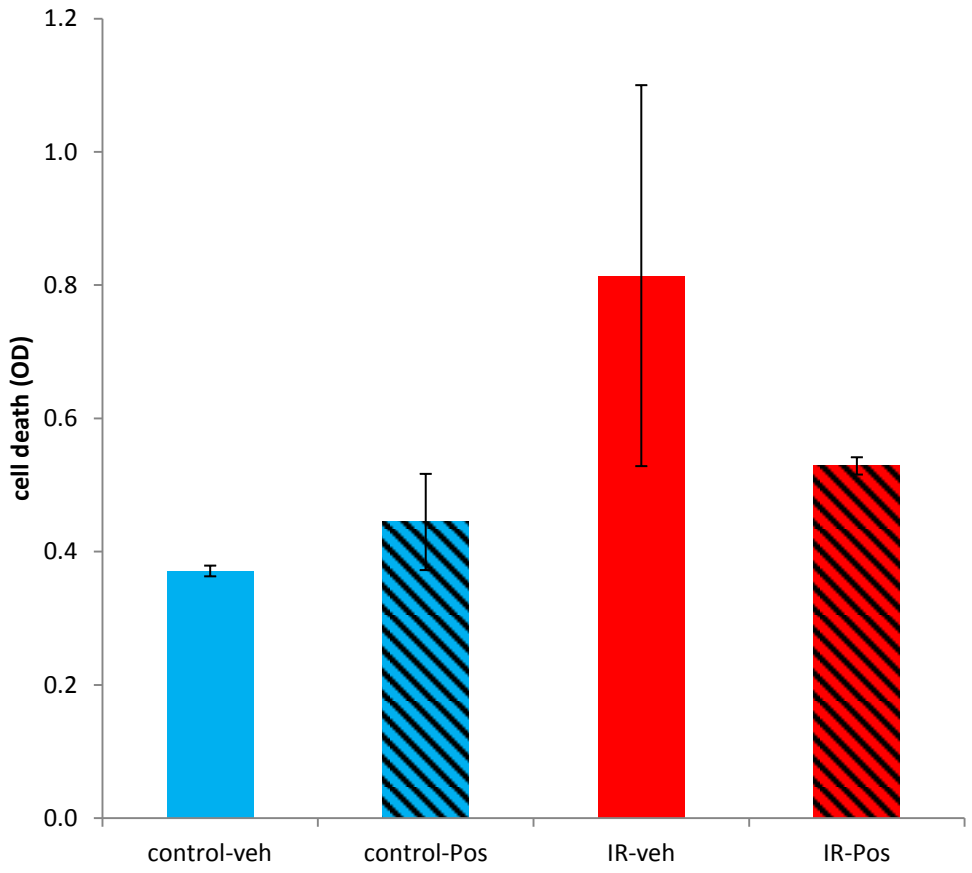
XQ Chen, Mobley Lab, UCSD

Iron Deposition in 3n Ts65dn vs. 2n primary neurons



Number of iron deposits associated with live cells at the time of fixation were counted and normalized to cells per field
Analyzed large and small deposits together and separately
5 fields per slide were quantified
2n primary neurons show about 25% lower iron content that 3n Ts65dn primary neurons

Acute Glaucoma: Posiphen Protects Retinal Cells in Rats



Acute glaucoma is induced by increasing intraocular pressure by micro-injection of saline into the anterior chamber. This induces large amounts of apoptotic cell death in the retina.

There are twice as many dead cells in high pressure retinas of rats treated with vehicle versus control untreated rats.

Posiphen rescues 72% of the retinal neurons.

Hershey Medical Center, Jeff Sundstrom's lab

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