



# **Development of a Novel Therapy for Alzheimer's Disease and Neurodegenerative Conditions**

**DONNA J. CROSS, PHD**

**Department of Radiology and Imaging Sciences  
University of Utah, Salt Lake City, U.S.A.**

# About Me:

- Aerospace Engineer (BSE)
- PhD in Neuroscience with 20 years experience using imaging to study Alzheimer's disease (AD) and CNS disorders.
- Associate Professor in the Department of Radiology and Imaging Sciences at the University of Utah
- President of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Brain Imaging Council (2023)
- Married for 34 years with two adult children – Ian and Chloe
- Gardener, baker, world traveler, athlete



# Satoshi Minoshima, MD, PhD

Chair of the University of Utah Department of Radiology and Imaging Sciences

Mentor for > 25 years



U HEALTH UNIVERSITY OF UTAH SCHOOL OF MEDICINE

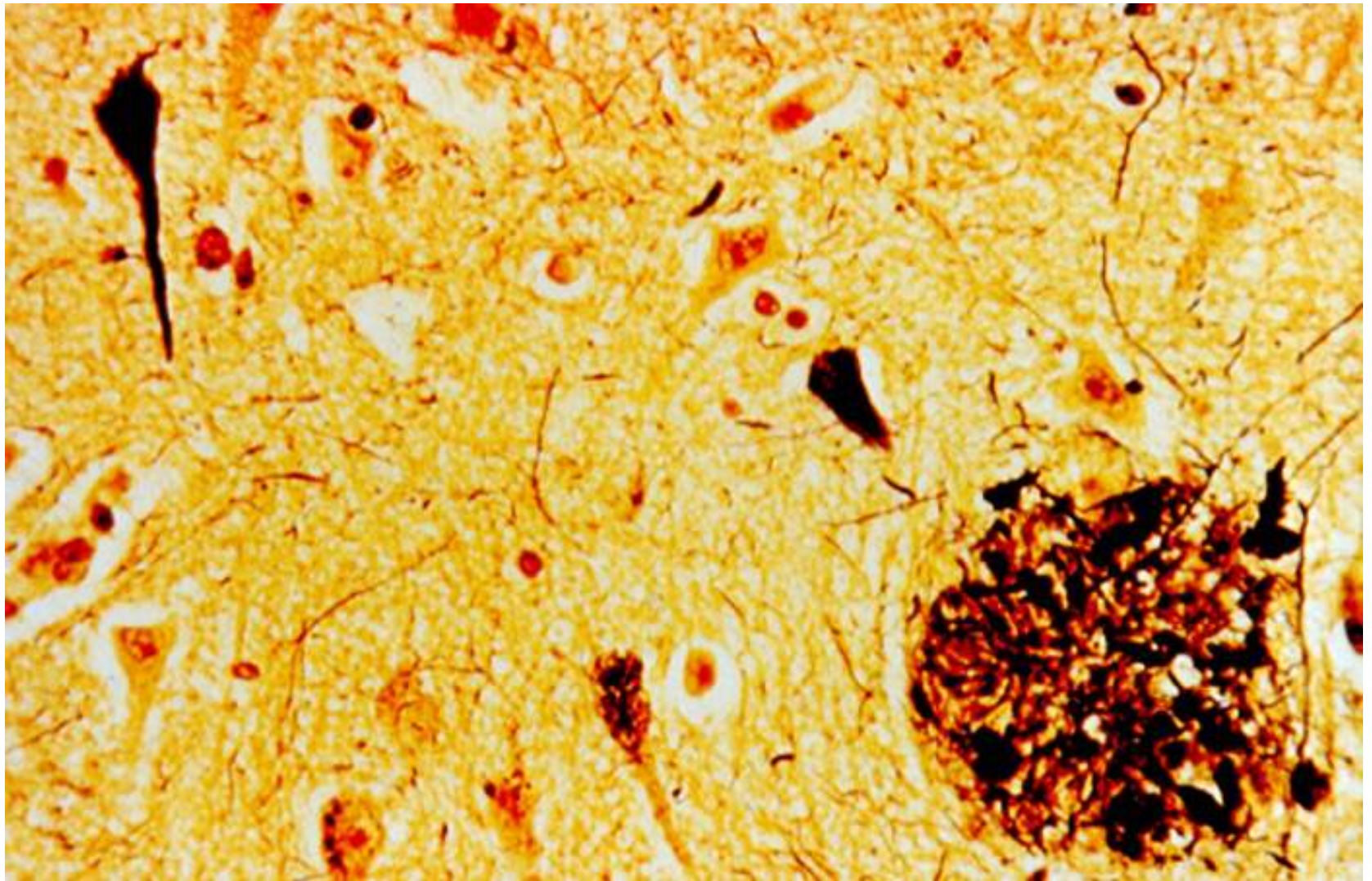
Home > Radiology

## DEPARTMENT OF RADIOLOGY AND IMAGING SCIENCES

**WELCOME FROM OUR CHAIR**

We improve healthcare through radiology practice, research investigation, and education. Our core values are to help people through compassion, innovation, perseverance, and unequivocal excellence. Our core purpose is to make people's lives free from suffering and illness by improving human health for the individual patient and for the community we serve.

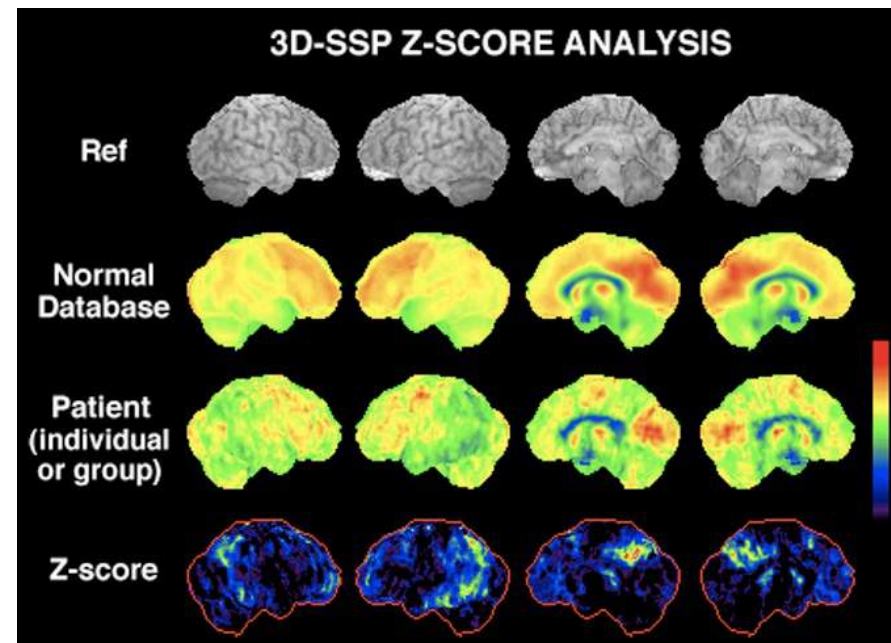
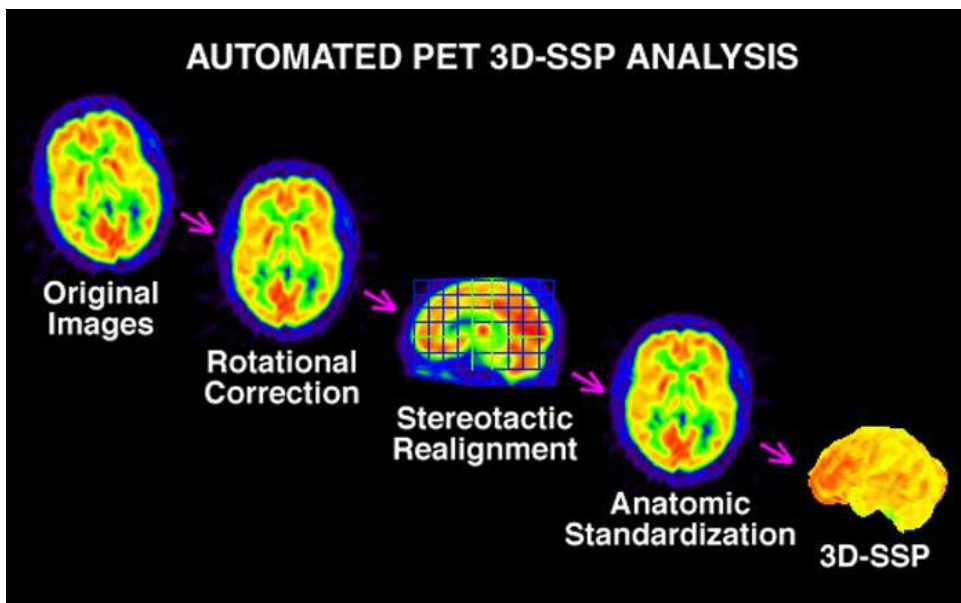
Satoshi Minoshima, MD, PhD



# A Diagnostic Approach in Alzheimer's Disease Using Three-Dimensional Stereotactic Surface Projections of Fluorine-18-FDG PET

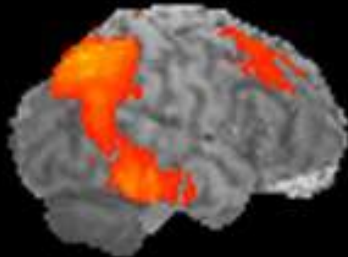
Satoshi Minoshima, Kirk A. Frey, Robert A. Koeppe, Norman L. Foster and David E. Kuhl

*Division of Nuclear Medicine, Department of Internal Medicine, and Departments of Neurology and Radiology, University of Michigan, Ann Arbor, Michigan*

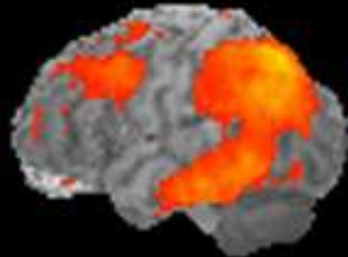


J Nucl Med 1995;36:1238-1248

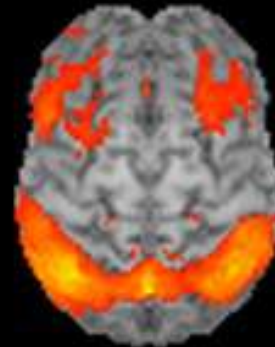
# Cerebral Metabolic Reduction in Alzheimer's Disease



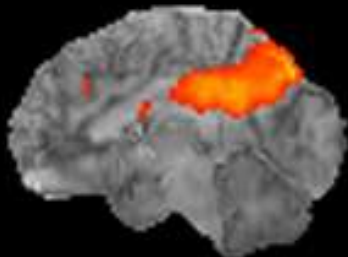
R.LAT



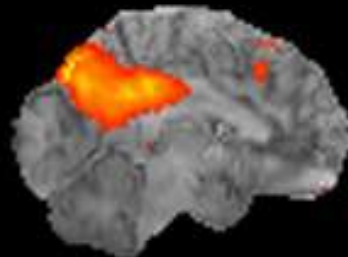
L.LAT



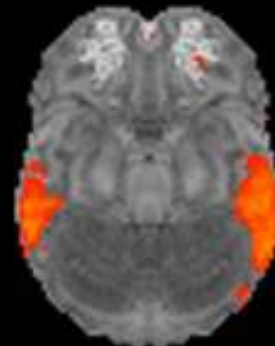
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R.MED



L.MED



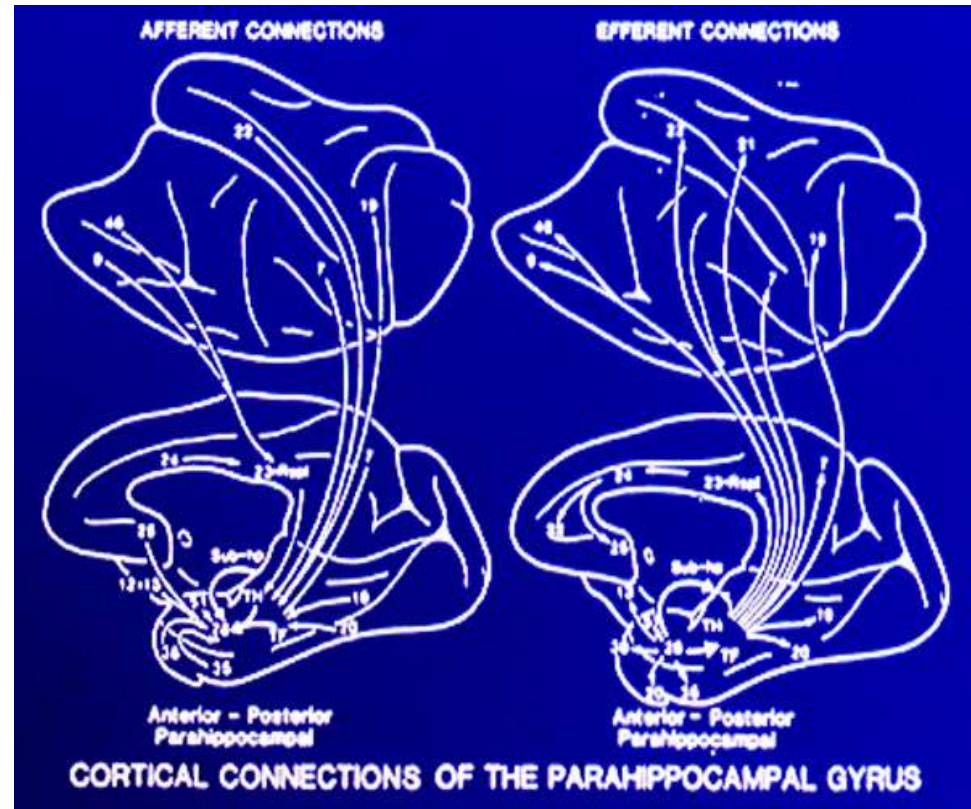
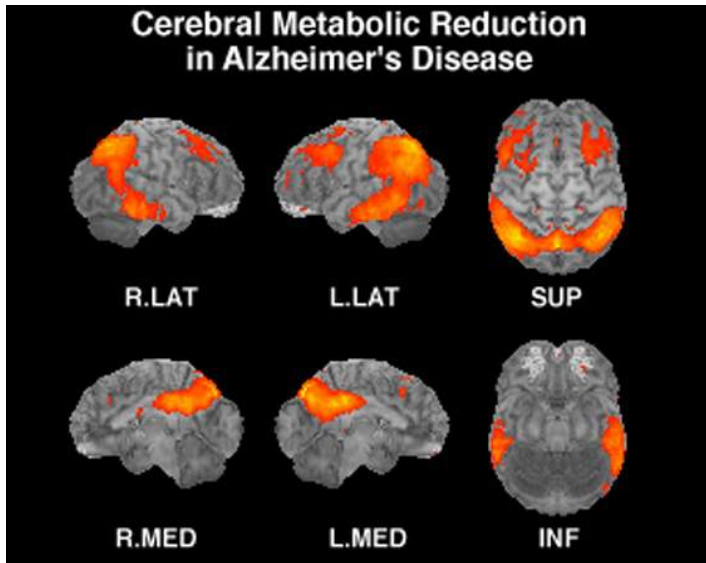
INF

# NEUROSTAT / 3D-SSP Users

<https://neurostat.neuro.utah.edu>

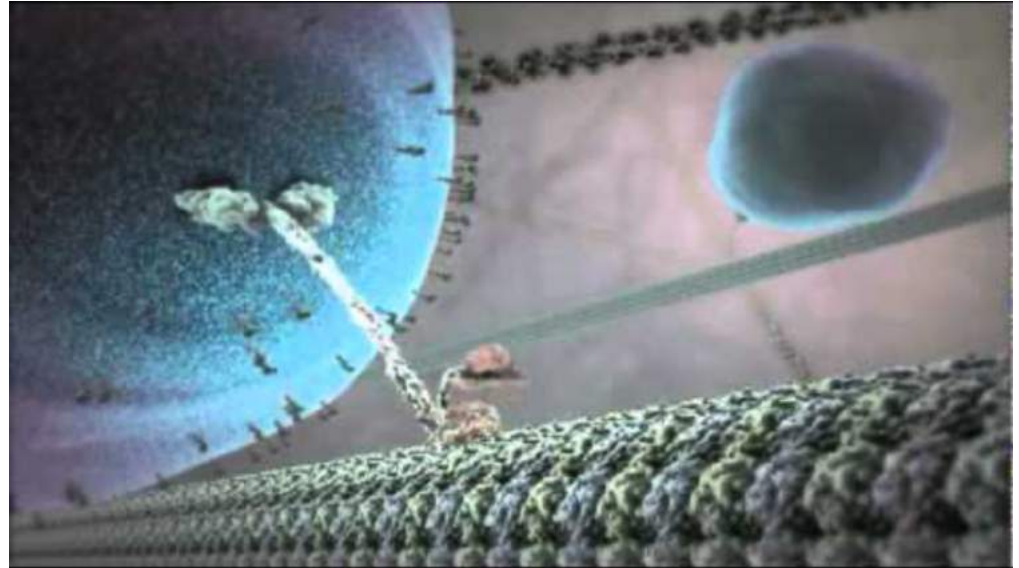
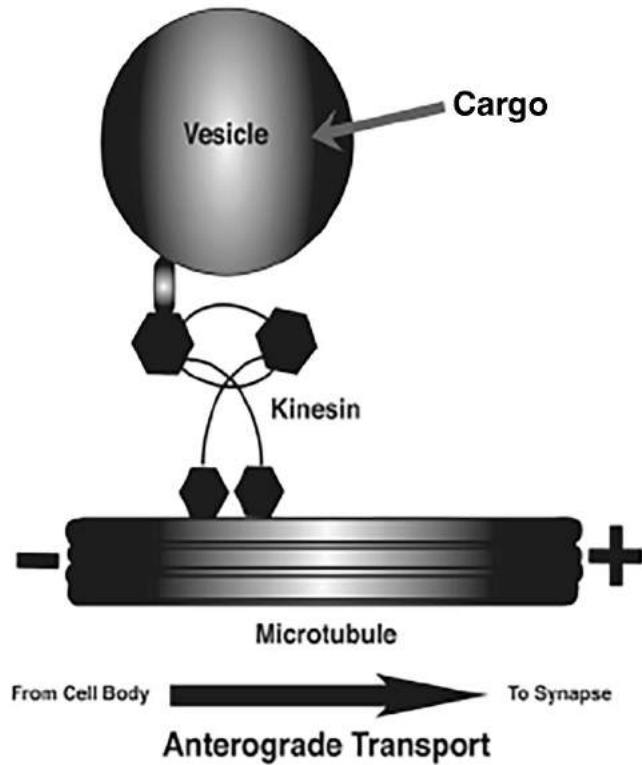
Approximately 1200 registered users, over 400 active  
Institutions - **59 countries**

USA	France	Lebanon	Slovakia
Argentina	Germany	Lithuania	Slovenia
Australia	Greece	Malaysia	South Africa
Austria	Hong Kong	Mexico	South Korea
Bangladesh	Hungary	New Zealand	Spain
Belgium	India	Norway	Switzerland
Brazil	Indonesia	Pakistan	Taiwan
Britain	Iran	Panama	Thailand
Canada	Ireland	Peru	The Netherlands
Chile	Israel	Philippines	Turkey
China	Italy	Poland	United Arab Emirates
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Denmark	Kazakhstan	Saudi Arabia	Zimbabwe
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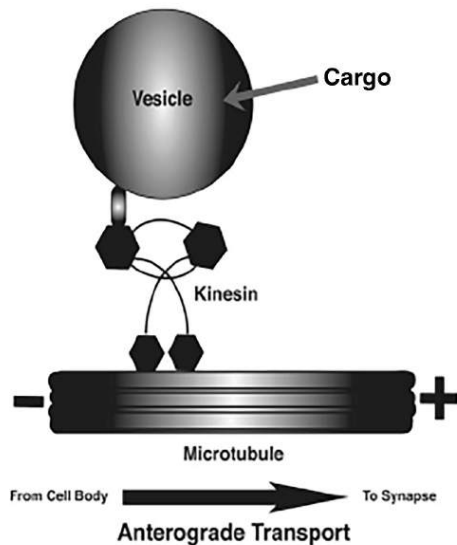


Van Hoesen 1982

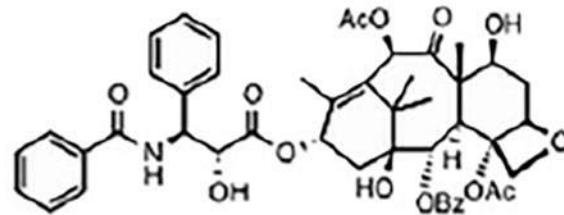
# Basic Components of Axonal Transport



# Microtubule stabilization for neurodegeneration and CNS injury



# Paclitaxel: Microtubule stabilizing drug



Paclitaxel

- Chemotherapy drug that stops microtubule-organized cell division
- In neurons, microtubules make up the cytoskeleton which supports axonal transport
- Limited studies indicated a neurotherapeutic effects (Adlard, et. al, Acta Neuropath 2000, Hellal, et. al. Science, 2011, Brunden et. al. J of Neuroscience -EpoD)
- **Paclitaxel does not cross the Blood-Brain-Barrier → INTRANASAL ADMINISTRATION**

# Microtubule stabilization in AD

Original research funded by the Alzheimer's Association research grant in 2011

Journal of Alzheimer's Disease 83 (2021) 379–394  
DOI 10.3233/JAD-210109  
IOS Press

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## Intranasal Paclitaxel Alters Alzheimer's Disease Phenotypic Features in 3xTg-AD Mice

Donna J. Cross<sup>a,\*</sup>, Bertrand R. Huber<sup>b,c</sup>, Michael A. Silverman<sup>d,e</sup>, Marcella M. Cline<sup>f,g</sup>, Trevor B. Gill<sup>d</sup>, Chloe G. Cross<sup>a</sup>, David G. Cook<sup>f,g</sup> and Satoshi Minoshima<sup>a</sup>

<sup>a</sup>Department of Radiology and Imaging Sciences, University of Utah, Salt Lake City, UT, USA

<sup>b</sup>Boston University Alzheimer's Disease and CTE Center, Boston University School of Medicine, Boston, MA, USA

<sup>c</sup>Department of Neurology, Boston University School of Medicine, Boston, MA, USA

<sup>d</sup>Department of Biological Sciences, Simon Fraser University, Burnaby, BC, Canada

<sup>e</sup>Centre for Cell Biology, Development, and Disease, Simon Fraser University, Burnaby, BC, Canada

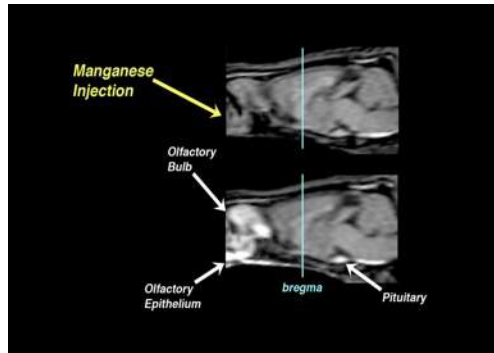
<sup>f</sup>The Geriatric Research, Education, and Clinical Center (GRECC), Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA

<sup>g</sup>Departments of Medicine, Pharmacology, Psychiatry & Behavioral Sciences, University of Washington, Seattle, WA, USA

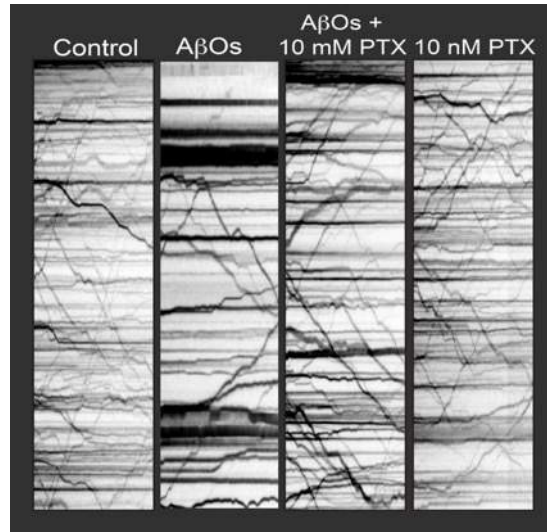
# Axonal Transport

In vitro cell cultures

MEMRI

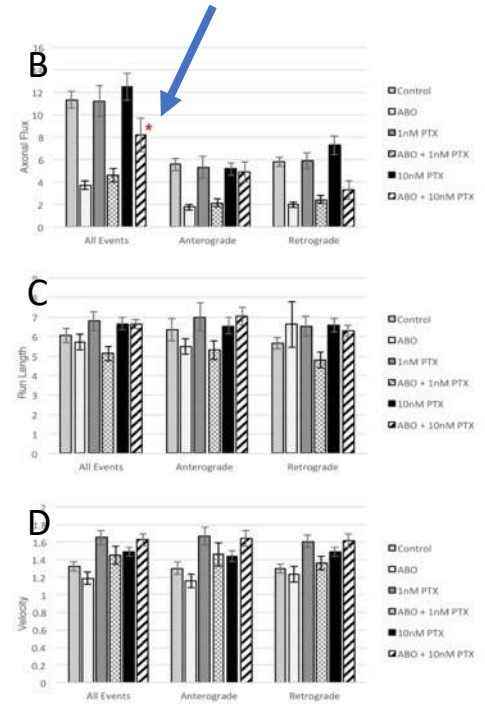
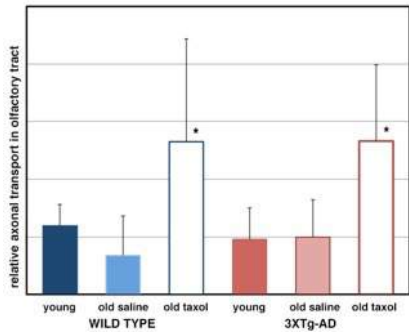


75 microns



25 sec

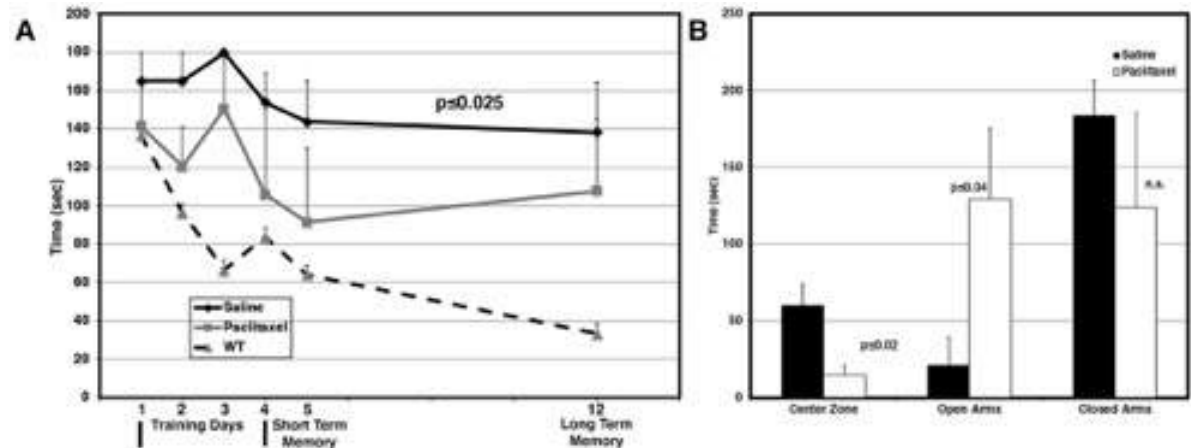
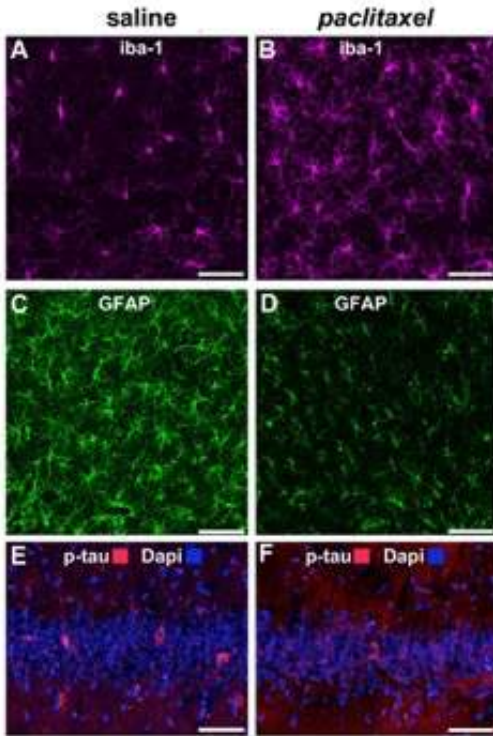
Low dose paclitaxel **IMPROVES AXONAL TRANSPORT** in AD mice and in cultured neuronal cells



Cross et al, J of Alz Dis, 2021

# Pathology and Cognition

Paclitaxel **REDUCES TAU** pathology and **INFLAMMATION** in 3xTg-AD mice. **No effect was observed on Amyloid pathology**



Radial Water Tread Maze shows **IMPROVED MEMORY** and elevated plus maze shows **REDUCED ANXIETY** in AGED mice after intranasal paclitaxel

Cross et al, J of Alz Dis, 2021

# Microtubule stabilization for Traumatic Brain Injury

Journal of Alzheimer's Disease 67 (2019) 859–874  
DOI 10.3233/JAD-180871  
IOS Press

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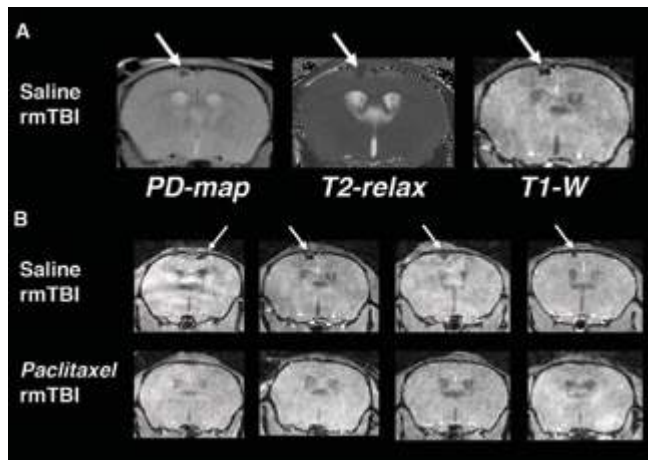
## *Paclitaxel* Reduces Brain Injury from Repeated Head Trauma in Mice

Donna J. Cross<sup>a,\*</sup>, James S. Meabon<sup>b,d</sup>, Marcella M. Cline<sup>c,e</sup>, Todd L. Richards<sup>f</sup>, Amanda J. Stump<sup>a</sup>,  
Chloe G. Cross<sup>a</sup>, Satoshi Minoshima<sup>a</sup>, William A. Banks<sup>c,g</sup> and David G. Cook<sup>c,h</sup>

## Paclitaxel Reduces Brain Injury from Repeated Head Trauma in Mice

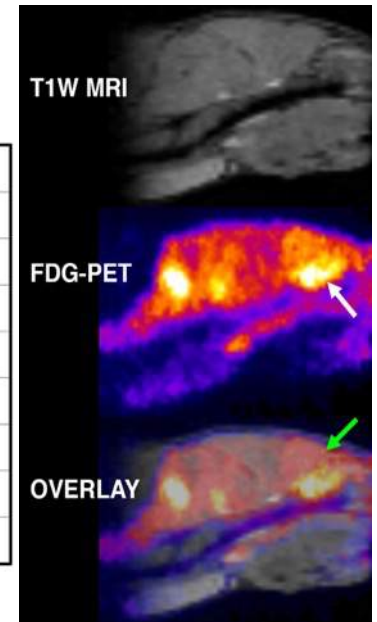
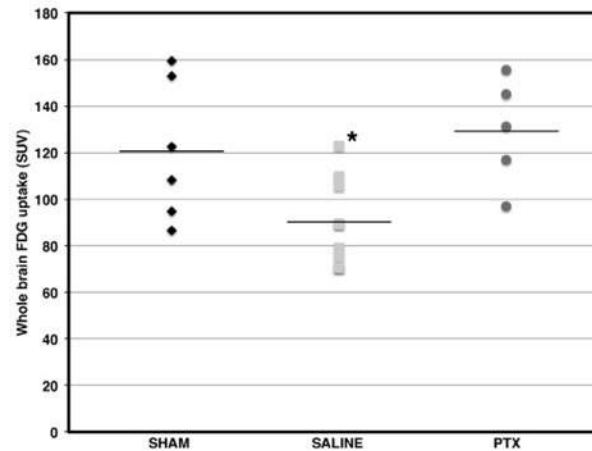
Donna J. Cross<sup>a,\*</sup>, James S. Meabon<sup>b,d</sup>, Marcella M. Cline<sup>c,e</sup>, Todd L. Richards<sup>f</sup>, Amanda J. Stump<sup>a</sup>, Chloe G. Cross<sup>a</sup>, Satoshi Minoshima<sup>g</sup>, William A. Banks<sup>c,h</sup> and David G. Cook<sup>c,h</sup>

**Repeat Concussion injury - 5 times in 5 days.**



“Microbleed” in the brain below impact area

**PACLITAXEL-TREATED SHOWED NO EVIDENCE OF THE BLEED.**

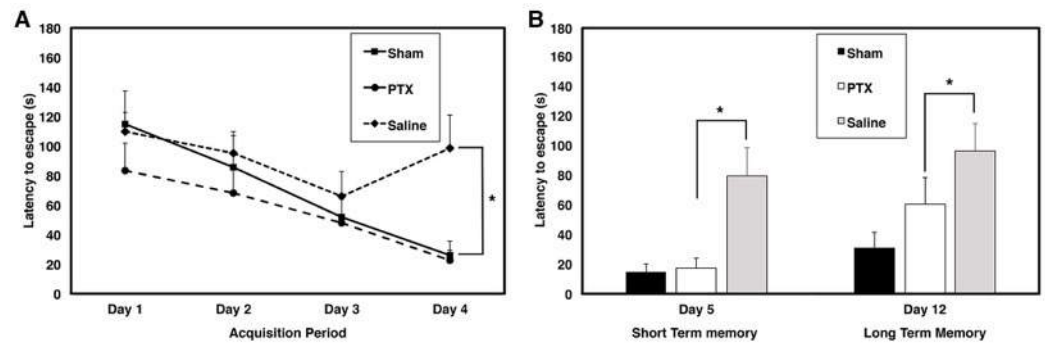


Injured mice had reduced overall brain activity

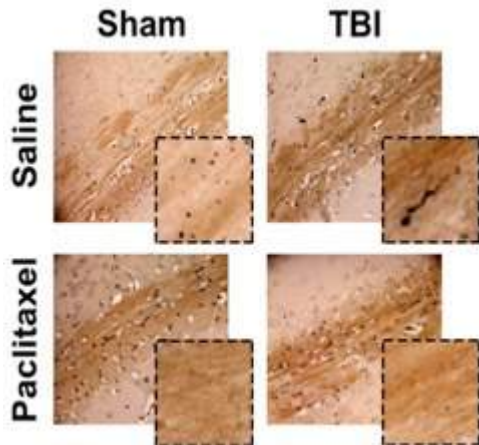
Paclitaxel-treated mice with brain injuries showed normal brain activity with PET imaging

## *Paclitaxel* Reduces Brain Injury from Repeated Head Trauma in Mice

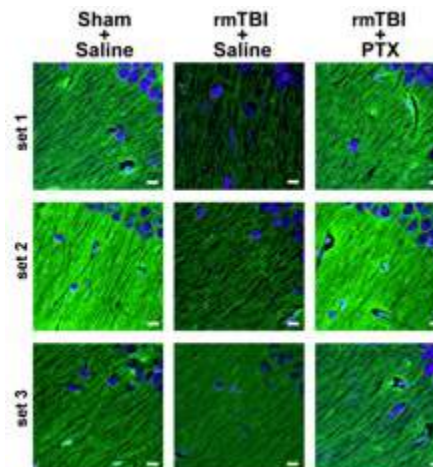
Donna J. Cross<sup>a,\*</sup>, James S. Meabon<sup>b,d</sup>, Marcella M. Cline<sup>e,c</sup>, Todd L. Richards<sup>f</sup>, Amanda J. Stump<sup>g</sup>, Chloe G. Cross<sup>a</sup>, Satoshi Minoshima<sup>a</sup>, William A. Banks<sup>c,f</sup> and David G. Cook<sup>c,h</sup>



Radial water tread maze memory test showed that paclitaxel-treated mice with brain injury were not different from mice without brain injuries



Pathology indicates no axonal injuries with paclitaxel treatment



PSD-95 stain reveals preservation of synapses in the hippocampus (memory region) with *paclitaxel* treatment

# Summary: Paclitaxel anti-neurodegenerative/injury effects

## Cognitive

- Memory rescued/restored (water tread maze)
- Anxiety improved (elevated plus)

## Neurons

- Axonal transport rescued (in vitro, MEMRI)
- Axonal injury prevented (silver stain, NOT found with DTI)
- Brain activity preserved (FDG-PET)
- Synaptic density maintained (PSD-95 stain)

## AD pathology

- Tau pathology reduced (AT8 stain)
- **Amyloid – unchanged**

## Other

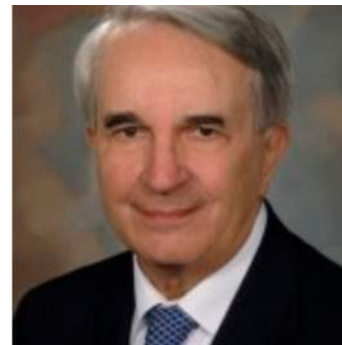
- **Brain Inflammation reduced** (GFAP, iba-1 stain + other studies of neuronal injury)

# NEXT PHASE: Backbone Degradable Polymer-drug Conjugate for Treatment of AD and TBI

COLLABORATORS (University of Utah College of  
Pharmacy)

Jindrich (Henry) Kopeček, PhD

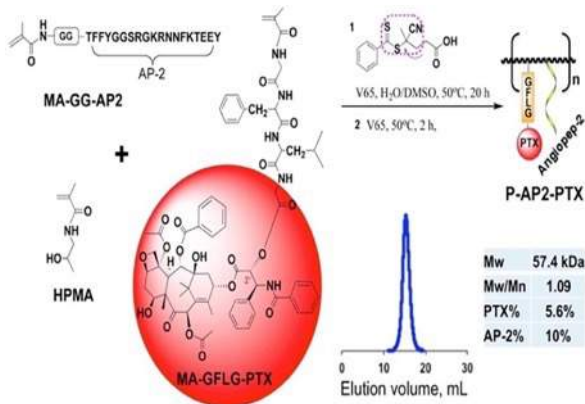
Jiyuan (Jane) Yang, PhD



Funding: Alzheimer's Association Research Grant

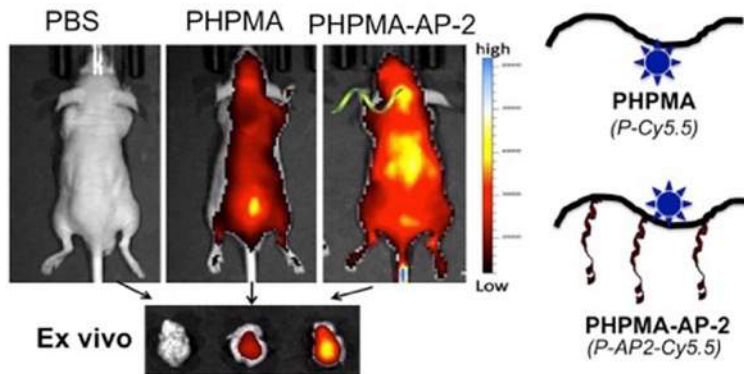
- Pharmacokinetics
- Biodistribution
- Radiolabeled drug and PET imaging

# PolyHPMA-paclitaxel Conjugate for Treatment of AD and TBI



## Synthetic scheme for the HPMA copolymer conjugate containing AP2 and PTX

- Optimizes therapeutic efficacy
- Reduces adverse effects by increasing long-circulation in the bloodstream
- Avoids drug-resistance due to the different mechanism of cell entry



AP-2 mediated crossing of blood-brain-barrier

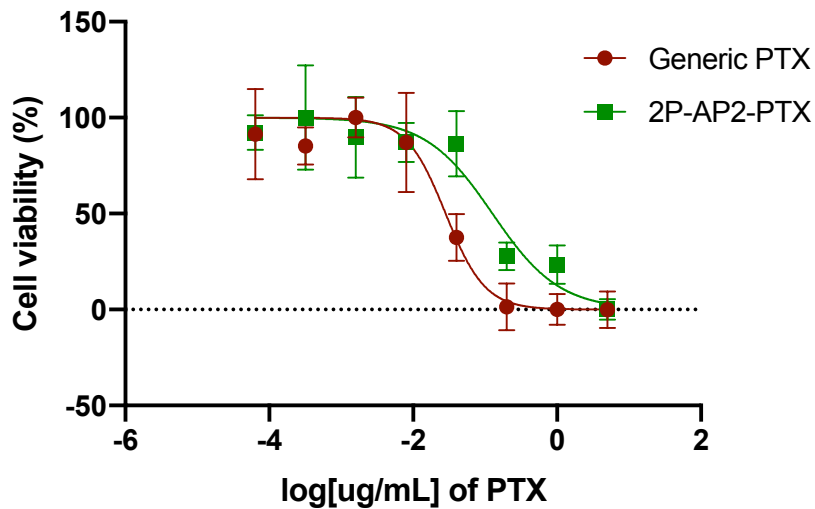
AP2 appears to be a highly efficient BBB-crossing agent.

# Cytotoxicity

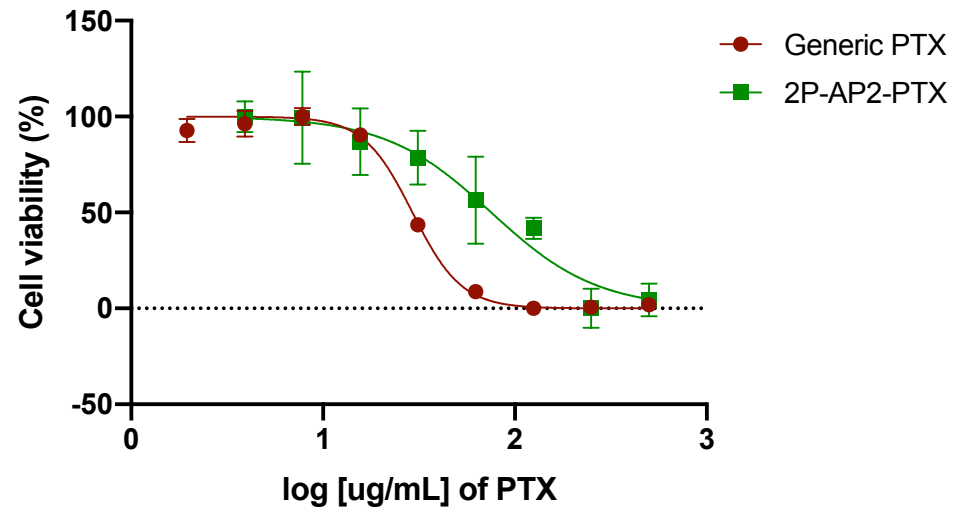


Shannuo Li

SHSY-5Y



b.END3



IC50 (ug/mL)	Generic PTX	P-PTX-AP2
b.END3	29.3	75.3
SH-SY5Y	0.029	0.127

# Gross organ toxicity (H&E)



Hasan Al Faruque, PhD

Liver

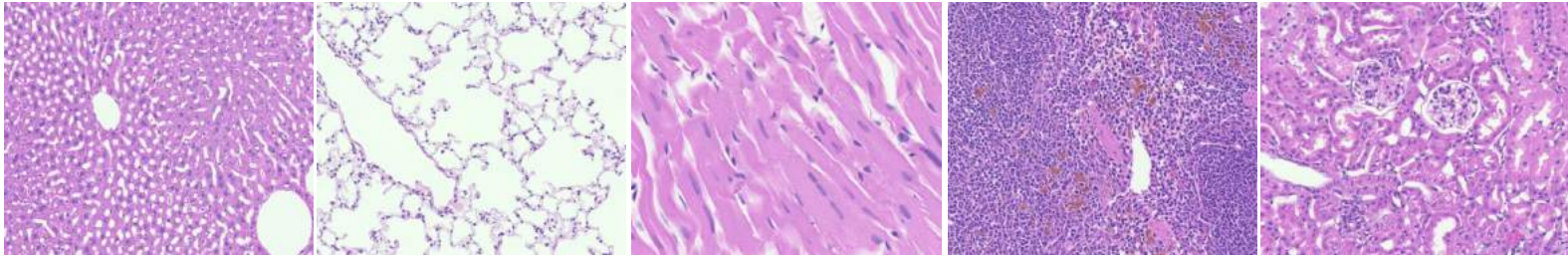
Lung

Heart

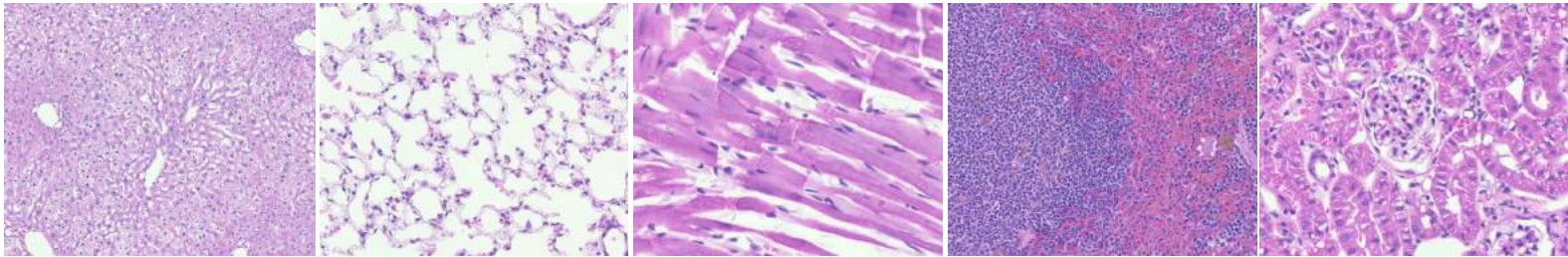
Spleen

Kidney

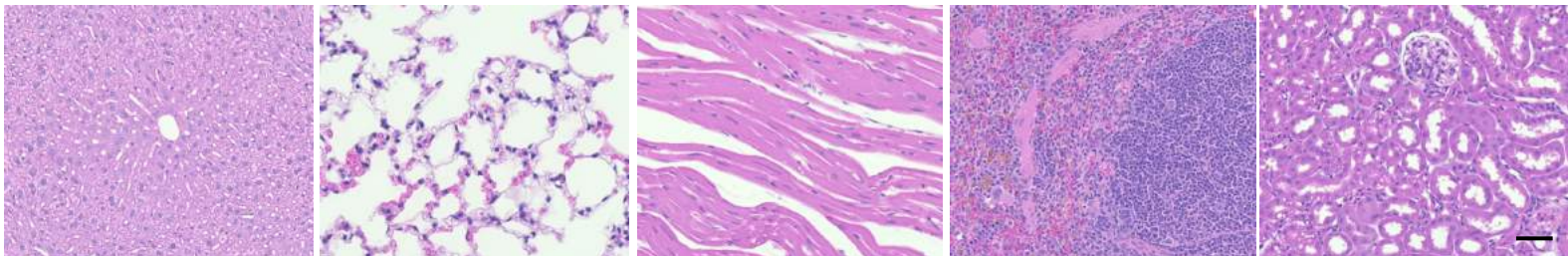
Vehicle, TG



Vehicle, WT

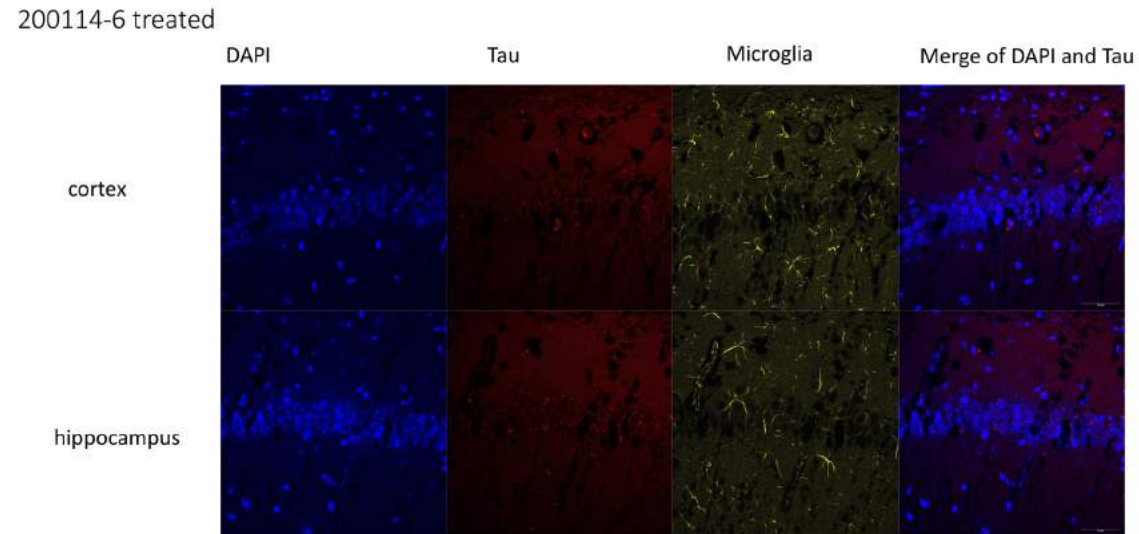
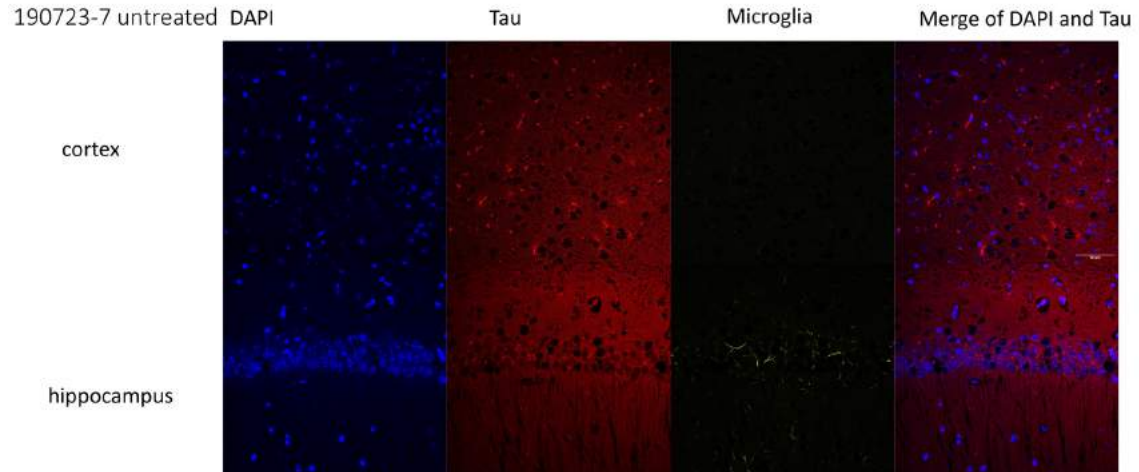
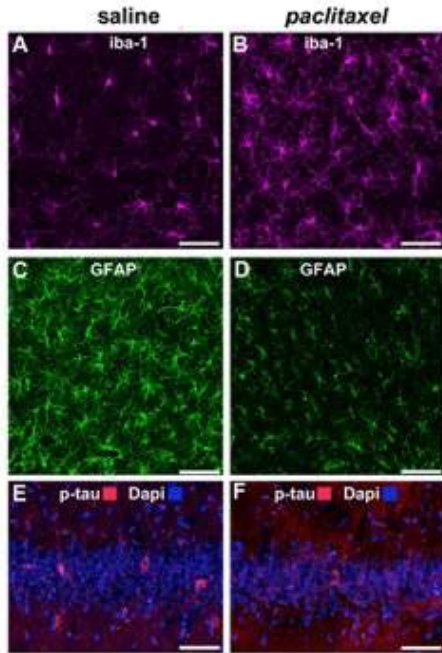


P-PTX-AP2, TG



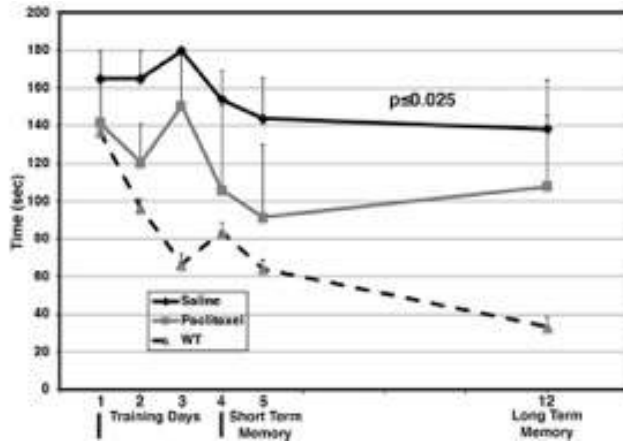
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# PolyHPMA-PTX Conjugate for Treatment of AD

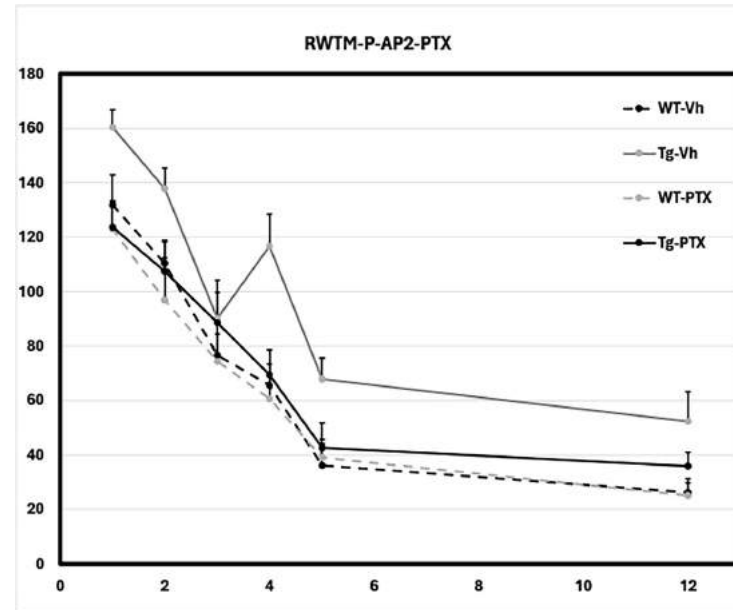


# PolyHPMA-PTX Conjugate for Treatment of AD

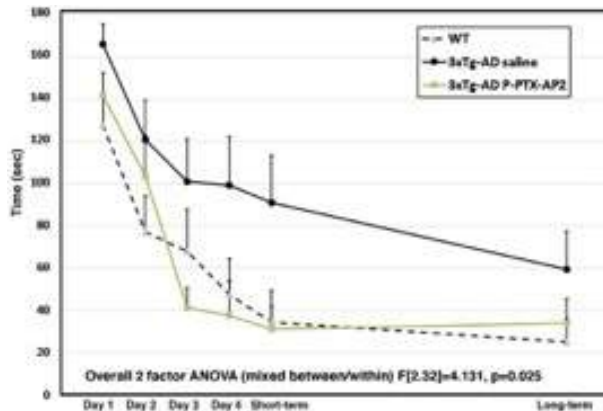
Water Tread Maze indicates improved treatment response with new drug PTX conjugate over intranasal generic PTX in AGED 3xTg-AD mice (12 months old)



Cross et al, 2021 PTX (intranasal)



P-PTX-AP2 (IV administration)





# THANK YOU!

## Neuroimaging and Biotechnology Lab

Department of Radiology and Imaging Sciences

University of Utah, Salt Lake City, UT, USA

**PIs:** Donna J. Cross, PhD

Yoshimi Anzai, MD, MPH

Satoshi Minoshima, MD, PhD

**Research Technologists:** Raghad Aljassimi and Ashton Jensen

**Students:** Caroline Giddings, Anika De Souza, Lana Hua, Mira Hua

**Collaborators:** University of Utah

**Jindrich Kopecek PhD**

Shannuo Li

**Jiyuan Yang, PhD**

Hasan Al Faruque, PhD

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